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Article

WNT-1/2B/3A/4/5A : Time Behavioural Study of 3rd Order Combinations in WNT3A Stimulated HEK 293 Cells

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Abstract: The WNT proteins are a family of a number of cysteine-rich glycoproteins which activate signal transduction cascades via three different pathways, the canonical WNT pathway, the noncanonical planar cell polarity (PCP) pathway, and the noncanonical WNT/ Ca^{2+} pathway. Here, a time behavioural study of 3rd order WNT combinations in WNT3A stimulated HEK 293 cells is presented. Gujral and MacBeath [1] provides a quantitative, and dynamic study of WNT3A-mediated stimulation of HEK 293 cells, where they record time based expression profiles of several response genes which correlated significantly with proliferation and migration. By monitoring the dynamics of gene expression using self-organizing maps, they identified clusters of genes that exhibit similar expression dynamics and uncovered previously unrecognized positive and negative feedback loops. However, their study depicts/uses singular measurements of individual gene expression at different time snapshots/points to infer the system wide analysis of the pathway. At any particular time point, it is often the case that genes are working synergistically in combinations, even though their expression measurements are singular in nature. Here, I • enumerate and rank all 2415 WNT (particular family member) related 3rd order combinations in a forest of ${}^{71}\text{C}_3$ combinations using four different sensitivity methods; • show the conserved rankings for WNT-X-X combinations, which point to existence of biological synergy of some of these combinations across the different sensitivity methods; and • study the behaviour of some of these combinations related to WNT3A response genes that are ranked by the machine learning search engine (Sinha [2]) in time. Patterns of combinations emerge, some of which have been tested in wet lab, while others require further wet lab analysis.

Keywords: sensitivity analysis; support vector ranking; Hilbert Schmidt Independence Criterion indices (HSIC) and Sobol indices; WNT3A

1. Significance

Sinha [2] recently demonstrated the use of machine learning based search engine to rank/reveal gene combinations at 2nd order for the time series data by Gujral and MacBeath [1] and showed how it is possible to locate combinations of priority that might be working synergistically, using sensitivity methods and powerful support vector ranking algorithm. However, the problem explodes combinatorially with even a small set of 71 recorded genes in the study by Gujral and MacBeath [1], when one steps to explore 3rd order combinations. With the total number of ${}^{71}\text{C}_3$ (= 57155) combinations, it becomes nearly impossible for any biologist to study the system wide dynamics of any pathway. Also, the amount of time usually needed to search for and test a combination is far more than the search down by the machine learning based search engine. Here, I extend the research work by Sinha [2] to conduct a behavioral study of 3rd order WNT related combinations using individual gene expressions measured in time, in WNT3A stimulated HEK 293 cells.

2. Introduction

The details of the machine learning based search engine has been recently published in Sinha [2] and deployed to explore the 2nd order combinations of genes in the data set provided by Gujral and MacBeath [1]. Nevertheless, here, I point to the fundamentals of the published work for completeness.

2.1. A Combinatorial Problem

Sensitivity analysis plays a major role in computing the strength of the influence of involved factors in any phenomena under investigation. When applied to expression profiles of various intra/extracellular factors that form an integral part of a signaling pathway, the variance and density based analysis yields a range of sensitivity indices for individual as well as various combinations of factors. These combinations denote the higher order interactions among the involved factors. Computation of higher order interactions is often time consuming but it gives a chance to explore the various combinations that might be of interest in the working mechanism of the pathway. For example, in a range of fourth order combinations among the various factors of the Wnt pathway, it would be easy to assess the influence of the destruction complex formed by APC, AXIN, CSKI and GSK3 interaction. But the effect of these combinations vary over time as measurements of fold changes and deviations in fold changes vary. So it is imperative to know how an interaction or a combination of the involved factors behave in time and Sinha [2] develops a procedure to track the behaviour by exploiting the influences of these involved factors.

2.2. A Possible Solution

In this work, after estimating the individual effects of factors for a higher order combination, the individual indices are considered as discriminative features. A combination, then, is a feature set in higher order (≥ 2 , i.e. multivariate). With an excessively large number of factors involved in the pathway, it is difficult to search for important combinations in a wide search space over different orders. Exploiting the analogy with the issues of prioritizing webpages using ranking algorithms, for a particular order, a full set of combinations of interactions can then be prioritized based on these features using a powerful ranking algorithm via support vectors Joachims [3]. Recording the changing rankings of the combinations over time reveals how higher order interactions behave within the pathway and when an intervention might be necessary to influence the interaction within the pathway.

2.3. Wnt Signaling and Secretion

Sharma [4]'s accidental discovery of the Wingless played a pioneering role in the emergence of a widely expanding research field of the Wnt signaling pathway. A majority of the work has focused on issues related to • the discovery of genetic and epigenetic factors affecting the pathway Thorstensen et al. [5] & Baron and Kneissel [6], • implications of mutations in the pathway and its dominant role on cancer and other diseases Clevers [7], • investigation into the pathway's contribution towards embryo development Sokol [8], homeostasis Pinto et al. [9] & Zhong et al. [10] and apoptosis Pećina-Šlaus [11] and • safety and feasibility of drug design for the Wnt pathway Kahn [12], Garber [13], Voronkov and Krauss [14], Blagodatski et al. [15] & Curtin and Lorenzi [16].

The Wnt phenomena can be roughly segregated into signaling and secretion part. The Wnt signaling pathway works when the WNT ligand gets attached to the Frizzled(FZD)/LRP coreceptor complex. FZD may interact with the Dishevelled (DVL) causing phosphorylation. It is also thought that Wnts cause phosphorylation of the LRP via casein kinase 1 (CK1) and kinase GSK3. These developments further lead to attraction of Axin which causes inhibition of the formation of the degradation complex. The degradation complex constitutes of AXIN, the β -catenin transportation complex APC, CK1 and GSK3. When the pathway is active the dissolution of the degradation complex leads to stabilization in the concentration of β -catenin in the cytoplasm. As β -catenin enters into the nucleus it displaces the GROUCHO and binds with transcription cell factor TCF thus instigating transcription of Wnt target genes. GROUCHO acts as lock on TCF and prevents the transcription of target genes which may induce cancer. In cases when the Wnt ligands are not captured by the

coreceptor at the cell membrane, AXIN helps in formation of the degradation complex. The degradation complex phosphorylates β -catenin which is then recognised by F BOX/WD repeat protein β -TRCP. β -TRCP is a component of ubiquitin ligase complex that helps in ubiquitination of β -catenin thus marking it for degradation via the proteasome.

Contrary to the signaling phenomena, the secretion phenomena is about the release and transportation of the WNT protein/ligand in and out of the cell, respectively. Briefly, the WNT proteins that are synthesized with the endoplasmic reticulum (ER), are known to be palmitoylated via the Porcupine (PORCN) to form the WNT ligand, which is then ready for transportation. It is believed that these ligands are then transported via the EVI/WNTLESS transmembrane complex out of the cell Bänziger et al. [17] & Bartscherer et al. [18]. The EVI/WNTLESS themselves are known to reside in the Golgi bodies and interaction with the WNT ligands for the later's glycosylation Kurayoshi et al. [19] & Gao and Hannoush [20]. Once outside the cell, the WNTs then interact with the cell receptors, as explained in the foregoing paragraph, to induce the Wnt signaling. Of importance is the fact that the EVI/WNTLESS also need a transporter in the form of a complex termed as Retromer.

3. Chronological Literature Review of Time Series Analysis of WNT Signaling Pathway

Cyclic activation of the Wnt/ β -catenin signaling pathway controls cell fusion-mediated somatic cell reprogramming. TCFs in complex with β -catenin, bind and regulate WNT target genes. Aulicino et al. [21] show that WNT/ β -catenin signaling needs to be off during the early reprogramming phases of mouse embryonic fibroblasts (MEFs) into iPSCs. In MEFs undergoing reprogramming, senescence genes are repressed and mesenchymal-to-epithelial transition is favored. This is correlated with a repressive activity of TCF1, which contributes to the silencing of WNT/ β -catenin signaling at the onset of reprogramming. In contrast, the WNT pathway needs to be active in the late reprogramming phases to achieve successful reprogramming. The authors show that time-dependent activation of WNT/ β -catenin pathway controls reprogramming of four-factor-induced MEFs by presenting experimental scheme of time course analysis of FACS-sorted cells and time-dependent expression of MET and senescence markers. They conclude that continued activation or inhibition of the WNT/ β -catenin signaling pathway is detrimental to the reprogramming of MEFs while, temporal perturbation of the pathway is essential for efficient reprogramming, and the "WNT-off" state can be considered an early reprogramming marker.

Experimental and computational studies have revealed characteristics of the WNT pathway, however a cell-specific spatial perspective have been lacking. Tan et al. [22] provide a novel 3D confocal quantitation protocol to acquire spatial (two cellular compartments: nucleus and cytosol-membrane) and temporal quantitative data on target protein (e.g. β -catenin and N-cadherin) concentrations in Human Epithelial Kidney cells (HEK293T) during perturbation (with either cycloheximide or WNT3A). Computational models of the Wnt pathway are constructed and interrogated based on this data. Huang et al. [23] showed by transcriptome analysis of cells along human pluripotent stem cells (PSC) differentiation to early and definitive neuroepithelia via time-course data, that downregulation of genes associated with TGF- β and canonical WNT/ β -CATENIN signaling, confirmed the roles of classical signaling in human neural induction. Their study revealed known and novel expression patterns of genes that are involved in DNA methylation, histone modification, as well as epithelial-mesenchymal transition, which play crucial roles of those genes and signaling pathways during neural differentiation.

To examine signal propagation and its effect on transcription levels in individual cells within a population, Kafri et al. [24] conducted real-time β -catenin dynamics in a cell population in response to WNT signaling. They observed that β -catenin levels increased simultaneously at adherens junctions and the centrosome, and a membrane-centrosome transport system was revealed. Correlating β -catenin nuclear dynamics to CCND1 transcriptional activation showed that the nuclear accumulation rate of change of the signaling factor correlated with the transcriptional output of the pathway.

Madan et al. [25] performed time-course analysis of WNT-dependent signaling pathways in an orthotopic model of WNT-addicted pancreatic cancer, using a PORCN inhibitor and validated key results in additional WNT-addicted models. Their temporal analysis of the drug-perturbed transcriptome demonstrated direct and indirect regulation of more than 3,500 WNT-activated genes. Further, their study identified a central role of WNT/ β -catenin/MYC/ribosome axis, in cancer proliferation.

Using a combination of time-resolved CUT&RUN against β -catenin, ATAC-seq, and perturbation assays in different cell types, Pagella et al. [26] showed that WNT/ β -catenin physical targets are tissue-specific, β -catenin "moves" on different loci over time, and its association to DNA accompanies changing chromatin accessibility landscapes that determine cell behavior.

In all the above experimental results till now, we find that time course analysis is a common way to study and decipher the dynamics of the signaling pathway. However, their studies depicts/uses singular measurements of individual gene expression at different time snapshots/points to infer the system wide analysis of the WNT pathway. At any particular time point, it is often the case that genes are working synergistically in combinations, even though their expression measurements are singular in nature. Sinha [2] recently demonstrated the use of machine learning based search engine to rank/reveal gene combinations at 2nd order for the time series data by Gujral and MacBeath [1] and showed how it is possible to locate combinations of priority that might be working synergistically, using sensitivity methods and powerful support vector ranking algorithm. However, the problem explodes combinatorially with even a small set of 71 recorded genes in the study by Gujral and MacBeath [1], when one steps to explore 3rd order combinations. With the total number of ${}^{71}C_3$ (= 57155) combinations, it becomes nearly impossible for any biologist to study the system wide dynamics of any pathway. Also, the amount of time usually needed to search for and test a combination is far more than the search down by the machine learning based search engine. Here, I extend the research work by Sinha [2] to conduct a time behavioral study of 3rd order WNT-(1,2B,3A,4,5A) related combinations using individual gene expressions measured in time, in WNT3A stimulated HEK 293 cells. Using this method, it is possible to find in time, which combinations at 3rd order are working synergistically. The work can be extended to explore higher order combinations also (i.e ≥ 4), with adequate computational resources.

Finally, from the computational perspective, Ding and Bar-Joseph [27] provide a review of data, methods, and analysis for reconstructing dynamic regulatory network models from high-throughput time-series data sets. They enlist a range of softwares for time-series GRN analysis methods that are basically based on correlation, regression, Granger causality, Probabilistic graph model and Graphical embedding. In comparison with these methods, the current manuscript uses sensitivity analysis based indices (computed via package in R by Pujol et al. [28]) to capture influence of involved factors in the signaling pathway and further use it as feature vectors in advanced support vector ranking algorithm by Joachims [3]. Thus, this is the first machine learning based method that can capture/identify/reveal higher order combinations in time and help biologists study the working of pathway.

4. Methods

Please refer to sections of Sinha [2] for methods, design of study and analysis of data for 2nd order combinations. The same method and design of study is used to generate results for 3rd order combinations presented in this study.

5. Time Series Data

Gujral and MacBeath [1] present a set of 71 WNT-related gene expression values for 6 different times points over a range of 24-hour period using qPCR. The changes represent the fold-change in the expression levels of genes in 200 ng/mL WNT3A-stimulated HEK 293 cells in time relative to their levels in unstimulated, serum-starved cells at 0-hour. Gujral and MacBeath [1] state that qPCR data are the means of three biological replicates. Only genes whose mean transcript levels changed by more than two-fold at one or more time points during the 24-hour time course were considered

significant. Positive (negative) numbers represent up (down) -regulation. We have already covered the issues related to these data sets in detail in Sinha [29]. Readers are requested to go through them in the pointed reference. The tools of study which are used here have been published in another foundational work in Sinha [29].

6. Design of Experiment

6.1. Pipeline for Time Series Data

For the case of time series data, interactions among the contributing factors are studied by comparing triplets of fold-changes at single time points. The procedure begins with the generation of distribution around measurements at single time points with added noise is done to estimate the indices. A distribution is generated for the fold changes at single time points. Then for every gene, there is a vector of values representing fold changes as well as deviations in fold changes for different time points and durations between time points, respectively. Next a listing of all C_k^n combinations for k number of genes from a total of n genes is generated. k is ≥ 2 and $\leq (n - 1)$. Each of the combination of order k represents a unique set of interaction between the involved genetic factors. After this, the datasets are combined in a specified format which go as input as per the requirement of a particular sensitivity analysis method. Thus for each p^{th} combination in C_k^n combinations, the dataset is prepared in the required format from the distributions for two separate cases which have been discussed above. (See .R code in mainScript-1-1.R). After the data has been transformed, vectorized programming is employed for density based sensitivity analysis and looping is employed for variance based sensitivity analysis to compute the required sensitivity indices for each of the p combinations. This procedure is done for different kinds of sensitivity analysis methods.

After the above sensitivity indices have been stored for each of the p^{th} combination, the next step in the design of experiment is conducted. Since there is only one recording of sensitivity index per combination, each combination forms a training example which is allotted a training index and the sensitivity indices of the individual genetic factors form the training example. Thus there are C_k^n training examples for k^{th} order interaction. Using this training set SVM_{learn}^{Rank} Joachims [3] is used to generate a model on default value C value of 20. In the current experiment on toy model C value has not been tuned. The training set helps in the generation of the model as the different gene combinations are numbered in order which are used as rank indices. The model is then used to generate score on the observations in the testing set using the $SVM_{classify}^{Rank}$ Joachims [3]. Note that due to availability of only one example per combination, after the model has been built, the same training data is used as test data to generate the scores. This procedure is executed for each and every sensitivity analysis method. This is followed by sorting of these scores along with the rank indices (i.e the training indices) already assigned to the gene combinations. The end result is a sorted order of the gene combinations based on the ranking score learned by the SVM^{Rank} algorithm. Finally, this entire procedure is computed for sensitivity indices generated for each and every fold change at time point and deviations in fold change at different durations. Observing the changing rank of a particular combination at different times and different time periods will reveal how a combination is behaving.

Note that the following is the order in which the files should be executed in R, in order, for obtaining the desired results (Note that the code will not be explained here) - • use source("mainScript-1-1.R") with arguments for Dynamic data • source("SVMRank-Results-D.R"), to rank the interactions (again this needs to be done separately for different kinds of SA methods), • use source("Combine-Time-files.R"), if computing indices separately via previous file, • source("Sort-n-Plot-D.R") to sort the interactions. Note that the sorting changes the interaction ranking in time. Thus • use source("Interaction-Priority-Intime.R") to find the prioritized ranking of each and every interaction over the different time points and finally • use source("Print-Ranking-AND-Interaction-Rank.R") to print individual ranking of the required input factor with other interaction factors.

7. Results & Discussion

7.1. Time Series Data by Gujral and MacBeath [1]

NOTE - Ranking was assigned on scores that were sorted in DECREASING values. So, 1 was assigned to highest score and vice versa.

Results for the 3rd order interactions are presented here. The results first discuss the behaviour of interactions across the snapshots of time using the computed sensitivities on fold change measurements per time snapshot. The analysis was done using 4 different sensitivity indices. Out of the ${}^{71}C_3$ combinations, I consider/present only those combinations that show a ranking within first 10,000 out of 57,155. This choice is liberal and biologists/oncologists can have a more stricter choice as per need. Two observations are made, • the ranking of a particular combination is conserved (i.e within the 10,000 range) in a particular time point or in the early phase or late phase of WNT3A stimulation, across the majority of the four sensitivity methods, which is a strict criteria of assessment or • the ranking of a particular combination is conserved across time points/phase (i.e they are within the 10,000 range) and the majority of the four sensitivity methods, which is relaxed criteria of assessment. Applying this filter helps reveal important combinations of interest that might be working synergistically at a higher order level in the cell.

Regarding technical points of implementation, the rankings were generated without scaling/normalizing the time series data provided by Gujral and MacBeath [1]. For estimating the sensitivity indices, a small gaussian distribution using the function **rnorm** that generates a vector of normally distributed random variables given a vector length n (here 9, the 10th one is the mean/recorded gene regulation itself), a population mean μ and population standard deviation σ . The syntax for using rnorm is as follows: **rnorm(n, mean, sd)**. Further, I use the **jitter** function to add a little bit of noise to the data. This helps to see if the generated rankings are robust or not.

7.2. Enumeration and Ranking of 2415 WNT-X-X Combinations from Gujral and MacBeath [1]

In the supplementary section, I present four files (for each of the WNT member analysed here) each containing the rankings of 3rd order combinations, that vary in time (shown for 5 time points). Each file represents the rankings computed using a particular sensitivity method. The changing rankings in time for a particular combination represents the importance of contribution/role that combination plays in the cell stimulated with WNT3A. The sensitivity methods used are Hilbert Schmidt Independence Criterion indices (HSIC) indices (with rbf and linear kernel in Da Veiga [30]) and Sobol indices (with 2002 implementation in Saltelli [31] and martinez implementation in Martinez [32] and Baudin et al. [33]).

7.3. Conserved Machine Learning Rankings for Tested WNT1-X-X Combinations

A total of 2415, 3rd order combinations involving WNT1 were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 2, 3 and 4 show the rankings for the same combinations as in Table 1, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

Table 1. Rankings of WNT1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear.

RANKING @ t_i USING HSIC - LINEAR											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
TLE2-WNT1-WNT2B	189	20461	1429	13090	57105	AXIN1-WNT1-WNT2	264	2793	8496	12308	50258
CCND2-WNT1-WNT4	361	1435	7615	22032	3874	TLE1-WNT1-WNT2B	422	24710	2210	9746	55494
TCF7L1-WNT1-WNT2B	434	3116	2757	14471	57112	CCND2-WNT1-WNT5A	649	4100	17754	49943	24216
TCF7L1-WNT1-WNT4	655	2370	4483	13462	55477	TLE1-WNT1-WNT4	667	32528	3738	7043	51569
AXIN1-WNT1-WNT3	678	6632	12015	3849	56880	SENP2-WNT1-WNT2B	701	40779	2190	9179	41846
PPP2CA-WNT1-WNT3A	732	6546	10800	53535	9982	FZD5-WNT1-WNT4	761	4701	2943	19535	17810
TLE2-WNT1-WNT2	781	9494	6256	20013	48997	FZD7-WNT1-WNT3A	796	6819	613	46978	36231
DKK1-WNT1-WNT2B	829	33707	24814	9762	55167	FBXW2-WNT1-WNT4	837	13006	10579	22224	30630
DVL1-WNT1-WNT2B	850	7844	1434	7855	55450	TLE1-WNT1-WNT3A	862	11066	907	29504	42805
CCND2-WNT1-WNT2B	867	3849	5828	18983	29898	SENP2-WNT1-WNT4	879	37625	2401	4412	29111
EP300-WNT1-WNT2	884	39083	11026	13187	5410	AES-AXIN1-WNT1	899	46807	28672	56480	51692
DKK1-WNT1-WNT4	937	35081	20751	8986	41364	EP300-WNT1-WNT2B	940	30973	2609	12191	47783
LRP5-WNT1-WNT2	943	331	10971	35335	28268	TCF7L1-WNT1-WNT5A	951	10419	14748	50321	56416
FZD6-WNT1-WNT2B	953	30498	22050	10632	41588	DAAM1-WNT1-WNT2B	991	40641	19923	4873	55071
SFRP4-WNT1-WNT3A	994	7835	823	32443	11457	APC-WNT1-WNT2	1042	5134	9813	11537	12838
FZD1-WNT1-WNT2	1079	453	10408	22692	12583	CCND3-WNT1-WNT5A	1130	34700	23749	48106	39841
RHOU-WNT1-WNT4	1198	602	1780	21941	43967	DVL1-WNT1-WNT4	1231	29200	3177	8357	51345
CCND2-WNT1-WNT3A	1238	24529	3203	46942	8642	CTNNB1-WNT1-WNT2	1241	22795	15433	20421	44078
KREMEN1-WNT1-WNT4	1280	5994	3234	2746	2189	PPP2R1A-WNT1-WNT4	1345	13482	18287	10132	56367
EP300-WNT1-WNT3A	1360	30527	695	53063	7375	FOSL1-WNT1-WNT2B	1381	1526	2254	11678	47870
TCF7L1-WNT1-WNT2	1413	4503	11516	20522	54978	FZD5-WNT1-WNT3A	1443	14058	943	50372	9921
FZD6-WNT1-WNT2	1464	34470	48080	8772	14072	TCF7L1-WNT1-WNT3A	1465	4078	1392	49037	48926
FZD5-WNT1-WNT2	1480	1516	8586	19681	10389	FBXW11-WNT1-WNT4	1484	28114	9144	7266	48038
FRZB-WNT1-WNT4	1551	27936	3165	17377	26548	SFRP4-WNT1-WNT5A	1578	781	17415	40518	24047
PPP2CA-WNT1-WNT4	1668	20515	14866	23920	21265	TLE1-WNT1-WNT2	1715	34910	11002	13426	45771
FZD6-WNT1-WNT3A	1761	55679	36296	46569	31443	FZD6-WNT1-WNT4	1853	43209	40276	6172	38442
AES-WNT1-WNT4	1876	46650	9370	48199	39204	CCND3-WNT1-WNT2	1903	43002	13802	26732	21315
TLE2-WNT1-WNT5A	1934	1735	16448	40349	48415	FBXW11-WNT1-WNT2	1978	19971	12210	7660	43038
FBXW4-WNT1-WNT2B	2008	53679	7037	14699	52059	APC-WNT1-WNT4	2022	10916	5447	12675	23929
LEF1-WNT1-WNT3	2058	3087	17051	9568	33832	TLE2-WNT1-WNT3	2060	24893	6736	7390	54114
SFRP4-WNT1-WNT4	2127	95	2835	6120	22533	DIXDC1-WNT1-WNT4	2134	8527	1926	11050	9192
LRP6-WNT1-WNT2B	2145	1643	1328	11521	56096	FRAT1-WNT1-WNT2B	2208	3244	1753	8833	56838
SFRP4-WNT1-WNT2B	2220	437	2312	9030	49285	LRP5-WNT1-WNT4	2229	1395	5749	39655	44313
FRZB-WNT1-WNT2	2245	21033	10770	26099	15078	LRP5-WNT1-WNT2B	2277	1532	4376	28353	52356
DKK1-WNT1-WNT2	2456	33533	35669	12680	52256	FOSL1-WNT1-WNT3A	2512	4481	499	34674	10423
CSNK2A1-WNT1-WNT2B	2524	14385	7157	10414	54122	CTBP2-WNT1-WNT2	2595	32176	7281	10255	33394
FOSL1-WNT1-WNT4	2598	5807	2371	11336	21308	SENP2-WNT1-WNT2	2624	41460	8906	8179	29163
FZD8-WNT1-WNT5A	2653	3688	15335	41914	55425	CXXC4-WNT1-WNT3A	2734	34306	282	36977	4488
CTNNBIP1-WNT1-WNT2B	2866	5053	3037	7574	53668	CSNK1D-WNT1-WNT2	2884	830	8568	25186	5895
LEF1-WNT1-WNT4	2885	69	3884	19634	31692	CTNNBIP1-WNT1-WNT5A	2892	2340	17541	31012	32743
PPP2R1A-WNT1-WNT3A	2989	13277	15619	27990	53390	BTRC-WNT1-WNT4	3062	33354	28305	33341	21189
PPP2CA-WNT1-WNT5A	3127	17958	20275	50785	22700	FRZB-WNT1-WNT3A	3221	19926	900	52289	15551
APC-WNT1-WNT5A	3260	5882	29068	48459	44398	SLC9A3R1-WNT1-WNT2	3380	417	3728	9299	15942
GSK3B-WNT1-WNT2	3464	694	3367	12227	13841	CSNK1D-WNT1-WNT4	3618	317	9161	25363	16241
TLE1-WNT1-WNT3	3639	28868	12097	2793	48831	CSNK1G1-WNT1-WNT3A	3690	42269	1886	38618	12595
TCF7-WNT1-WNT2	3709	15553	19513	21919	21644	FBXW2-WNT1-WNT2B	3792	31925	10926	21585	21925
DVL1-WNT1-WNT2	3827	18149	11171	8952	41573	FOSL1-WNT1-WNT5A	3911	934	9883	39216	24538
SENP2-WNT1-WNT3A	3925	51191	778	45722	31784	LRP5-WNT1-WNT5A	4047	7108	21074	49106	36111
DKK1-WNT1-WNT5A	4068	35503	45563	48503	45432	SFRP1-WNT1-WNT2	4069	534	7762	9546	28696
KREMEN1-WNT1-WNT5A	4086	1014	15715	19712	13437	FZD7-WNT1-WNT2B	4094	6079	1907	14533	53101
CTBP2-WNT1-WNT2B	4104	35097	2391	6836	53844	PITX2-WNT1-WNT2B	4158	13925	1462	19718	12422
PPP2CA-WNT1-WNT2B	4221	27679	5501	15908	49412	CSNK1G1-WNT1-WNT2B	4328	28137	2519	15191	52986
MYC-WNT1-WNT2B	4351	18878	15116	23178	50417	SFRP4-WNT1-WNT2	4361	7528	10000	7985	15544
PPP2CA-WNT1-WNT2	4386	21784	14643	23802	9147	KREMEN1-WNT1-WNT2	4398	27636	11699	2952	2731
TCF7-WNT1-WNT2B	4467	22049	13939	15878	47639	CTBP1-WNT1-WNT4	4497	2676	3999	13351	27396
LRP6-WNT1-WNT4	4527	3772	2457	18175	54287	DIXDC1-WNT1-WNT3A	4533	9078	186	50073	4440
TCF7L1-WNT1-WNT3	4558	22802	7559	7929	51558	FBXW4-WNT1-WNT5A	4581	30084	19370	45293	28364
PPP2R1A-WNT1-WNT2B	4605	18188	17233	10188	57155	CTNNBIP1-WNT1-WNT3	4631	1664	11134	3796	40164
FBXW2-WNT1-WNT2	4677	17053	16207	29692	12211	PITX2-WNT1-WNT4	4724	908	3272	33901	10244
CTBP2-WNT1-WNT3A	4805	33304	996	32325	20268	FBXW11-WNT1-WNT3A	4814	28389	1617	38298	25579
FZD2-WNT1-WNT3A	4828	34628	531	9553	13118	CXXC4-WNT1-WNT2B	4887	28110	3210	10517	46705
FZD2-WNT1-WNT2	4900	18529	4514	564	2691	DAAM1-WNT1-WNT4	4925	41074	37527	4457	52415
FZD2-WNT1-WNT5A	4992	34448	12933	13131	24695						

Table 2. Rankings of WNT1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf.

RANKING @ t_i USING HSIC - RBF											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
TLE2-WNT1-WNT2B	6950	27605	29445	9814	44123	AXIN1-WNT1-WNT2	3625	10630	49528	9154	15672
CCND2-WNT1-WNT4	2977	14277	27528	561	23008	TLE1-WNT1-WNT2B	13179	5610	13964	224	26765
TCF7L1-WNT1-WNT2B	2635	2641	24523	210	37831	CCND2-WNT1-WNT5A	2628	30300	41874	37956	39959
TCF7L1-WNT1-WNT4	2999	2222	48449	1665	32919	TLE1-WNT1-WNT4	11603	13045	36391	33	21812
AXIN1-WNT1-WNT3	6823	11867	42464	6687	27989	SENP2-WNT1-WNT2B	2021	43379	30860	2867	24069
PPP2CA-WNT1-WNT3A	4487	6874	35552	24125	19493	FZD5-WNT1-WNT4	953	2772	39511	2938	32504
TLE2-WNT1-WNT2	12349	7281	54421	3112	8048	FZD7-WNT1-WNT3A	2224	19292	34884	35013	23800
DKK1-WNT1-WNT2B	1427	29543	44949	34992	19834	FBXW2-WNT1-WNT4	11293	2661	26185	11977	4635
DVL1-WNT1-WNT2B	15873	18998	26270	88	9209	TLE1-WNT1-WNT3A	21715	17829	32814	37959	6447
CCND2-WNT1-WNT2B	5263	5867	3189	15	13075	SENP2-WNT1-WNT4	595	42309	31627	659	12885
EP300-WNT1-WNT2	1580	44154	51942	5979	10465	AES-AXIN1-WNT1	45487	43736	29729	41515	5980
DKK1-WNT1-WNT4	3280	26528	35802	8296	26214	EP300-WNT1-WNT2B	2458	13992	29930	2629	26795
LRP5-WNT1-WNT2	17816	1790	56019	30798	14094	TCF7L1-WNT1-WNT5A	4746	24167	45178	15067	34701
FZD6-WNT1-WNT2B	1547	39201	26442	188	15436	DAAM1-WNT1-WNT2B	14817	47333	17911	1242	1180
SFRP4-WNT1-WNT3A	11755	16260	28669	23387	22304	APC-WNT1-WNT2	3080	3644	52781	10483	29755
FZD1-WNT1-WNT2	8676	1934	56187	5374	14999	CCND3-WNT1-WNT5A	3522	45126	4446	40031	11792
RHO-WNT1-WNT4	751	1923	30562	18071	6917	DVL1-WNT1-WNT4	6554	24157	44308	144	3395
CCND2-WNT1-WNT3A	4465	36473	38095	30987	12981	CTNNB1-WNT1-WNT2	2210	19770	31475	3387	16403
KREMEN1-WNT1-WNT4	2412	6480	36977	30144	18633	PPP2R1A-WNT1-WNT4	13056	3776	48355	444	25289
EP300-WNT1-WNT3A	1327	24404	26980	31626	25194	FOSL1-WNT1-WNT2B	8040	5830	31727	31	46871
TCF7L1-WNT1-WNT2	1929	4745	55432	7088	14819	FZD5-WNT1-WNT3A	1830	18724	34025	38182	14214
FZD6-WNT1-WNT2	1755	35791	32237	6789	28940	TCF7L1-WNT1-WNT3A	795	7154	34307	17085	15742
FZD5-WNT1-WNT2	339	2770	50596	11417	29085	FBXW11-WNT1-WNT4	981	22983	17188	12039	8862
FRZB-WNT1-WNT4	2247	16822	45170	603	48278	SFRP4-WNT1-WNT5A	20172	24000	21092	15854	30684
PPP2CA-WNT1-WNT4	1316	18383	42717	1659	16550	TLE1-WNT1-WNT2	6951	6172	45856	4408	24525
FZD6-WNT1-WNT3A	5732	56781	23090	25529	3318	FZD6-WNT1-WNT4	2093	43237	30056	300	18080
AES-WNT1-WNT4	41018	46572	36752	8655	32178	CCND3-WNT1-WNT2	3217	39026	46571	5626	7013
TLE2-WNT1-WNT5A	6864	5968	35981	23184	14484	FBXW11-WNT1-WNT2	2049	11831	32546	6429	20043
FBXW4-WNT1-WNT2B	3114	52426	37613	1129	42822	APC-WNT1-WNT4	3183	2118	45782	4710	30780
LEF1-WNT1-WNT3	13604	18250	32514	8446	19104	TLE2-WNT1-WNT3	5408	36584	35384	15826	17265
SFRP4-WNT1-WNT4	19664	2692	41573	2007	32211	DIXDC1-WNT1-WNT4	8940	3055	44478	355	3113
LRP6-WNT1-WNT2B	71	6443	27906	10182	34473	FRAT1-WNT1-WNT2B	2332	26098	25477	468	37575
SFRP4-WNT1-WNT2B	15204	5478	24278	26454	34214	LRP5-WNT1-WNT4	17296	2208	27685	2301	15486
FRZB-WNT1-WNT2	4116	20072	51933	9201	30319	LRP5-WNT1-WNT2B	21763	7302	16792	1764	40328
DKK1-WNT1-WNT2	1058	27648	39587	13410	22947	FOSL1-WNT1-WNT3A	9692	5532	35479	30879	13078
CSNK2A1-WNT1-WNT2B	8045	25594	32444	62	44806	CTBP2-WNT1-WNT2	1374	11613	48726	4109	36580
FOSL1-WNT1-WNT4	4799	4228	46889	440	32783	SENP2-WNT1-WNT2	387	44958	53906	6558	29900
FZD8-WNT1-WNT5A	759	20769	42200	32929	23343	CXXC4-WNT1-WNT3A	1236	41816	5972	30693	33822
CTNNBIP1-WNT1-WNT2B	8584	366	20860	61	55344	CSNK1D-WNT1-WNT2	3841	8374	55936	27925	28491
LEF1-WNT1-WNT4	8880	7636	44357	23	28028	CTNNBIP1-WNT1-WNT5A	2110	11579	40080	21974	43169
PPP2R1A-WNT1-WNT3A	2644	9345	37570	29489	17577	BTRC-WNT1-WNT4	32427	25452	32871	49	5853
PPP2CA-WNT1-WNT5A	1188	16609	32224	18050	32772	FRZB-WNT1-WNT3A	6977	20832	38003	35393	38215
APC-WNT1-WNT5A	4247	4366	51707	29496	46072	SLC9A3R1-WNT1-WNT2	25360	2360	45806	1804	30736
GSK3B-WNT1-WNT2	1109	25764	39938	7835	39257	CSNK1D-WNT1-WNT4	2475	13139	28187	2712	22029
TLE1-WNT1-WNT3	34100	6101	36255	13869	27062	CSNK1G1-WNT1-WNT3A	10871	47854	9882	20452	14786
TCF7-WNT1-WNT2	59	3570	55754	1613	22748	FBXW2-WNT1-WNT2B	10906	14780	7364	3997	20627
DVL1-WNT1-WNT2	19959	10516	55266	1616	10159	FOSL1-WNT1-WNT5A	5033	6402	35717	26574	39026
SENP2-WNT1-WNT3A	1571	55369	22016	26046	17241	LRP5-WNT1-WNT5A	8985	6457	18102	28743	39412
DKK1-WNT1-WNT5A	7312	29238	24298	21731	36669	SFRP1-WNT1-WNT2	4736	8242	49486	3308	3672
KREMEN1-WNT1-WNT5A	4362	35794	22223	40251	36925	FZD7-WNT1-WNT2B	5474	1746	31075	11160	4905
CTBP2-WNT1-WNT2B	746	14025	28794	2488	48177	PITX2-WNT1-WNT2B	26078	12206	23538	5721	30071
PPP2CA-WNT1-WNT2B	5623	15143	40493	2300	24871	CSNK1G1-WNT1-WNT2B	2936	41754	37609	291	13143
MYC-WNT1-WNT2B	24829	42124	31183	4829	42920	SFRP4-WNT1-WNT2	2932	3961	51009	14352	17064
PPP2CA-WNT1-WNT2	3972	8354	38693	9968	20877	KREMEN1-WNT1-WNT2	2297	22262	52447	804	14219
TCF7-WNT1-WNT2B	114	8462	39039	10077	32029	CTBP1-WNT1-WNT4	5927	3621	38350	2	48671
LRP6-WNT1-WNT4	33	6346	51737	1	39634	DIXDC1-WNT1-WNT3A	7299	38164	37547	30689	298
TCF7L1-WNT1-WNT3	11903	2323	44154	19397	37950	FBXW4-WNT1-WNT5A	2762	44748	28649	28672	28184
PPP2R1A-WNT1-WNT2B	5938	9442	48081	2520	9983	CTNNBIP1-WNT1-WNT3	12972	727	43846	17638	45358
FBXW2-WNT1-WNT2	8054	3036	25852	1726	6286	PITX2-WNT1-WNT4	32926	5300	37141	2973	19943
CTBP2-WNT1-WNT3A	524	15330	26192	36050	30967	FBXW11-WNT1-WNT3A	2131	41152	30788	27993	12853
FZD2-WNT1-WNT3A	1663	42579	6220	19634	24095	CXXC4-WNT1-WNT2B	1663	42579	6220	19634	24095
FZD2-WNT1-WNT2	2053	22120	49079	29895	23374	DAAM1-WNT1-WNT4	14322	45285	27500	1279	3124
FZD2-WNT1-WNT5A	4025	22760	45461	15274	35474						

Table 3. Rankings of WNT1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOLO; Implementation - 2002

RANKING @ t_i USING SOBOLO - 2002											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
TLE2-WNT1-WNT2B	40245	22669	37689	29819	30399	AXIN1-WNT1-WNT2	9947	20463	4596	18188	31804
CCND2-WNT1-WNT4	37427	5486	57083	52869	12235	TLE1-WNT1-WNT2B	44201	2292	42877	38512	19669
TCF7L1-WNT1-WNT2B	49295	4478	33582	55669	18987	CCND2-WNT1-WNT5A	26348	908	6977	2060	37746
TCF7L1-WNT1-WNT4	6797	53924	5514	15758	36704	TLE1-WNT1-WNT4	11578	46284	18979	24705	42168
AXIN1-WNT1-WNT3	775	29473	12425	15453	43978	SEN2-WNT1-WNT2B	31781	23905	56648	48582	12552
PPP2CA-WNT1-WNT3A	40524	9682	46210	50633	28358	FZD5-WNT1-WNT4	5854	22531	7374	3906	26585
EP300-WNT1-WNT2	16977	34311	19497	27346	26878	FZD7-WNT1-WNT3A	1438	7881	25103	25538	10719
DKK1-WNT1-WNT2B	38884	6393	34240	30384	22894	FBXW2-WNT1-WNT4	19904	7193	17462	26313	34455
DVL1-WNT1-WNT2B	30250	50468	45283	44194	6705	TLE1-WNT1-WNT3A	45532	17196	56383	56904	289
CCND2-WNT1-WNT2B	26615	12983	5711	75	50116	SEN2-WNT1-WNT4	27482	37862	8657	159	32055
EP300-WNT1-WNT2	32997	22960	44300	32979	4761	AES-AXIN1-WNT1	12788	16361	2080	24988	30557
DKK1-WNT1-WNT4	14034	47678	15738	28358	36674	EP300-WNT1-WNT2B	24766	7961	7149	6651	57039
LRP5-WNT1-WNT2	7820	38949	1770	11738	54071	TCF7L1-WNT1-WNT5A	50375	3147	51646	41475	20572
FZD6-WNT1-WNT2B	50360	38778	41647	35013	7193	DAAM1-WNT1-WNT2B	45462	20187	47757	48914	24934
SFRP4-WNT1-WNT3A	19672	39835	4609	14591	47471	APC-WNT1-WNT2	17679	28070	2976	20907	24550
FZD1-WNT1-WNT2	14024	13294	26501	7956	28675	CCND3-WNT1-WNT5A	33845	7291	36752	42568	20426
RHO-WNT1-WNT4	11749	31988	13883	25949	25686	DVL1-WNT1-WNT4	26875	9515	14492	15387	33351
CCND2-WNT1-WNT3A	19781	51583	73	4270	44933	CTNNB1-WNT1-WNT2	36313	35232	52339	56072	21027
KREMEN1-WNT1-WNT4	15955	22656	18139	572	9093	PPP2R1A-WNT1-WNT4	11965	38223	20939	13880	37473
EP300-WNT1-WNT3A	23045	8793	21877	20602	35795	FOSL1-WNT1-WNT2B	27112	14023	16313	6628	52241
TCF7L1-WNT1-WNT2	7914	52611	23563	1481	38154	FZD5-WNT1-WNT3A	46539	42443	44834	49091	38028
FZD6-WNT1-WNT2	6832	18506	15462	22144	49920	TCF7L1-WNT1-WNT3A	47046	10502	49803	53053	33064
FZD5-WNT1-WNT2	8391	31473	15942	8247	24307	FBXW11-WNT1-WNT4	26765	21608	22134	8381	42819
FRZB-WNT1-WNT4	3817	9962	13664	27247	1304	SFRP4-WNT1-WNT5A	4974	43429	15860	5146	51227
PPP2CA-WNT1-WNT4	8831	44953	16654	15477	52783	TLE1-WNT1-WNT2	12955	54812	14266	18693	37682
FZD6-WNT1-WNT3A	56029	34810	37658	39310	933	FZD6-WNT1-WNT4	2254	41747	26122	12348	47338
AES-WNT1-WNT4	27010	28528	10812	21640	40683	CCND3-WNT1-WNT2	8988	27601	27621	25275	38514
TLE2-WNT1-WNT5A	39711	21605	38989	30871	11764	FBXW11-WNT1-WNT2	28514	9198	5994	6978	43111
FBXW4-WNT1-WNT2B	45929	18615	31454	47272	11773	APC-WNT1-WNT4	21833	42532	14975	17983	28168
LEF1-WNT1-WNT3	1983	26982	13156	18572	55617	TLE2-WNT1-WNT3	26494	36975	21221	27983	41759
SFRP4-WNT1-WNT4	37496	17229	52547	42549	9682	DIXDC1-WNT1-WNT4	45923	10872	37922	33117	17030
LRP6-WNT1-WNT2B	6839	6150	2906	5063	52210	FRAT1-WNT1-WNT2B	43636	48026	38928	45488	13195
SFRP4-WNT1-WNT2B	20769	54746	996	813	46517	LRP5-WNT1-WNT4	6306	53328	564	3576	53083
FRZB-WNT1-WNT2	16061	173	18203	24366	4072	LRP5-WNT1-WNT2B	49250	18461	55390	45409	3073
DKK1-WNT1-WNT2	18271	50790	22929	26807	34193	FOSL1-WNT1-WNT3A	15630	39992	11099	5546	48850
CSNK2A1-WNT1-WNT2B	56439	49339	39830	36489	2125	CTBP2-WNT1-WNT2	17630	14017	879	4848	35480
FOSL1-WNT1-WNT4	41560	17077	46101	51615	8307	SEN2-WNT1-WNT2	25385	33016	503	8604	44591
FZD8-WNT1-WNT5A	55340	46156	39368	53203	20930	CXXC4-WNT1-WNT3A	46602	51045	38468	51607	4562
CTNNBIP1-WNT1-WNT2B	43186	52591	44068	50529	21618	CSNK1D-WNT1-WNT2	14398	26421	6595	6539	29319
LEF1-WNT1-WNT4	3003	50013	24760	22408	35262	CTNNBIP1-WNT1-WNT5A	39178	36630	45107	49287	14044
PPP2R1A-WNT1-WNT3A	44486	25983	55160	38768	876	BTRC-WNT1-WNT4	16066	29448	23493	10082	11232
PPP2CA-WNT1-WNT5A	48329	11938	40478	41705	4471	FRZB-WNT1-WNT3A	47750	57036	42232	37002	55623
APC-WNT1-WNT5A	35340	14411	42165	39241	29207	SLC9A3R1-WNT1-WNT2	11090	26701	17372	19651	11492
GSK3B-WNT1-WNT2	4457	44994	25363	8200	49595	CSNK1D-WNT1-WNT4	20721	8116	11826	6782	37040
TLE1-WNT1-WNT3	11647	39545	771	253	56864	CSNK1G1-WNT1-WNT3A	10811	5687	16886	21507	41231
TCF7-WNT1-WNT2	52015	18441	38813	32337	1462	FBXW2-WNT1-WNT2B	30496	50806	50644	31640	2585
DVL1-WNT1-WNT2	26912	6633	11823	12924	50430	FOSL1-WNT1-WNT5A	25484	1744	15300	2521	38727
SEN2-WNT1-WNT3A	34690	19702	55187	53391	16705	LRP5-WNT1-WNT5A	50803	3849	56592	53600	4056
DKK1-WNT1-WNT5A	43200	9393	41473	28806	20289	SFRP1-WNT1-WNT2	22196	42792	11617	19785	51156
KREMEN1-WNT1-WNT5A	41161	34326	39043	56585	47900	FZD7-WNT1-WNT2B	2809	52839	24572	26365	4005
CTBP2-WNT1-WNT2B	39457	42673	56271	52313	21687	PITX2-WNT1-WNT2B	3768	50433	24960	15608	43963
PPP2CA-WNT1-WNT2B	39456	965	50325	49872	8953	CSNK1G1-WNT1-WNT2B	9195	40906	21870	17708	33874
MYC-WNT1-WNT2B	54903	56291	55821	42199	15243	SFRP4-WNT1-WNT2	40867	6824	35108	52014	6453
PPP2CA-WNT1-WNT2	17723	56145	6791	7281	48201	KREMEN1-WNT1-WNT2	20577	22196	17273	2803	8495
TCF7-WNT1-WNT2B	11990	36568	1883	2452	55808	CTBP1-WNT1-WNT4	20319	30648	24073	7159	34053
LRP6-WNT1-WNT4	56750	10543	51225	53310	4764	DIXDC1-WNT1-WNT3A	11296	46224	19237	24043	40093
TCF7L1-WNT1-WNT3	10163	46455	7343	4097	24458	FBXW4-WNT1-WNT5A	36308	26390	55507	53187	11273
PPP2R1A-WNT1-WNT2B	37389	8862	42260	31184	21206	CTNNBIP1-WNT1-WNT3	16525	51076	8623	21683	38604
FBXW2-WNT1-WNT2	26645	6386	6550	25556	54582	PITX2-WNT1-WNT4	55244	8137	33549	51863	7332
CTBP2-WNT1-WNT3A	43003	23189	55733	35545	22292	FBXW11-WNT1-WNT3A	32476	49645	50046	55378	6370
FZD2-WNT1-WNT3A	37067	13859	41274	51071	5543	CXXC4-WNT1-WNT2B	38395	36005	42214	55216	4304
FZD2-WNT1-WNT2	4568	9992	18719	16065	20554	DAAM1-WNT1-WNT4	3024	53884	20593	12024	56331
FZD2-WNT1-WNT5A	55233	54207	42446	47868	26353						

Table 4. Rankings of WNT1-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez.

RANKING @ t_i USING SOBOL - MARTINEZ											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
TLE2-WNT1-WNT2B	40200	2166	49574	41995	42003	AXIN1-WNT1-WNT2	53838	57022	56362	46291	4340
CCND2-WNT1-WNT4	56311	32819	51920	32545	37821	TLE1-WNT1-WNT2B	34900	4162	23677	15497	48629
TCF7L1-WNT1-WNT2B	32996	5243	28606	285	39952	CCND2-WNT1-WNT5A	8935	56664	50350	50391	11278
TCF7L1-WNT1-WNT4	32094	40529	21150	6996	1659	TLE1-WNT1-WNT4	36555	15670	21408	7024	45023
AXIN1-WNT1-WNT3	7505	57062	32941	50771	644	SENP2-WNT1-WNT2B	16555	17079	41227	9388	56362
PPP2CA-WNT1-WNT3A	51242	1279	28051	1456	15170	FZD5-WNT1-WNT4	47089	43274	11221	47423	52439
TLE2-WNT1-WNT2	25404	4009	47531	14738	26017	FZD7-WNT1-WNT3A	4926	33896	22789	22507	2977
DKK1-WNT1-WNT2B	5148	39741	99	25462	25379	FBXW2-WNT1-WNT4	12354	12266	47167	24853	6316
DVL1-WNT1-WNT2B	44615	10931	27851	20224	47773	TLE1-WNT1-WNT3A	44592	1282	36683	33143	36702
CCND2-WNT1-WNT2B	8206	22475	56331	33393	19889	SENP2-WNT1-WNT4	23302	15994	3637	19774	7442
EP300-WNT1-WNT2	46394	8408	1307	35073	31460	AES-AXIN1-WNT1	36110	10668	16091	33674	7482
DKK1-WNT1-WNT4	4150	8692	11857	26791	3627	EP300-WNT1-WNT2B	40403	45788	6306	37531	53145
LRP5-WNT1-WNT2	32344	41286	36505	1152	37327	TCF7L1-WNT1-WNT5A	44025	2425	32527	20064	38205
FZD6-WNT1-WNT2B	14865	55096	2854	19971	18190	DAAM1-WNT1-WNT2B	8310	11548	37506	38188	47486
SFRP4-WNT1-WNT3A	48735	26194	4852	2971	25528	APC-WNT1-WNT2	22326	12717	12419	12095	40106
FZD1-WNT1-WNT2	7933	13069	16390	43074	7316	CCND3-WNT1-WNT5A	43181	44716	14441	14980	34724
RHO-WNT1-WNT4	14697	29770	55730	10370	1690	DVL1-WNT1-WNT4	17136	51482	9987	16743	1726
CCND2-WNT1-WNT3A	38052	26165	56279	42744	11694	CTNNB1-WNT1-WNT2	18248	6792	38698	40389	35231
KREMEN1-WNT1-WNT4	2199	38104	48857	13973	4782	PPP2R1A-WNT1-WNT4	37092	5843	25053	14666	48915
EP300-WNT1-WNT3A	35049	51879	24918	13081	9432	FOSL1-WNT1-WNT2B	16777	24758	43097	23275	38302
TCF7L1-WNT1-WNT2	28709	5864	12967	8885	2243	FZD5-WNT1-WNT3A	39449	21065	43152	2693	25098
FZD6-WNT1-WNT2	39576	54013	17728	25266	47807	TCF7L1-WNT1-WNT3A	43995	1480	24915	310	42232
FZD5-WNT1-WNT2	45166	48687	41677	42473	48306	FBXW11-WNT1-WNT4	11180	25231	49052	48653	18382
FRZB-WNT1-WNT4	6698	54817	3429	48430	7937	SFRP4-WNT1-WNT5A	42835	17358	40048	7805	5629
PPP2CA-WNT1-WNT4	45922	51703	31831	5639	9	TLE1-WNT1-WNT2	412	17784	26338	8506	17450
FZD6-WNT1-WNT3A	36284	56172	25948	12051	29929	FZD6-WNT1-WNT4	7233	45016	15516	10015	3188
AES-WNT1-WNT4	35587	7864	26131	9828	43837	CCND3-WNT1-WNT2	4917	50332	55675	50211	46082
TLE2-WNT1-WNT5A	46888	6306	53838	23255	34200	FBXW11-WNT1-WNT2	13419	18508	51943	51794	39942
FBXW4-WNT1-WNT2B	49985	4684	49002	50868	27871	APC-WNT1-WNT4	917	11941	13711	9897	48253
LEF1-WNT1-WNT3	4840	57034	32528	55084	27000	TLE2-WNT1-WNT3	1025	1802	22526	21128	13268
SFRP4-WNT1-WNT4	27168	3150	38903	887	56174	DIXDC1-WNT1-WNT4	31540	9049	855	15412	43794
LRP6-WNT1-WNT2B	36446	24137	5630	33510	45100	FRAT1-WNT1-WNT2B	56016	2730	27669	6169	12853
SFRP4-WNT1-WNT2B	44940	29647	17880	4049	29427	LRP5-WNT1-WNT4	38582	11835	11954	12770	51873
FRZB-WNT1-WNT2	38733	38681	32656	44565	5467	LRP5-WNT1-WNT2B	12988	51717	21924	6174	15567
DKK1-WNT1-WNT2	107	11450	10770	15064	26033	FOSL1-WNT1-WNT3A	14387	17574	45609	36527	7338
CSNK2A1-WNT1-WNT2B	34224	30137	54159	43767	28506	CTBP2-WNT1-WNT2	51459	37665	13118	8187	36350
FOSL1-WNT1-WNT4	40112	4912	51361	40583	39621	SENP2-WNT1-WNT2	47103	32558	23935	22535	28811
FZD8-WNT1-WNT5A	55382	28883	536	42970	27045	CXNC4-WNT1-WNT3A	47935	18433	28000	8963	43231
CTNNBIP1-WNT1-WNT2B	55819	37814	4438	14049	29002	CSNK1D-WNT1-WNT2	40567	28297	16569	6336	51007
LEF1-WNT1-WNT4	2712	26579	51004	53571	711	CTNNBIP1-WNT1-WNT5A	52693	11674	3169	39076	16576
PPP2R1A-WNT1-WNT3A	43905	2516	24424	44521	46746	BTRC-WNT1-WNT4	2996	53539	2844	6885	23127
PPP2CA-WNT1-WNT5A	51641	38045	26358	31132	12482	FRZB-WNT1-WNT3A	51243	19304	7397	21580	29759
APC-WNT1-WNT5A	37251	37308	4578	24642	44801	SLC9A3R1-WNT1-WNT2	29161	29549	9110	17826	3831
GSK3B-WNT1-WNT2	2781	17321	33083	48977	18591	CSNK1D-WNT1-WNT4	4934	23696	3275	40685	48358
TLE1-WNT1-WNT3	14154	5331	17730	14825	14645	CSNK1G1-WNT1-WNT3A	7756	30860	56406	56754	31743
TCF7-WNT1-WNT2	55473	2461	31570	1088	53002	FBXW2-WNT1-WNT2B	6646	1897	43670	43128	52166
DVL1-WNT1-WNT2	35455	45846	26959	6048	6160	FOSL1-WNT1-WNT5A	2153	54808	25487	36688	13369
SENP2-WNT1-WNT3A	47421	6035	39529	13763	43324	LRP5-WNT1-WNT5A	30334	45784	31282	41567	9655
DKK1-WNT1-WNT5A	7853	29582	28794	6214	37984	SFRP1-WNT1-WNT2	24346	7628	46715	57118	37314
KREMEN1-WNT1-WNT5A	8580	19453	28068	44618	42482	FZD7-WNT1-WNT2B	22213	23438	16829	41309	44350
CTBP2-WNT1-WNT2B	17223	1366	34440	26601	37966	PITX2-WNT1-WNT2B	916	11204	30439	49466	42032
PPP2CA-WNT1-WNT2B	40253	4960	32537	41490	12692	CSNK1G1-WNT1-WNT2B	3556	10982	24518	57054	10395
MYC-WNT1-WNT2B	42663	49024	41944	1485	43699	SFRP4-WNT1-WNT2	29579	19698	40338	7631	35163
PPP2CA-WNT1-WNT2	47070	37815	41146	13827	21611	KREMEN1-WNT1-WNT2	3834	55331	45210	17031	40259
TCF7-WNT1-WNT2B	25835	19139	22259	20797	17167	CTBP1-WNT1-WNT4	53157	17740	47607	11893	40854
LRP6-WNT1-WNT4	18977	49192	44744	7577	47653	DIXDC1-WNT1-WNT3A	18412	6892	9455	15061	47654
TCF7L1-WNT1-WNT3	10016	23494	24929	5198	28776	FBXW4-WNT1-WNT5A	39385	854	53445	15372	35604
PPP2R1A-WNT1-WNT2B	18951	635	29488	22306	31222	CTNNBIP1-WNT1-WNT3	3687	14762	12557	7374	45093
FBXW2-WNT1-WNT2	25666	43297	11784	30266	36231	PITX2-WNT1-WNT4	29539	42190	49683	54991	25868
CTBP2-WNT1-WNT3A	18464	638	30331	29559	43296	FBXW11-WNT1-WNT3A	44360	16974	28732	49857	31375
FZD2-WNT1-WNT3A	8076	50370	581	1528	45315	CXNC4-WNT1-WNT2B	29371	16863	32810	8310	28741
FZD2-WNT1-WNT2	45458	3594	5070	4394	2696	DAAM1-WNT1-WNT4	40383	17074	10778	17613	39321
FZD2-WNT1-WNT5A	48674	41210	577	33184	38986						

7.3.1. Examining the Behaviour of FZD-WNT1-X Combinations

In their review, Corda and Sala [34] observe that frizzled class receptor 6 (FZD6) binds to WNT1, along with other members of WNT family. Looking at the tables above, one finds the following combinations for members of FZD family along with WNT1, to be prominent at 3rd order level - FZD6-WNT1-WNT2B, FZD1-WNT1-WNT2, FZD6-WNT1-WNT2, FZD5-WNT1-WNT2, FZD6-WNT1-WNT3A, FZD8-WNT1-WNT5A, FZD2-WNT1-WNT3A, FZD2-WNT1-WNT2, FZD2-WNT1-WNT5A, FZD5-WNT1-WNT4, FZD7-WNT1-WNT3A, FZD5-WNT1-WNT3A, FZD6-WNT1-WNT4, and FZD7-WNT1-WNT2B. All these combinations

indicate the existence of a synergy when they take a higher rank in the list of combinations. Interestingly, it can also be observed that the WNT1 forms combinations with other WNT members. This phenomena is not seen for combinations of other WNT members as will be discussed later.

7.3.2. Examining the Behaviour of LRP-WNT1-X Combinations

Belenkov et al. [35] showed that data analysis of the group with obstructive coronary artery disease indicated a moderate correlation between WNT1 and low density lipoprotein receptor-related protein 6 (LRP6). Looking at the tables above, one finds the following combinations for members of LRP family along with WNT1, to be prominent at 3rd order level - LRP5-WNT1-WNT2, LRP6-WNT1-WNT2B, LRP6-WNT1-WNT4, LRP5-WNT1-WNT4, LRP5-WNT1-WNT2B, and LRP5-WNT1-WNT5A. All these combinations indicate the existence of a synergy when they take a higher rank in the list of combinations.

7.3.3. Examining the Behaviour of RHOU-WNT1-X Combinations

ras homolog family member U (RHOU) was first identified as a WNT-1-inducible mRNA and subsequently shown to act on the actin cytoskeleton by stimulating filopodia formation and stress fibre dissolution. Schiavone et al. [36] in their study, show that WNT-1-mediated RHOU induction occurs at the transcriptional level. The tables show one combination of RHOU-WNT1-WNT4 to be prominent among the combinations, working in time.

7.3.4. Examining the Behaviour of CTBP-WNT1-X Combinations

Valenta et al. [37] showed that the C-terminal binding protein 1 (CTBP1) associates with the TCF-4 C-terminus and that CtBP1 overexpression in WNT-1-stimulated 293 cells represses transcription from the WNT-responsive reporter and also decreases the activity of the endogenous AXIN2 promoter. Also, Gujral and MacBeath [1] highlighted CTBP1 as a transcription factor that contributes to positive feedback during the early phases of WNT signaling and serves as a novel marker for colorectal cancer progression. Looking at the tables above, one finds the following combinations for members of CTBP family along with WNT1, to be prominent at 3rd order level - CTBP2-WNT1-WNT2B, CTBP2-WNT1-WNT3A, CTBP2-WNT1-WNT2, and CTBP1-WNT1-WNT4. All these combinations indicate the existence of a synergy when they take a higher rank in the list of combinations.

7.3.5. Examining the Behaviour of TLE-WNT1-X Combinations

Gessler et al. [38] indicate that in the WNT OFF state TCF/LEF transcriptional activity is blocked by their association to Groucho (GRO)/Transducin-Like Enhancer of split (TLE) transcriptional repressors. In the WNT ON state nuclear CTNNB1 displaces TLE and facilitates formation of multimeric complexes with transcriptional coactivators which leads to widespread chromatin opening and accessibility. Looking at the tables above, one finds the following combinations for members of TLE family along with WNT1, to be prominent at 3rd order level - TLE2-WNT1-WNT2B, TLE2-WNT1-WNT2, TLE2-WNT1-WNT5A, TLE1-WNT1-WNT3, TLE1-WNT1-WNT2B, TLE1-WNT1-WNT4, TLE1-WNT1-WNT3A, TLE1-WNT1-WNT2, and TLE2-WNT1-WNT3. All these combinations indicate the existence of a synergy when they take a higher rank in the list of combinations.

7.3.6. Examining the Behaviour of TCF7L1-WNT1-X Combinations

Data by Shy et al. [39] indicate that in human mammary tumors, stimulation of WNT/ β -catenin is strongly correlated with decreased nuclear transcription factor 7 like 1 (TCF7L1). Looking at the tables above, one finds the following combinations for TCF7L1 along with WNT1, to be prominent at 3rd order level - TCF7L1-WNT1-WNT2B, TCF7L1-WNT1-WNT4, TCF7L1-WNT1-WNT2, TCF7L1-WNT1-WNT3, TCF7L1-WNT1-WNT5A, and TCF7L1-WNT1-WNT3A. All these combinations indicate the existence of a synergy when they take a higher rank in the list of combinations.

7.4. Conserved Machine Learning Rankings for Tested WNT2B-X-X Combinations

A total of 2415, 3rd order combinations involving WNT2B were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 6, 7 and 8 show the rankings for the same combinations as in Table 5, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

Table 5. Rankings of WNT2B-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear.

RANKING @ t_i USING HSIC - LINEAR												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CTNNB1P1-WIF1-WNT2B	5	716	18217	51222	29536	AES-AXIN1-WNT2B	21	42226	26426	31368	54700	
LRP6-TCF7-WNT2B	43	10692	4853	48176	26671	DKK1-JUN-WNT2B	56	5221	53944	55625	44612	
CXXC4-PORCN-WNT2B	60	17097	46765	26682	32940	TLE1-WIF1-WNT2B	65	13326	20278	36821	11947	
CSNK1D-FGF4-WNT2B	82	23581	20638	52449	10903	CCND1-WIF1-WNT2B	86	32096	35653	38353	29538	
APC-DIXDC1-WNT2B	89	27000	33475	27891	27710	FZD7-NKD1-WNT2B	140	22580	30435	30959	23507	
TLE2-WIF1-WNT2B	162	206	11704	50552	55877	FOXN1-KREMEN1-WNT2B	170	28253	38493	15670	30910	
CSNK2A1-T-WNT2B	184	3390	21468	32926	48474	TLE2-WNT1-WNT2B	189	20461	1429	13090	57105	
FRAT1-FZD1-WNT2B	227	40140	33748	53349	33191	CCND1-FGF4-WNT2B	236	52522	47611	46447	13813	
DVL1-EP300-WNT2B	247	6893	42213	52392	47037	CSNK1D-SFRP1-WNT2B	268	48716	36593	46538	17001	
PPP2CA-SFRP4-WNT2B	341	52722	25356	52978	1988	DVL2-JUN-WNT2B	350	44599	38931	37935	16078	
FGF4-SFRP1-WNT2B	370	37435	43048	42260	31787	FZD6-PORCN-WNT2B	379	19259	55786	24330	16739	
DKK1-DVL2-WNT2B	389	6767	19714	49653	54386	AXIN1-FZD2-WNT2B	416	21758	21068	33734	11136	
TLE1-WNT1-WNT2B	422	24710	2210	9746	55494	TCF7L1-WNT1-WNT2B	434	3116	2757	14471	57112	
LRP5-SFRP1-WNT2B	435	20296	30967	34267	33184	FZD5-NKD1-WNT2B	450	18227	31166	30382	5811	
CXXC4-FZD7-WNT2B	472	12278	44001	31202	33433	AES-DVL1-WNT2B	520	45445	49972	36707	54854	
CSNK1D-PORCN-WNT2B	573	51683	44617	47981	16208	FBXW11-GSK3B-WNT2B	592	49622	2389	29900	47620	
PITX2-PORCN-WNT2B	630	42884	44910	50269	15186	DKK1-GSK3A-WNT2B	637	11948	24932	51752	48181	
CSNK2A1-MYC-WNT2B	662	17569	55958	14302	27991	FOSL1-PORCN-WNT2B	670	19667	46545	40946	19709	
FSHB-NKD1-WNT2B	699	45757	26960	8191	17214	SENP2-WNT1-WNT2B	701	40779	2190	9179	41846	
PYGO1-WNT2-WNT2B	707	39634	53492	38813	24079	FOSL1-WIF1-WNT2B	727	2770	23114	37617	17980	
LEF1-T-WNT2B	739	5852	6639	47821	35271	FZD8-WNT1-WNT2B	745	1694	1668	7586	57148	
FBXW11-TCF7-WNT2B	768	56201	14780	53735	24876	DAAM1-FGF4-WNT2B	773	44990	54366	44263	16007	
FBXW11-JUN-WNT2B	795	49304	52661	53929	54016	DKK1-FGF4-WNT2B	797	14004	54579	50721	31962	
FOSL1-SFRP1-WNT2B	802	20624	39428	24273	52148	SENP2-SFRP1-WNT2B	804	39477	39510	38291	12235	
FBXW11-GSK3A-WNT2B	812	55736	14360	54703	35145	FZD8-JUN-WNT2B	814	45692	37162	26955	54126	
DKK1-WNT1-WNT2B	829	33707	24814	9762	55167	DVL1-WNT1-WNT2B	850	7844	1434	7855	55450	
FRZB-NKD1-WNT2B	861	8764	29474	26264	14733	DKK1-FOXN1-WNT2B	864	31296	16351	4633	30734	
CCND2-WNT1-WNT2B	867	3849	5828	18983	29898	FZD1-T-WNT2B	868	18866	10080	50380	16044	
FBXW11-RHOU-WNT2B	887	56605	51928	47819	44859	DAAM1-T-WNT2B	901	38916	30634	18661	34795	
DKK1-NKD1-WNT2B	912	10412	49963	52787	8425	EP300-WNT1-WNT2B	940	30973	2609	12191	47783	
CTBP2-CTNNB1-WNT2B	947	49967	49546	42990	40963	FZD6-WNT1-WNT2B	953	30498	22050	10632	41588	
FBXW11-WIF1-WNT2B	980	2151	19852	53626	35239	FBXW11-FOXN1-WNT2B	989	38275	4532	5886	43707	
DAAM1-WNT1-WNT2B	991	40641	19923	4873	55071	NLK-PORCN-WNT2B	1006	26349	37659	35498	4512	
TCF7L1-WIF1-WNT2B	1008	31286	33213	39169	51635	CTBP2-T-WNT2B	1012	44271	1973	37802	4806	
FBXW11-NKD1-WNT2B	1027	51970	24642	25865	43366	CSNK2A1-FOXN1-WNT2B	1037	3175	7624	2538	6838	
DKK1-PYGO1-WNT2B	1041	14062	34049	32775	7169	FBXW11-PORCN-WNT2B	1048	54134	36167	45459	15114	
CCND3-NKD1-WNT2B	1067	19542	49729	33902	7166	FBXW11-FZD2-WNT2B	1086	51272	31485	45352	31130	
CSNK1G1-FZD2-WNT2B	1144	10281	11030	49965	37172	DAAM1-JUN-WNT2B	1152	51606	37010	32012	42370	
DAAM1-DVL2-WNT2B	1174	32045	51094	41937	43272	FZD1-PORCN-WNT2B	1214	23191	49164	44140	14132	
DKK1-MYC-WNT2B	1215	17325	49314	54587	40306	DKK1-PORCN-WNT2B	1222	26601	56978	25305	51044	
FZD8-T-WNT2B	1251	32856	3216	26449	52860	DAAM1-LRP6-WNT2B	1282	52882	52168	19705	36790	
FRZB-FZD2-WNT2B	1309	8669	14015	44385	26991	CSNK1D-FOXN1-WNT2B	1328	17615	2986	7052	5219	
FZD1-WIF1-WNT2B	1329	23	38111	30027	18511	LRP5-PORCN-WNT2B	1349	12551	28905	56410	16845	
FBXW11-SLC9A3R1-WNT2B	1355	52940	23862	29838	38478	CXXC4-DVL2-WNT2B	1361	15018	7269	31481	39016	
FBXW11-FGF4-WNT2B	1372	54955	42859	53156	22936	FOSL1-WNT1-WNT2B	1381	1526	2254	11678	47870	
BCL9-PORCN-WNT2B	1394	28608	33398	47599	21197	KREMEN1-NKD1-WNT2B	1400	34496	34759	43275	20181	
KREMEN1-PORCN-WNT2B	1401	36444	47192	17886	28451	FOSL1-NLK-WNT2B	1425	3331	440	49507	31594	
CTBP1-FGF4-WNT2B	1487	28989	34409	34222	14602	DAAM1-FOXN1-WNT2B	1503	50616	30398	2836	38247	
FZD6-PITX2-WNT2B	1504	10725	14634	54318	17213	FBXW2-NKD1-WNT2B	1547	22973	29232	13160	53054	
KREMEN1-PPP2CA-WNT2B	1585	14425	197	53141	37098	FZD1-JUN-WNT2B	1648	10746	47422	41725	9336	
CSNK2A1-FSHB-WNT2B	1655	8809	48217	20614	27385	LRP5-NKD1-WNT2B	1686	21363	28403	16564	24813	
LRP5-NKD1-WNT2B	1686	21363	28403	16564	24813	FZD8-GSK3A-WNT2B	1696	42493	8212	43675	53692	
LRP5-NLK-WNT2B	1725	4903	8642	34617	54453	CSNK1D-WNT1-WNT2B	1760	3377	3805	17345	50447	
FRZB-GSK3A-WNT2B	1779	9801	7248	51968	31318	FZD6-GSK3A-WNT2B	1794	11589	22435	52656	45662	
FRAT1-PORCN-WNT2B	1796	26246	45830	36444	11708	DAAM1-FZD2-WNT2B	1809	48671	51601	34844	29258	
CCND2-LRP6-WNT2B	1827	10665	28916	33276	6590	FRZB-T-WNT2B	1833	7114	4823	46312	4584	
FZD1-NLK-WNT2B	1840	1616	1306	53698	22012	FZD7-PPP2CA-WNT2B	1854	16103	178	39687	33132	
CCND3-WNT1-WNT2B	1871	43142	11213	19290	51620	FBXW11-PYGO1-WNT2B	1888	54480	51998	19913	52577	
FZD7-PORCN-WNT2B	1892	48697	42677	33490	16364	BTRC-GSK3A-WNT2B	1933	56634	52638	55432	37508	
JUN-PYGO1-WNT2B	1971	11759	22992	23296	32538	FBXW4-WNT1-WNT2B	2008	53679	7037	14699	52059	
FBXW11-T-WNT2B	2020	55625	21630	50429	53482	DVL1-FOXN1-WNT2B	2025	34956	3080	2911	43071	
KREMEN1-WNT1-WNT2B	2036	35623	4394	5538	18503	FZD8-NKD1-WNT2B	2038	34027	33288	19731	46263	
EP300-GSK3B-WNT2B	2076	31297	1204	24013	16338	FZD5-DVL2-WNT2B	2087	17738	10392	23649	35917	

Table 6. Rankings of WNT2B-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf.

RANKING @ t_i USING HSIC - RBF											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CTNNBIP1-WIF1-WNT2B	38092	3733	8392	37231	50461	AES-AXIN1-WNT2B	40966	43839	31440	26846	9969
LRP6-TCF7-WNT2B	8702	5235	40220	35007	4082	DKK1-JUN-WNT2B	23590	25652	38169	27335	22936
CXXC4-PORCN-WNT2B	11272	21120	2288	41634	56160	TLE1-WIF1-WNT2B	39953	13690	3178	37473	11178
CSNK1D-FGF4-WNT2B	2842	20288	7801	35728	43120	CCND1-WIF1-WNT2B	36761	20542	11221	38644	7317
APC-DIXDC1-WNT2B	33671	16882	4145	48106	51792	FZD7-NKD1-WNT2B	47917	26281	13366	54412	1630
TLE2-WIF1-WNT2B	39741	6829	13257	43555	31091	FOXN1-KREMEN1-WNT2B	20404	27973	36396	884	30778
CSNK2A1-T-WNT2B	38723	10644	19106	40549	37163	TLE2-WNT1-WNT2B	6950	27605	29445	9814	44123
FRAT1-FZD1-WNT2B	32803	42239	28688	52215	27867	CCND1-FGF4-WNT2B	21085	49383	9451	42420	11828
DVL1-EP300-WNT2B	53233	2104	15799	56735	2280	CSNK1D-SFRP1-WNT2B	7873	54928	11692	34070	52974
PPP2CA-SFRP4-WNT2B	55580	46429	27467	46270	1672	DVL2-JUN-WNT2B	35904	41234	30718	47010	18770
FGF4-SFRP1-WNT2B	39785	39441	5909	50353	52814	FZD6-PORCN-WNT2B	47	9685	16997	36922	48852
DKK1-DVL2-WNT2B	30054	11006	42662	15953	2499	AXIN1-FZD2-WNT2B	19640	10980	37938	11186	26435
TLE1-WNT1-WNT2B	13179	5610	13964	224	26765	TCF7L1-WNT1-WNT2B	2635	2641	24523	210	37831
LRP5-SFRP1-WNT2B	24362	31966	30181	37100	46651	FZD5-NKD1-WNT2B	18497	19475	22567	24649	24247
CXXC4-FZD7-WNT2B	3497	13030	1072	53710	54739	AES-DVL1-WNT2B	19399	35944	18278	22178	26836
CSNK1D-PORCN-WNT2B	8595	53305	9816	26691	42121	FBXW11-GSK3B-WNT2B	28340	54433	907	12470	3331
PITX2-PORCN-WNT2B	6802	25276	16938	13140	54357	DKK1-GSK3A-WNT2B	76	11011	47102	15898	19458
CSNK2A1-MYC-WNT2B	1714	9603	40200	31690	23030	FOSL1-PORCN-WNT2B	4296	5489	1279	29512	55035
FSHB-NKD1-WNT2B	24792	50507	25909	42911	36692	SENP2-WNT1-WNT2B	2021	43379	30860	2867	24069
PYGO1-WNT2-WNT2B	42713	30786	13433	45795	1718	FOSL1-WIF1-WNT2B	41773	13018	2276	54404	49689
LEF1-T-WNT2B	4043	15103	15608	21225	12447	FZD8-WNT1-WNT2B	1302	19	29799	354	19089
FBXW11-TCF7-WNT2B	35364	55673	1310	14191	3082	DAAMI-FGF4-WNT2B	1448	41378	13135	45446	17389
FBXW11-JUN-WNT2B	30736	52338	1286	29236	8641	DKK1-FGF4-WNT2B	2163	8554	28809	20482	48779
FOSL1-SFRP1-WNT2B	21116	7705	2123	56839	56883	SENP2-SFRP1-WNT2B	12477	36645	18903	52949	54446
FBXW11-GSK3A-WNT2B	3891	54907	19679	12118	3846	FZD8-JUN-WNT2B	30397	45061	16498	26458	9398
DKK1-WNT1-WNT2B	1427	29543	44949	34992	19834	DVL1-WNT1-WNT2B	15873	18998	26270	88	9209
FRZB-NKD1-WNT2B	26947	18964	19602	32120	37731	DKK1-FOXN1-WNT2B	1531	23991	43537	22407	32006
CCND2-WNT1-WNT2B	5263	5867	3189	15	13075	FZD1-T-WNT2B	38075	8619	20316	40538	36073
FBXW11-RHOU-WNT2B	34750	57120	1020	11008	24856	DAAMI-T-WNT2B	38077	48304	11694	47924	6436
DKK1-NKD1-WNT2B	33321	46336	43515	12948	3783	EP300-WNT1-WNT2B	2458	13992	29930	2629	26795
CTBP2-CTNNB1-WNT2B	36257	43633	7888	56627	41687	FZD6-WNT1-WNT2B	1547	39201	26442	188	15436
FBXW11-WIF1-WNT2B	38776	30910	903	8803	21329	FBXW11-FOXN1-WNT2B	3637	18134	11920	13018	6771
DAAMI-WNT1-WNT2B	14817	47333	17911	1242	1180	NLK-PORCN-WNT2B	30300	3466	8133	31316	44880
TCF7L1-WIF1-WNT2B	17438	28330	20158	41636	47785	CTBP2-T-WNT2B	12738	34451	25925	48123	42558
FBXW11-NKD1-WNT2B	42436	56089	5208	5851	6025	CSNK2A1-FOXN1-WNT2B	1203	7766	40805	5216	17738
DKK1-PYGO1-WNT2B	2010	10992	36338	13891	29481	FBXW11-PORCN-WNT2B	4588	54697	1382	3672	49591
CCND3-NKD1-WNT2B	31750	9905	43256	46510	4045	FBXW11-FZD2-WNT2B	18346	54018	1322	6284	1184
CSNK1G1-FZD2-WNT2B	31344	5642	34740	5475	23273	DAAMI-JUN-WNT2B	34628	49211	11090	56716	4721
DAAMI-DVL2-WNT2B	6942	14480	18352	38461	5669	FZD1-PORCN-WNT2B	12628	31292	8901	34846	55210
DKK1-MYC-WNT2B	2720	3916	32917	27454	26540	DKK1-PORCN-WNT2B	6263	7902	41853	840	49894
FZD8-T-WNT2B	15847	32806	8042	19815	9401	DAAMI-LRP6-WNT2B	19994	49638	18834	51013	3681
FRZB-FZD2-WNT2B	18182	6700	6577	13974	41022	CSNK1D-FOXN1-WNT2B	2477	5135	39962	11954	23525
FZD1-WIF1-WNT2B	46438	3992	11382	45997	45602	LRP5-PORCN-WNT2B	13427	8220	27519	32046	55939
FBXW11-SLC9A3R1-WNT2B	35442	56713	645	7849	1242	CXXC4-DVL2-WNT2B	14916	7821	10829	36605	32745
FBXW11-FGF4-WNT2B	7080	54386	714	19379	16509	FOSL1-WNT1-WNT2B	8040	5830	31727	31	46871
BCL9-PORCN-WNT2B	7648	28196	20793	10962	34371	KREMEN1-NKD1-WNT2B	10715	45017	15095	25349	17172
KREMEN1-PORCN-WNT2B	4060	34624	13586	33545	46659	FOSL1-NLK-WNT2B	20492	705	35136	30860	53018
CTBP1-FGF4-WNT2B	3838	22868	10303	52844	53469	DAAMI-FOXN1-WNT2B	1209	51245	29982	6041	1467
FZD6-PITX2-WNT2B	8135	7300	14987	7418	3456	FBXW2-NKD1-WNT2B	33781	33859	11109	13486	210
KREMEN1-PPP2CA-WNT2B	25164	28694	34566	35971	17687	FZD1-JUN-WNT2B	49546	6083	15156	54576	28886
CSNK2A1-FSHB-WNT2B	14373	4327	52378	10457	6308	LRP5-NKD1-WNT2B	32145	41013	38068	34089	24010
LRP5-NKD1-WNT2B	32145	41013	38068	34089	24010	FZD8-GSK3A-WNT2B	750	34363	43071	24851	7386
LRP5-NLK-WNT2B	28396	1960	19941	23600	55297	CSNK1D-WNT1-WNT2B	3674	5014	26127	3017	32922
FRZB-GSK3A-WNT2B	1619	7239	47111	39827	42272	FZD6-GSK3A-WNT2B	2435	10468	36364	50835	5185
FRAT1-PORCN-WNT2B	5506	22998	20346	48317	52835	DAAMI-FZD2-WNT2B	28698	41371	17118	4063	2227
CCND2-LRP6-WNT2B	11171	11125	4049	53108	11661	FRZB-T-WNT2B	17363	23133	2973	38410	49610
FZD1-NLK-WNT2B	28935	4414	27054	36546	52981	FZD7-PPP2CA-WNT2B	54842	24004	41817	52487	4145
CCND3-WNT1-WNT2B	5662	36122	43485	1250	11198	FBXW11-PYGO1-WNT2B	7490	53715	924	4743	16840
FZD7-PORCN-WNT2B	35742	42851	5084	32980	11716	BTRC-GSK3A-WNT2B	9987	55898	47839	49215	4144
JUN-PYGO1-WNT2B	2703	20164	23828	23294	38517	FBXW4-WNT1-WNT2B	3114	52426	37613	1129	42822
FBXW11-T-WNT2B	23753	56671	897	4228	17584	DVL1-FOXN1-WNT2B	14274	29565	47737	20496	2243
KREMEN1-WNT1-WNT2B	7206	28407	30386	2208	20264	FZD8-NKD1-WNT2B	49791	35392	25199	27885	3968
EP300-GSK3B-WNT2B	17031	3072	9839	9763	7695	FZD5-DVL2-WNT2B	11786	13958	21829	28234	6764

Table 7. Rankings of WNT2B-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002.

RANKING @ t_i USING SOBOL - 2002											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CTNNBIP1-WIF1-WNT2B	32269	9564	44982	43273	5808	AES-AXIN1-WNT2B	3629	31781	1126	27740	52489
LRP6-TCF7-WNT2B	9173	15520	2142	1846	43832	DKK1-JUN-WNT2B	55363	40120	46822	38204	3471
CXXC4-PORCN-WNT2B	39582	44080	51571	43634	12796	TLE1-WIF1-WNT2B	42718	23842	52893	55585	8492
CSNK1D-FGF4-WNT2B	28074	51541	15533	12033	30048	CCND1-WIF1-WNT2B	53452	50296	53198	44416	331
APC-DIXDC1-WNT2B	32686	46138	57032	49706	8604	FZD7-NKD1-WNT2B	56201	48723	45825	38106	22510
TLE2-WIF1-WNT2B	35013	18233	37906	28769	3346	FOXN1-KREMEN1-WNT2B	48078	14775	45903	47094	15768
CSNK2A1-T-WNT2B	14346	8714	2556	866	56003	TLE2-WNT1-WNT2B	40245	22669	37689	29819	30399
FRAT1-FZD1-WNT2B	43184	45767	55957	45461	9098	CCND1-FGF4-WNT2B	1271	16968	23159	21229	39055
DVL1-EP300-WNT2B	44498	7790	46717	29455	10013	CSNK1D-SFRP1-WNT2B	14464	28189	8702	8326	25216
PPP2CA-SFRP4-WNT2B	45917	16377	56750	51527	8872	DVL2-JUN-WNT2B	40463	48141	46668	43995	4463
FGF4-SFRP1-WNT2B	17695	38619	13360	27949	40245	FZD6-PORCN-WNT2B	31884	54376	34870	43757	175
DKK1-DVL2-WNT2B	11607	18789	19566	26257	36056	AXIN1-FZD2-WNT2B	13078	46421	9134	3535	56514
TLE1-WNT1-WNT2B	44201	2292	42877	38512	19669	TCF7L1-WNT1-WNT2B	49295	4478	33582	55669	18987
LRP5-SFRP1-WNT2B	2020	796	19380	20779	1060	FZD5-NKD1-WNT2B	1021	7682	6037	13559	34507
CXXC4-FZD7-WNT2B	49726	31087	32815	31314	18255	AES-DVL1-WNT2B	24665	8966	13653	21215	2061
CSNK1D-PORCN-WNT2B	39627	20751	32331	36708	28715	FBXW11-GSK3B-WNT2B	26943	804	26801	1082	52742
PITX2-PORCN-WNT2B	9536	5794	12824	18961	17911	DKK1-GSK3A-WNT2B	533	30975	18469	11508	29654
CSNK2A1-MYC-WNT2B	40989	30656	53975	49615	2007	FOSL1-PORCN-WNT2B	9686	2290	2189	14059	39340
FSHB-NKD1-WNT2B	44401	54732	42873	52925	7821	SENP2-WNT1-WNT2B	31781	23905	56648	48582	12552
PYGO1-WNT2-WNT2B	35098	23545	34784	49087	46216	FOSL1-WIF1-WNT2B	25173	2114	24567	1335	44580
LEF1-T-WNT2B	14224	20300	7495	265	47970	FZD8-WNT1-WNT2B	51664	44478	38109	40380	35203
FBXW11-TCF7-WNT2B	30352	16888	44808	42493	7236	DAAM1-FGF4-WNT2B	23184	55519	15829	13855	31157
FBXW11-JUN-WNT2B	29211	26070	34684	38249	15818	DKK1-FGF4-WNT2B	5181	13583	19476	28501	11610
FOSL1-SFRP1-WNT2B	36889	18888	44464	53547	13962	SENP2-SFRP1-WNT2B	7482	33180	11485	14807	20446
FBXW11-GSK3A-WNT2B	22556	12928	3029	4009	52731	FZD8-JUN-WNT2B	53721	5288	39583	33282	9288
DKK1-WNT1-WNT2B	38884	6393	34240	30384	22894	DVL1-WNT1-WNT2B	30250	50468	45283	44194	6705
FRZB-NKD1-WNT2B	16138	5567	23173	23193	50096	DKK1-FOXN1-WNT2B	55818	51616	29843	30059	41899
CCND2-WNT1-WNT2B	26615	12983	5711	75	50116	FZD1-T-WNT2B	17356	15997	26197	2810	33591
FBXW11-RHOU-WNT2B	31931	54618	43300	44261	19228	DAAM1-T-WNT2B	23003	8949	18729	22669	44999
DKK1-NKD1-WNT2B	16505	52805	21482	25919	33616	EP300-WNT1-WNT2B	24766	7961	7149	6651	57039
CTBP2-CTNNB1-WNT2B	29939	31301	39087	52855	26416	FZD6-WNT1-WNT2B	50360	38778	41647	35013	7193
FBXW11-WIF1-WNT2B	29590	51803	34137	33592	22138	FBXW11-FOXN1-WNT2B	38643	50360	51216	56044	10628
DAAM1-WNT1-WNT2B	45462	20187	47757	48914	24934	NLK-PORCN-WNT2B	53778	43223	50000	50320	693
TCF7L1-WIF1-WNT2B	46419	20351	52066	55826	19213	CTBP2-T-WNT2B	6821	22296	6124	9606	43942
FBXW11-NKD1-WNT2B	2665	20622	20959	28247	43772	CSNK2A1-FOXN1-WNT2B	53238	9771	44983	35149	2439
DKK1-PYGO1-WNT2B	54188	35764	37921	46266	24833	FBXW11-PORCN-WNT2B	33797	43559	32346	51083	11772
CCND3-NKD1-WNT2B	27627	1999	24899	12345	29380	FBXW11-FZD2-WNT2B	23532	3530	10144	25174	49705
CSNK1G1-FZD2-WNT2B	43957	8905	55685	37469	3334	DAAM1-JUN-WNT2B	52248	43893	48230	50763	39740
DAAM1-DVL2-WNT2B	20771	46186	8841	3792	51630	FZD1-PORCN-WNT2B	53071	43558	43509	40293	16263
DKK1-MYC-WNT2B	41021	983	42832	50572	13552	DKK1-PORCN-WNT2B	41383	41457	40170	35729	7578
FZD8-T-WNT2B	11750	5176	23231	19560	52516	DAAM1-LRP6-WNT2B	45219	41641	34094	48928	25060
FRZB-FZD2-WNT2B	17755	36646	17037	1266	17860	CSNK1D-FOXN1-WNT2B	34971	36541	30580	44435	4295
FZD1-WIF1-WNT2B	41197	35896	29093	49255	31536	LRP5-PORCN-WNT2B	53023	48201	48575	48454	8907
FBXW11-SLC9A3R1-WNT2B	24284	33812	24367	891	20731	CXXC4-DVL2-WNT2B	6744	50339	17055	22295	46522
FBXW11-FGF4-WNT2B	25936	11195	20618	18729	32916	FOSL1-WNT1-WNT2B	27112	14023	16313	6628	52241
BCL9-PORCN-WNT2B	619	12023	16698	20050	36808	KREMEN1-NKD1-WNT2B	3720	31186	24394	8640	52443
KREMEN1-PORCN-WNT2B	52764	52181	54179	35890	32504	FOSL1-NLK-WNT2B	42013	9877	52887	52662	11462
CTBP1-FGF4-WNT2B	15907	2856	754	18068	33714	DAAM1-FOXN1-WNT2B	49677	19444	42826	45397	19848
FZD6-PITX2-WNT2B	42547	47083	32974	29428	5335	FBXW2-NKD1-WNT2B	6500	43410	325	13681	45117
KREMEN1-PPP2CA-WNT2B	2599	25978	4343	22180	25119	FZD1-JUN-WNT2B	34517	30754	39634	38168	4014
CSNK2A1-FSHB-WNT2B	56035	49999	49902	45966	16417	LRP5-NKD1-WNT2B	6733	21320	13120	11007	47150
LRP5-NKD1-WNT2B	6733	21320	13120	11007	47150	FZD8-GSK3A-WNT2B	16883	32110	17993	5422	40875
LRP5-NLK-WNT2B	5246	28793	23635	4377	51925	CSNK1D-WNT1-WNT2B	42719	30480	50555	50603	27505
FRZB-GSK3A-WNT2B	27783	13118	20027	17784	24093	FZD6-GSK3A-WNT2B	14460	51037	20362	6739	56613
FRAT1-PORCN-WNT2B	37208	46905	41078	48022	2109	DAAM1-FZD2-WNT2B	21589	11905	16194	15774	27169
CCND2-LRP6-WNT2B	6636	56088	3124	21004	48482	FRZB-T-WNT2B	24201	10815	17479	15334	45319
FZD1-NLK-WNT2B	26886	12820	19770	537	36921	FZD7-PPP2CA-WNT2B	49373	38171	36850	38963	35731
CCND3-WNT1-WNT2B	48160	29114	29530	31870	18669	FBXW11-PYGO1-WNT2B	33541	53563	42544	44866	11547
FZD7-PORCN-WNT2B	5088	17699	18559	1094	44896	BTRC-GSK3A-WNT2B	8517	28470	17221	9308	40220
JUN-PYGO1-WNT2B	784	29200	21789	1189	45268	FBXW4-WNT1-WNT2B	45929	18615	31454	47272	11773
FBXW11-T-WNT2B	19469	44633	26413	20803	44750	DVL1-FOXN1-WNT2B	42127	9502	36314	42347	27070
KREMEN1-WNT1-WNT2B	36576	35166	39887	54348	48410	FZD8-NKD1-WNT2B	7879	40127	24943	28578	45650
EP300-GSK3B-WNT2B	30525	47975	41708	29146	6959	FZD5-DVL2-WNT2B	21058	49799	6043	28547	35739

Table 8. Rankings of WNT2B-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez.

RANKING @ t_i USING SOBOL - MARTINEZ												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CTNNBIP1-WIF1-WNT2B	11399	24367	25017	23530	21484	AES-AXIN1-WNT2B	12663	8851	4385	30838	53104	
LRP6-TCF7-WNT2B	3861	31924	15999	20260	1723	DKK1-JUN-WNT2B	16474	6155	31575	3599	21858	
CXXC4-PORCN-WNT2B	14191	46734	705	50002	13918	TLE1-WIF1-WNT2B	22858	4824	44491	36814	47038	
CSNK1D-FGF4-WNT2B	11099	33067	21662	18628	9514	CCND1-WIF1-WNT2B	41667	49854	1695	14733	9964	
APC-DIXDC1-WNT2B	33667	9816	37410	33932	21947	FZD7-NKD1-WNT2B	56222	35279	4725	54614	43292	
TLE2-WIF1-WNT2B	32197	2739	53514	46829	47415	FOXN1-KREMEN1-WNT2B	21687	4778	50738	46118	18804	
CSNK2A1-T-WNT2B	5760	12660	53417	53139	1959	TLE2-WNT1-WNT2B	40200	2166	49574	41995	42003	
FRAT1-FZD1-WNT2B	9353	10394	44162	36655	40931	CCND1-FGF4-WNT2B	27190	52288	44069	26037	33209	
DVL1-EP300-WNT2B	8726	18065	22256	42886	36883	CSNK1D-SFRP1-WNT2B	45504	25704	37754	9982	35219	
PPP2CA-SFRP4-WNT2B	13418	45868	44709	51672	55851	DVL2-JUN-WNT2B	50622	8656	8692	8248	41711	
FGF4-SFRP1-WNT2B	2215	4984	42493	13876	33910	FZD6-PORCN-WNT2B	5774	40911	34822	40189	42079	
DKK1-DVL2-WNT2B	6263	22609	16657	25832	34913	AXIN1-FZD2-WNT2B	37386	51493	15577	12660	1933	
TLE1-WNT1-WNT2B	34900	4162	23677	15497	48629	TCF7L1-WNT1-WNT2B	32996	5243	28606	285	39952	
LRP5-SFRP1-WNT2B	50657	25330	23317	7661	960	FZD5-NKD1-WNT2B	27769	32100	5018	27110	12151	
CXXC4-FZD7-WNT2B	47761	31077	51924	46061	8191	AES-DVL1-WNT2B	9253	4149	13719	20634	42491	
CSNK1D-PORCN-WNT2B	55457	33746	2831	17934	52535	FBXW11-GSK3B-WNT2B	6446	25466	48443	9756	981	
PITX2-PORCN-WNT2B	32916	28214	19614	42831	17840	DKK1-GSK3A-WNT2B	46435	22075	14989	21647	18101	
CSNK2A1-MYC-WNT2B	33055	55999	36655	287	9236	FOSL1-PORCN-WNT2B	51756	54848	26032	20042	1751	
FSHB-NKD1-WNT2B	55721	42851	2627	5107	7553	SENP2-WNT1-WNT2B	16555	17079	41227	9388	56362	
PYGO1-WNT2-WNT2B	23785	7527	40262	615	38247	FOSL1-WIF1-WNT2B	12903	16845	50910	16896	7421	
LEF1-T-WNT2B	48424	50113	47991	1522	2960	FZD8-WNT1-WNT2B	31837	25698	25477	38489	25104	
FBXW11-TCF7-WNT2B	41108	33848	28348	48942	26369	DAAMI-FGF4-WNT2B	16000	9089	55066	40863	27056	
FBXW11-JUN-WNT2B	33659	37203	20213	9874	32143	DKK1-FGF4-WNT2B	103	10354	20410	29259	46133	
FOSL1-SFRP1-WNT2B	6277	10803	37453	46689	25622	SENP2-SFRP1-WNT2B	40240	50851	56622	9242	9004	
FBXW11-GSK3A-WNT2B	20409	22617	34216	48084	5873	FZD8-JUN-WNT2B	47390	29843	6652	5804	30618	
DKK1-WNT1-WNT2B	5148	39741	99	25462	25379	DVL1-WNT1-WNT2B	44615	10931	27851	20224	47773	
FRZB-NKD1-WNT2B	3508	55779	21413	56958	54884	DKK1-FOXN1-WNT2B	22219	29187	3624	37031	31136	
CCND2-WNT1-WNT2B	8206	22475	56331	33393	19889	FZD1-T-WNT2B	10987	38809	11964	13374	51442	
FBXW11-RHOU-WNT2B	40385	21306	912	54428	46020	DAAMI-T-WNT2B	23320	9302	18677	25820	50860	
DKK1-NKD1-WNT2B	2	21468	4661	31962	47604	EP300-WNT1-WNT2B	40403	45788	6306	37531	53145	
CTBP2-CTNNB1-WNT2B	7875	19830	34195	23465	32213	FZD6-WNT1-WNT2B	14865	55096	2854	19971	18190	
FBXW11-WIF1-WNT2B	36968	5122	16875	36018	40185	FBXW11-FOXN1-WNT2B	55663	32223	6184	10160	38098	
DAAMI-WNT1-WNT2B	8310	11548	37506	38188	47486	NLK-PORCN-WNT2B	23304	40640	40983	7483	30297	
TCF7L1-WIF1-WNT2B	38177	34	28918	2665	24315	CTBP2-T-WNT2B	53395	8911	12910	8267	38289	
FBXW11-NKD1-WNT2B	46316	49834	31463	34942	54972	CSNK2A1-FOXN1-WNT2B	56377	38665	54391	50687	12268	
DKK1-PYGO1-WNT2B	9922	1845	49860	25488	36909	FBXW11-PORCN-WNT2B	35745	24457	1321	41380	44484	
CCND3-NKD1-WNT2B	29468	17702	29050	41716	43213	FBXW11-FZD2-WNT2B	3308	32854	50919	52505	53174	
CSNK1G1-FZD2-WNT2B	16988	38740	33148	19223	15749	DAAMI-JUN-WNT2B	54799	36164	2157	26110	26593	
DAAMI-DVL2-WNT2B	15381	5625	50468	46525	49297	FZD1-PORCN-WNT2B	56201	55890	2978	45069	8402	
DKK1-MYC-WNT2B	7585	27260	2699	34894	52083	DKK1-PORCN-WNT2B	13119	7914	33768	34345	53916	
FZD8-T-WNT2B	828	38497	56911	52032	4429	DAAMI-LRP6-WNT2B	56089	47777	32504	8528	21823	
FRZB-FZD2-WNT2B	6148	17323	30176	51069	4378	CSNK1D-FOXN1-WNT2B	40727	20657	11342	28759	54605	
FZD1-WIF1-WNT2B	45148	33096	22965	3267	28017	LRP5-PORCN-WNT2B	18108	55585	52704	49602	30842	
FBXW11-SLC9A3R1-WNT2B	32360	3783	53535	55838	5608	CXXC4-DVL2-WNT2B	35400	16086	45800	56946	44441	
FBXW11-FGF4-WNT2B	39346	16482	33435	8074	1498	FOSL1-WNT1-WNT2B	16777	24758	43097	23275	38302	
BCL9-PORCN-WNT2B	31320	49751	15858	56923	5674	KREMEN1-NKD1-WNT2B	41860	50698	42188	13420	1100	
KREMEN1-PORCN-WNT2B	25373	52290	22610	2903	12826	FOSL1-NLK-WNT2B	14329	18478	43731	32209	46898	
CTBP1-FGF4-WNT2B	301	21245	14872	56780	43226	DAAMI-FOXN1-WNT2B	29721	26744	32942	6037	9724	
FZD6-PITX2-WNT2B	10663	27608	9003	33499	56550	FBXW2-NKD1-WNT2B	51198	7198	8275	25665	44537	
KREMEN1-PPP2CA-WNT2B	36014	45601	55143	6929	4063	FZD1-JUN-WNT2B	40470	56406	19457	34145	8292	
CSNK2A1-FSHB-WNT2B	57093	25886	24846	4769	8081	LRP5-NKD1-WNT2B	6506	56675	30108	35596	51172	
LRP5-NKD1-WNT2B	6506	56675	30108	35596	51172	FZD8-GSK3A-WNT2B	9103	8669	15155	42693	27422	
LRP5-NLK-WNT2B	12533	30603	27930	42546	28598	CSNK1D-WNT1-WNT2B	31537	11063	42528	38828	9460	
FRZB-GSK3A-WNT2B	2610	26089	53894	55872	38044	FZD6-GSK3A-WNT2B	4557	22541	14486	35375	21117	
FRAT1-PORCN-WNT2B	20944	46462	334	27557	17691	DAAMI-FZD2-WNT2B	17163	7944	13520	39457	4542	
CCND2-LRP6-WNT2B	33693	21023	53000	51329	28570	FRZB-T-WNT2B	923	43383	42589	7043	21178	
FZD1-NLK-WNT2B	3078	19116	35164	4311	41638	FZD7-PPP2CA-WNT2B	16737	33330	1637	33682	42332	
CCND3-WNT1-WNT2B	56781	48641	12692	21153	53121	FBXW11-PYGO1-WNT2B	38516	3021	34825	23473	34676	
FZD7-PORCN-WNT2B	22739	11163	28241	3088	23003	BTRC-GSK3A-WNT2B	3582	20261	29185	8102	27659	
JUN-PYGO1-WNT2B	8806	9304	56999	30033	36730	FBXW4-WNT1-WNT2B	49985	4684	49002	50868	27871	
FBXW11-T-WNT2B	8167	5125	56206	52284	24972	DVL1-FOXN1-WNT2B	8379	36905	17227	46425	37614	
KREMEN1-WNT1-WNT2B	9185	50045	47503	42420	14152	FZD8-NKD1-WNT2B	9631	7680	43019	11274	51358	
EP300-GSK3B-WNT2B	39896	34405	6246	29749	20434	FZD5-DVL2-WNT2B	812	9099	50058	12589	49298	

7.4.1. Examining the Behaviour of PORCN-WNT2B-X Combinations

The *Drosophila* segment polarity gene product Porcupine (Porc) was first identified as being necessary for processing Wingless (Wg), a *Drosophila* Wnt (Wnt) family member. Tanaka et al. [40] identified Mouse (Mporc) and *Xenopus* (Xporc) homologs of porc and found that they encode endoplasmic reticulum (ER) proteins with multiple transmembrane domains. Further, Mporc mRNA was differentially expressed during embryogenesis and in various adult tissues, demonstrating that the alternative splicing is regulated to synthesize the specific types of Mporc. In transfected mammalian cells, they found all types of Mporc affected the processing of mouse WNT1, WNT3A, WNT4, WNT6,

and WNT7B but not WNT5A. Lastly, they also found that all types of Mporc co-immunoprecipitated with various WNT proteins. Their results suggested that Mporc may function as a chaperone-like molecule for WNT.

Liu et al. [41] indicate that post-translational modification of WNTs includes lipid modification and glycosylation. The former is performed by PORCN. PORCN is a membrane-bound O-acyltransferase located in the endoplasmic reticulum and can add palmitoleate groups to WNT proteins that is necessary for WNT ligand secretion, and it is a member of the membrane-bound O-acyltransferases (MBOATs). Lipid modification is necessary for Wnt activity, and the opposite is true for glycosylation as observed by Willert et al. [42]. However, I was unable to find existing literature that document PORCN and post-translational modification of WNT2B via PORCN. Looking at the tables above, one finds the following combinations for PORCN along with WNT2B, to be prominent at 3rd order level - CXXC4-PORCN-WNT2B, CSNK1D-PORCN-WNT2B, PITX2-PORCN-WNT2B, BCL9-PORCN-WNT2B, KREMEN1-PORCN-WNT2B, FRAT1-PORCN-WNT2B, FZD7-PORCN-WNT2B, FZD6-PORCN-WNT2B, FOSL1-PORCN-WNT2B, NLK-PORCN-WNT2B, FBXW11-PORCN-WNT2B, FZD1-PORCN-WNT2B, DKK1-PORCN-WNT2B, and LRP5-PORCN-WNT2B. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.4.2. Examining the Behaviour of FZD-WNT2B-X Combinations

Ortiz-Masia et al. [43] observed that fibrosis and expression of epithelial-mesenchymal transition (EMT) markers were detected in samples from Crohn's disease (CD) patients irrespective of the clinical behaviour. They show that an increased EMT, associated with increased WNT2B-FZD4 interaction, was detected in intestinal tissue from CD patients with a penetrating behaviour. Normal development of peripheral eye structures is also regulated by Wnt signaling, with WNT2B and FZD4 acting as the primary WNT ligand and receptor. Ohta et al. [44] show that the secreted protein Tsukushi (TSK) functioned as a WNT signaling inhibitor by binding directly to the cysteine-rich domain of FZD4 and competed with WNT2B. Conversely, their targeted inactivation of the TSK gene in mice caused expansion of the ciliary body and up-regulation of WNT2B and FZD4 expression in the developing peripheral eye. Looking at the tables above, one finds the following combinations for members of FZD family along with WNT2B, to be prominent at 3rd order level - FRAT1-FZD1-WNT2B, CXXC4-FZD7-WNT2B, CSNK1G1-FZD2-WNT2B, FZD8-T-WNT2B, FRZB-FZD2-WNT2B, FZD1-WIF1-WNT2B, FZD6-PITX2-WNT2B, FZD1-NLK-WNT2B, FZD7-PORCN-WNT2B, FZD7-NKD1-WNT2B, FZD6-PORCN-WNT2B, AXIN1-FZD2-WNT2B, TCF7L1-WNT1-WNT2B, FZD5-NKD1-WNT2B, FZD8-WNT1-WNT2B, FZD8-JUN-WNT2B, FZD1-T-WNT2B, FZD6-WNT1-WNT2B, FBXW11-FZD2-WNT2B, FZD1-PORCN-WNT2B, FZD1-JUN-WNT2B, FZD8-GSK3A-WNT2B, FZD6-GSK3A-WNT2B, DAAM1-FZD2-WNT2B, FZD7-PPP2CA-WNT2B, FZD8-NKD1-WNT2B and FZD5-DVL2-WNT2B. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.4.3. Examining the Behaviour of CCND-WNT2B-X Combinations

WNT2B is a key regulator of downstream target β -catenin and cyclin D1 (CCND1) in Wnt signaling pathway. Zhu et al. [45] checked the expression of WNT2B, β -catenin and CCND1, and found that after high glucose treatment, the expression of all three were significantly upregulated (thus enhancing cell proliferation and inflammation, and increase fibrosis-related protein expression), but Hottip silencing could inhibit their expression which could be reversed by miR-455-3p inhibitor. These data indicated that WNT2B was a target of miR-455-3p and Wnt pathway was involved in diabetic nephropathy (DN). Looking at the tables above, one finds the following combinations for members of CCND family along with WNT2B, to be prominent at 3rd order level - CCND2-WNT1-WNT2B, CCND3-NKD1-WNT2B, CCND2-LRP6-WNT2B, CCND3-WNT1-WNT2B, CCND1-WIF1-WNT2B, and CCND1-FGF4-WNT2B. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.4.4. Examining the Behaviour of FBXW11-WNT2B-X Combinations

Nodular and superficial are the most common subtypes of basal cell carcinoma (BCC) and WNT signaling is associated with BCC phenotypic variation. Do Carmo et al. [46] observed that nodular BCC presented up-regulation of CSNK1D, RAB23, PRKACB, PRKX, WNT5A, BMP6, FBXW11, IFT52, and SIAH1; and down-regulation of PRKACA, WIF1, WNT2B, WNT3, WNT10A, WNT10B, WNT16, FKBP8, NPC1, and MAPK1. In conclusion they found that PRKX (up-regulated), WNT3 (down-regulated) and WNT16 (down-regulated) genes, belonging to the WNT signaling pathway, are involved in the tumorigenic process of nodular BCC.

Dalle Carbonare et al. [47] show that FBXW11 is highly modulated during differentiation and that increased levels of FBXW11 cause a decrease in the target β -catenin levels under normal conditions. Under pathological conditions such as cleidocranial dysplasia (CCD) the relationship between FBXW11 and RUNX2 or β -catenin changes from normal conditions, suggesting the lack of β -catenin degradation by FBXW11. It has been reported in Dalle Carbonare et al. [47] that WNT signalling and RUNX2 mutually regulate their expression. In this disease model, FBXW11 levels might be elevated to counteract the dysregulated levels of β -catenin. Conversely, in osteosarcoma cells, the reduction of FBXW11 protein levels increases β -catenin. Since β -catenin promotes tumour formation and progression, reduced FBXW11 levels in osteosarcoma may be considered a negative prognostic factor.

Looking at the tables above, one finds the following combinations for FBXW11 along with WNT2B, to be prominent at 3rd order level - FBXW11-TCF7-WNT2B, FBXW11-JUN-WNT2B, FBXW11-GSK3A-WNT2B, FBXW11-RHO-WNT2B, FBXW11-WIF1-WNT2B, FBXW11-NKD1-WNT2B, FBXW11-SLC9A3R1-WNT2B, FBXW11-FGF4-WNT2B, FBXW11-T-WNT2B, FBXW11-GSK3B-WNT2B, FBXW11-FOXN1-WNT2B, FBXW11-PORCN-WNT2B, FBXW11-FZD2-WNT2B and FBXW11-PYGO1-WNT2B. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.4.5. Examining the Behaviour of LRP-WNT2B-X Combinations

To assess the potential role of WNT/TCF signaling in invasive trophoblast differentiation, Pollheimer et al. [48] investigated the role of selected WNT ligands and frizzled receptors. WNT2B, WNT7B, FZD3, FZD6, and LRP6 mRNAs were expressed in all tissues and cell types analyzed, suggesting that functional WNT receptors (FZD/LRP6) could be formed in human trophoblasts. As part of their study, Pollheimer et al. [48] demonstrated mRNA expression of WNT2B, WNT7B, FZD3, FZD6, and LRP6 in all trophoblast cell types strengthening the idea that these and other WNT/FZD factors could play a role in autocrine WNT signaling. Looking at the tables above, one finds the following combinations for members of LRP family along with WNT2B, to be prominent at 3rd order level - LRP6-TCF7-WNT2B, LRP5-SFRP1-WNT2B, LRP5-NKD1-WNT2B, LRP5-NLK-WNT2B, CCND2-LRP6-WNT2B, DAAM1-LRP6-WNT2B, LRP5-PORCN-WNT2B and LRP5-NKD1-WNT2B. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.4.6. Examining the Behaviour of FOSL1-WNT2B-X Combinations

Bonci et al. [49] report downregulation of miRs in B-cell chronic lymphocytic leukemia (CLL) as well as prostate carcinoma where additional WNT-related targets included SMAD7, SOX5, WNT2B and FOSL1. FOSL1 is known as a β -catenin/WNT signaling target gene, transcribed when WNT signaling is activated. Hachim et al. [50] decided to decipher the role of WNT signaling on bronchial fibroblast biology and their transcriptomics profiling of fibroblasts from asthmatic patients compared to healthy ones confirmed their in silico analysis, as members of canonical WNT signaling (WNT1, FOSL1, WNT2B, LRP5, WNT2, WNT16, and CCND2) were significantly upregulated in fibroblasts from asthmatic patients. Looking at the tables above, one finds the following combinations for FOSL1 along with WNT2B, to be prominent at 3rd order level - FOSL1-SFRP1-WNT2B, FOSL1-PORCN-WNT2B, FOSL1-WIF1-WNT2B, FOSL1-WNT1-WNT2B and FOSL1-NLK-WNT2B. All these

combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.5. Conserved Machine Learning Rankings for Tested WNT3A-X-X Combinations

A total of 2415, 3rd order combinations involving WNT3A were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 10, 11 and 12 show the rankings for the same combinations as in table 9, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

Table 9. Rankings of WNT3A-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear.

RANKING @ t_i USING HSIC - LINEAR											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
FZD8-FBXW4-WNT3A	145	14722	464	49602	17899	SENP2-FBXW4-WNT3A	274	39131	29	44525	46327
DKK1-JUN-WNT3A	289	6120	44241	52638	12402	AES-AXIN1-WNT3A	300	53570	33402	33493	7041
DVL2-JUN-WNT3A	322	31939	32028	29113	4760	TLE1-WIF1-WNT3A	449	13164	8253	51282	7381
AES-DVL1-WNT3A	454	42413	16222	33799	31908	CCND1-FGF4-WNT3A	513	52076	47881	31710	26148
FBXW2-WNT3A-WNT4	532	33676	31112	1276	53531	JUN-PYGO1-WNT3A	570	14118	6423	19469	36536
CTNNB1P1-WIF1-WNT3A	603	57	12000	57039	19928	DAAM1-FBXW4-WNT3A	715	40167	9213	50253	45515
PPP2CA-WNT1-WNT3A	732	6546	10800	53535	9982	FZD7-PORCN-WNT3A	780	35610	948	25632	12174
FZD7-WNT1-WNT3A	796	6819	613	46978	36231	CCND1-PYGO1-WNT3A	859	46424	26699	23831	49470
TLE1-WNT1-WNT3A	862	11066	907	29504	42805	CXXC4-FGF4-WNT3A	905	28520	52397	52668	30693
AXIN1-DVL1-WNT3A	931	6900	28087	51866	19748	SFRP4-WNT1-WNT3A	994	7835	823	32443	11457
FBXW11-FBXW4-WNT3A	995	33770	89	41396	23538	FRAT1-NLK-WNT3A	1005	19771	7884	9479	10249
KREMEN1-PYGO1-WNT3A	1064	30070	1340	20277	52737	CTNNB1P1-JUN-WNT3A	1110	7698	46119	54862	31125
DKK1-FGF4-WNT3A	1181	38076	34967	42717	15527	CCND2-WNT1-WNT3A	1238	24529	3203	46942	8642
FBXW2-PYGO1-WNT3A	1243	46844	41378	10348	56667	FZD7-JUN-WNT3A	1250	17078	32637	21100	43381
FBXW11-LRP6-WNT3A	1267	46922	30660	12401	30214	EP300-WNT1-WNT3A	1360	30527	695	53063	7375
KREMEN1-PORCN-WNT3A	1377	25809	2588	12830	26801	CXXC4-FRAT1-WNT3A	1421	24998	29856	17406	1342
PPP2CA-T-WNT3A	1435	46308	13460	20855	21652	FZD5-WNT1-WNT3A	1443	14058	943	50372	9921
TCF7L1-WNT1-WNT3A	1465	4078	1392	49037	48926	FOSL1-NLK-WNT3A	1512	2335	4160	3374	12963
FOSL1-JUN-WNT3A	1542	4890	20754	29478	5342	BCL9-FGF4-WNT3A	1545	4871	55810	38541	37087
CCND3-FOXN1-WNT3A	1640	42647	14999	19304	19369	TLE2-WIF1-WNT3A	1645	195	4085	52703	19685
AES-SLC9A3R1-WNT3A	1649	50445	53711	29727	31801	FZD7-NKDI-WNT3A	1664	5491	2056	28279	37124
CCND3-FGF4-WNT3A	1666	48541	24627	42342	22550	DKK1-PYGO1-WNT3A	1670	37660	30663	36831	4685
FZD5-FGF4-WNT3A	1678	10370	56144	43866	11767	DVL2-FGF4-WNT3A	1706	31123	51974	39714	28294
FBXW4-WNT3A-WNT4	1716	50053	13154	14680	40891	CXXC4-WIF1-WNT3A	1745	353	12465	51440	34488
FZD6-WNT1-WNT3A	1761	55679	36296	46569	31443	PPP2R1A-WNT3-WNT3A	1817	55448	5096	45267	43648
CTBP1-FGF4-WNT3A	1841	5230	55626	51583	10691	CCND3-SFRP1-WNT3A	1848	50249	51613	12702	11723
BTRC-GSK3A-WNT3A	1946	45085	56552	39291	36207	FZD7-NLK-WNT3A	1957	2219	4173	15212	30086
CCND3-NKDI-WNT3A	1995	32953	30709	40159	23393	TCF7L1-WIF1-WNT3A	2015	7414	38348	38153	24687
NKDI-WIF1-WNT3A	2028	3129	43733	48011	30914	KREMEN1-FBXW4-WNT3A	2114	13176	100	22815	19325
FZD7-T-WNT3A	2142	42066	4203	1701	36597	PITX2-WNT3-WNT3A	2155	50776	27010	46543	38273
CCND1-WIF1-WNT3A	2203	19821	39265	34450	38713	DVL1-FOXN1-WNT3A	2232	41159	6747	12944	33691
FSHB-T-WNT3A	2242	34175	56516	9226	7363	FSHB-FZD2-WNT3A	2298	5294	54044	44316	3638
CCND3-FZD2-WNT3A	2329	41088	38338	37278	1771	FZD6-PORCN-WNT3A	2394	56979	41510	33895	6602
FBXW11-FOXN1-WNT3A	2396	2939	7434	18375	6211	AXIN1-MYC-WNT3A	2439	8891	14689	6272	37521
CTNNB1-FOXN1-WNT3A	2450	2310	9829	19274	20611	BCL9-JUN-WNT3A	2492	808	53814	42860	28316
FOSL1-WNT1-WNT3A	2512	4481	499	34674	10423	FOSL1-FBXW4-WNT3A	2570	6332	206	39656	6459
DKK1-GSK3A-WNT3A	2600	35402	42900	54934	30633	FBXW11-FGF4-WNT3A	2605	40212	42342	53886	2588
LRP5-WNT1-WNT3A	2674	6803	1423	45127	28226	KREMEN1-NKDI-WNT3A	2675	23678	2816	47552	40285
CSNK1D-WNT3-WNT3A	2727	49625	22336	55596	44252	CXXC4-WNT1-WNT3A	2734	34306	282	36977	4488
CSNK1D-JUN-WNT3A	2740	3878	56083	44551	46162	CCND2-LRP6-WNT3A	2746	39921	17378	19134	17966
KREMEN1-WIF1-WNT3A	2762	721	11586	56871	31145	KREMEN1-WNT3-WNT3A	2788	47193	12084	27016	19027
CXXC4-FOXN1-WNT3A	2796	53	5860	22254	12575	CCND3-LRP6-WNT3A	2824	48608	19945	32728	25411
DKK1-FOXN1-WNT3A	2859	5191	36256	16450	1748	CCND3-CSNK1A1-WNT3A	2882	32791	9744	16123	5109
DVL2-PYGO1-WNT3A	2944	11528	11111	13103	36306	FRAT1-FBXW4-WNT3A	2950	1626	150	55124	17849
CCND3-GSK3A-WNT3A	2984	45295	31574	8988	26511	PPP2R1A-WNT1-WNT3A	2989	13277	15619	27990	53390
DKK1-PORCN-WNT3A	3027	51411	42480	14175	39772	FZD5-CCND2-WNT3A	3096	41702	14175	37261	53046
DKK1-FBXW4-WNT3A	3172	11326	10275	19536	18392	FZD5-GSK3A-WNT3A	3176	26274	10429	35512	33685
CXXC4-DVL2-WNT3A	3186	7341	5733	24584	2313	FRZB-WNT1-WNT3A	3221	19926	900	52289	15551
FZD7-WIF1-WNT3A	3300	22512	13048	31811	10684	FRAT1-WIF1-WNT3A	3328	15377	26382	55074	7682
LEF1-PYGO1-WNT3A	3330	4637	9706	492	45999	PPP2CA-TCF7-WNT3A	3403	35126	15557	53522	39901
KREMEN1-MYC-WNT3A	3433	19129	6220	28682	38858	FBXW11-JUN-WNT3A	3438	21481	29928	50261	15749
CCND3-PYGO1-WNT3A	3454	44362	41213	28500	14947	NKDI-WNT2B-WNT3A	3477	51633	33941	7298	45111
CCND3-PITX2-WNT3A	3484	43666	17937	5868	27350	CCND3-T-WNT3A	3489	45724	10406	23614	102
CTBP2-T-WNT3A	3498	50012	4697	8661	6051	SFRP1-WNT3-WNT3A	3510	39054	12426	27569	44656
DIXDC1-JUN-WNT3A	3551	836	21850	41587	6942	CCND3-MYC-WNT3A	3563	41874	14702	4017	36721
KREMEN1-SLC9A3R1-WNT3A	3580	17181	25435	54188	25643	FZD6-GSK3A-WNT3A	3594	53588	35897	18833	55286
FZD7-PYGO1-WNT3A	3597	13080	6229	10048	9938	LRP5-WNT3-WNT3A	3611	25911	30682	26320	29360
CSNK1G1-FOXN1-WNT3A	3634	7199	9792	30313	10861	BTRC-WNT2-WNT3A	3667	53111	52839	51977	37208
CSNK1D-NLK-WNT3A	3672	3466	7618	26301	5357	CSNK1G1-WNT1-WNT3A	3690	42269	1886	38618	12595
BCL9-WNT3-WNT3A	3715	24411	28195	43748	28562	DAAM1-FGF4-WNT3A	3756	49690	53434	53503	17500
CSNK1G1-JUN-WNT3A	3774	3727	52028	22145	682	APC-GSK3A-WNT3A	3849	6781	15492	26625	29835
FOSL1-PORCN-WNT3A	3900	15019	1518	39920	12124	SENP2-WNT1-WNT3A	3925	51191	778	45722	31784
FBXW11-PYGO1-WNT3A	3985	37584	56193	14716	37160	FOSL1-FRAT1-WNT3A	4035	2654	13405	47524	18665

Table 10. Rankings of WNT3A-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf.

RANKING @ t_i USING HSIC - RBF											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
FZD8-FBXW4-WNT3A	20619	3629	53249	29648	303	SEN2-FBXW4-WNT3A	27065	27541	40533	55578	8502
DKK1-JUN-WNT3A	10634	402	10397	46299	3270	AES-AXIN1-WNT3A	44301	49473	26232	27600	11298
DVL2-JUN-WNT3A	25797	23440	31750	21568	1485	TLE1-WIF1-WNT3A	50523	24823	48636	56307	10235
AES-DVL1-WNT3A	29401	45255	5093	37036	20749	CCND1-FGF4-WNT3A	20339	51659	33176	36373	2796
FBXW2-WNT3A-WNT4	41397	25061	14067	24192	5301	JUN-PYGO1-WNT3A	10181	579	35737	33610	43746
CTNNBIP1-WIF1-WNT3A	28101	8157	26911	47091	41515	DAAM1-FBXW4-WNT3A	17278	46399	38042	50218	2460
PPP2CA-WNT1-WNT3A	4487	6874	35552	24125	19493	FZD7-PORCN-WNT3A	7046	46922	42358	23913	36667
FZD7-WNT1-WNT3A	2224	19292	34884	35013	23800	CCND1-PYGO1-WNT3A	2014	38925	42108	33199	4343
TLE1-WNT1-WNT3A	21715	17829	32814	37959	6447	CXXC4-FGF4-WNT3A	376	11041	597	49220	57138
AXIN1-DVL1-WNT3A	11069	4918	11450	55352	33473	SFRP4-WNT1-WNT3A	11755	16260	28669	23387	22304
FBXW11-FBXW4-WNT3A	26939	26457	29630	45627	2113	FRAT1-NLK-WNT3A	51049	30143	52377	44271	42168
KREMEN1-PYGO1-WNT3A	7864	26771	50128	43544	15239	CTNNBIP1-JUN-WNT3A	24780	5944	45858	50803	13854
DKK1-FGF4-WNT3A	4166	17858	5679	30944	57050	CCND2-WNT1-WNT3A	4465	36473	38095	30987	12981
FBXW2-PYGO1-WNT3A	7391	48320	9248	34651	2524	FZD7-JUN-WNT3A	6578	3907	45657	38691	15081
FBXW11-LRP6-WNT3A	4398	36975	26538	31998	11795	EP300-WNT1-WNT3A	1327	24404	26980	31626	25194
KREMEN1-PORCN-WNT3A	8946	29482	33980	6745	37128	CXXC4-FRAT1-WNT3A	5682	22392	33504	50525	42228
PPP2CA-T-WNT3A	5197	44818	17755	38317	4985	FZD5-WNT1-WNT3A	1830	18724	34025	38182	14214
TCF7L1-WNT1-WNT3A	795	7154	34307	17085	15742	FOSL1-NLK-WNT3A	51755	5242	44005	49978	52983
FOSL1-JUN-WNT3A	37744	27522	48171	53533	24924	BCL9-FGF4-WNT3A	21656	7138	34183	51050	57004
CCND3-FOXN1-WNT3A	1170	42424	49947	36625	9095	TLE2-WIF1-WNT3A	40072	5491	24360	49488	34844
AES-SLC9A3R1-WNT3A	27911	53364	5344	27251	24128	FZD7-NKD1-WNT3A	16651	467	45031	55399	13378
CCND3-FGF4-WNT3A	263	53391	5905	50246	9076	DKK1-PYGO1-WNT3A	1315	30284	30530	24495	19085
FZD5-FGF4-WNT3A	3473	4265	35669	53993	57079	DVL2-FGF4-WNT3A	9868	16034	8886	17654	56545
FBXW4-WNT3A-WNT4	12835	41912	3061	4307	23428	CXXC4-WIF1-WNT3A	11746	12153	2343	56809	35373
FZD6-WNT1-WNT3A	5732	56781	23090	25529	3318	PPP2R1A-WNT3-WNT3A	9441	54192	34392	53766	7535
CTBP1-FGF4-WNT3A	8308	4009	36169	55681	56958	CCND3-SFRP1-WNT3A	9608	51246	2223	54986	19086
BTRC-GSK3A-WNT3A	12858	35286	25253	43232	19671	FZD7-NLK-WNT3A	23365	3018	51679	44843	19133
CCND3-NKD1-WNT3A	19177	14820	26493	56175	64	TCF7L1-WIF1-WNT3A	2909	25918	43790	53902	35000
NKD1-WIF1-WNT3A	48793	3970	17300	56778	21427	KREMEN1-FBXW4-WNT3A	49105	7228	49337	28152	8690
FZD7-T-WNT3A	3884	36637	47776	31821	37282	PITX2-WNT3-WNT3A	36927	41437	49172	9526	14468
CCND1-WIF1-WNT3A	22745	5551	30083	51087	4790	DVL1-FOXN1-WNT3A	4248	43920	50848	47064	9942
FSHB-T-WNT3A	37189	29725	873	25128	8181	FSHB-FZD2-WNT3A	10002	6702	2404	44003	56141
CCND3-FZD2-WNT3A	8329	31657	13384	30632	4736	FZD6-PORCN-WNT3A	75	57089	15014	7701	45470
FBXW11-FOXN1-WNT3A	1436	1677	40456	28639	873	AXIN1-MYC-WNT3A	28398	5982	50308	53667	3744
CTNNB1-FOXN1-WNT3A	15788	5414	49911	40803	23438	BCL9-JUN-WNT3A	34709	926	55356	53174	7223
FOSL1-WNT1-WNT3A	9692	5532	35479	30879	13078	DVL2-FBXW4-WNT3A	40808	8862	52958	56668	7351
DKK1-GSK3A-WNT3A	60	28159	48806	35302	44957	FBXW11-FGF4-WNT3A	8897	26541	9766	20101	47787
LRP5-WNT1-WNT3A	14614	22492	43733	37764	22905	KREMEN1-NKD1-WNT3A	9700	7837	52991	45907	10853
CSNK1D-WNT3-WNT3A	4832	51374	56476	26830	11649	CXXC4-WNT1-WNT3A	1236	41816	5972	30693	33822
CSNK1D-JUN-WNT3A	3991	7790	52423	12387	1862	CCND2-LRP6-WNT3A	8184	44311	52569	51142	13842
KREMEN1-WIF1-WNT3A	38760	4243	33739	39807	7207	KREMEN1-WNT3-WNT3A	13113	51425	51324	32502	6247
CXXC4-FOXN1-WNT3A	2235	1906	54317	41438	43489	CCND3-LRP6-WNT3A	3531	48100	27710	44059	3100
DKK1-FOXN1-WNT3A	1472	17560	29991	26863	22001	CCND3-CSNK1A1-WNT3A	17118	24899	2478	56125	79
DVL2-PYGO1-WNT3A	18087	2223	36690	1889	26351	FRAT1-FBXW4-WNT3A	9047	7060	50667	48783	9181
CCND3-GSK3A-WNT3A	1094	43778	55604	51021	6348	PPP2R1A-WNT1-WNT3A	2644	9345	37570	29489	17577
DKK1-PORCN-WNT3A	3656	53268	6994	22200	48539	FZD5-CCND2-WNT3A	6120	47234	56065	55258	35257
DKK1-FBXW4-WNT3A	12647	753	39108	46782	2266	FZD5-GSK3A-WNT3A	6043	40468	54992	52291	56281
CXXC4-DVL2-WNT3A	5548	8944	24906	33696	42805	FRZB-WNT1-WNT3A	6977	20832	38003	35393	38215
FZD7-WIF1-WNT3A	3521	32340	43606	53450	22727	FRAT1-WIF1-WNT3A	9771	4923	24250	54851	24596
LEF1-PYGO1-WNT3A	7948	34410	45811	27590	17447	PPP2CA-TCF7-WNT3A	36467	12019	36560	49458	39632
KREMEN1-MYC-WNT3A	10637	5567	56637	35572	1429	FBXW11-JUN-WNT3A	12922	7009	24204	32352	1608
CCND3-PYGO1-WNT3A	782	47470	16204	30209	9636	NKD1-WNT2B-WNT3A	50905	55634	51652	46273	6139
CCND3-PITX2-WNT3A	14471	39233	2731	800	1147	CCND3-T-WNT3A	16919	45958	10525	46128	1089
CTBP2-T-WNT3A	2552	43203	27518	36551	13398	SFRP1-WNT3-WNT3A	26158	40876	48765	52296	6149
DIXDC1-JUN-WNT3A	26524	53	54094	51456	1811	CCND3-MYC-WNT3A	4583	44095	29482	55800	1173
KREMEN1-SLC9A3R1-WNT3A	5894	4234	35325	31271	14229	FZD6-GSK3A-WNT3A	8511	55686	50518	43306	37494
FZD7-PYGO1-WNT3A	2200	3030	44689	22869	39525	LRP5-WNT3-WNT3A	31453	12512	52372	44108	34882
CSNK1G1-FOXN1-WNT3A	7916	4786	40233	7694	33821	BTRC-WNT2-WNT3A	31077	52852	5122	22613	1175
CSNK1D-NLK-WNT3A	12770	9632	43802	42949	37641	CSNK1G1-WNT1-WNT3A	10871	47854	9882	20452	14786
BCL9-WNT3-WNT3A	12754	19725	38705	53029	6499	DAAM1-FGF4-WNT3A	2588	48679	1464	46798	25162
CSNK1G1-JUN-WNT3A	8236	643	17222	17109	5337	APC-GSK3A-WNT3A	5761	38390	52609	49492	54574
FOSL1-PORCN-WNT3A	1761	8657	47396	12988	53731	SEN2-WNT1-WNT3A	1571	55369	22016	26046	17241
FBXW11-PYGO1-WNT3A	5958	23716	24819	17645	5707	FOSL1-FRAT1-WNT3A	41058	173	49766	43236	36519

Table 11. Rankings of WNT3A-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002.

RANKING @ t_i USING SOBOL - 2002											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
FZD8-FBXW4-WNT3A	37163	14519	40451	32936	12343	SEN2-FBXW4-WNT3A	32061	15253	50111	35264	22955
DKK1-JUN-WNT3A	51531	12300	46409	53700	3796	AES-AXIN1-WNT3A	7792	24132	1607	25930	54940
DVL2-JUN-WNT3A	35727	49416	40820	44967	1537	TLE1-WIF1-WNT3A	50693	6752	56468	57096	11947
AES-DVL1-WNT3A	25130	20756	22584	26521	48898	CCND1-FGF4-WNT3A	12635	24029	16295	7779	50619
FBXW2-WNT3A-WNT4	645	48140	5748	27685	37510	JUN-PYGO1-WNT3A	1610	17601	24757	13846	37085
CTNNBIP1-WIF1-WNT3A	41974	54167	46904	51223	14244	DAAM1-FBXW4-WNT3A	46983	16004	31724	37539	28514
PPP2CA-WNT1-WNT3A	40524	9682	46210	50633	28358	FZD7-PORCN-WNT3A	20917	23923	24750	6039	49403
FZD7-WNT1-WNT3A	1438	7881	25103	25538	10719	CCND1-PYGO1-WNT3A	39080	19013	56205	51729	13572
TLE1-WNT1-WNT3A	45532	17196	56383	56904	289	CXXC4-FGF4-WNT3A	7493	411	15315	24389	48926
AXIN1-DVL1-WNT3A	17158	2599	23950	24990	26879	SFRP4-WNT1-WNT3A	19672	39835	4609	14591	47471
FBXW11-FBXW4-WNT3A	42391	26218	31369	55873	4622	FRAT1-NLK-WNT3A	21933	31321	12151	6237	52766
KREMEN1-PYGO1-WNT3A	52932	56977	53771	37472	14726	CTNNBIP1-JUN-WNT3A	47078	14611	51686	48296	5008
DKK1-FGF4-WNT3A	3178	11584	22425	8017	10360	CCND2-WNT1-WNT3A	19781	51583	73	4270	44933
FBXW2-PYGO1-WNT3A	52031	31884	46340	31823	2792	FZD7-JUN-WNT3A	1386	53880	25449	20632	45908
FBXW11-LRP6-WNT3A	34355	56789	38495	44740	5646	EP300-WNT1-WNT3A	23045	8793	21877	20602	35795
KREMEN1-PORCN-WNT3A	36088	42706	41171	37942	19003	CXXC4-FRAT1-WNT3A	7869	2751	20454	26029	9961
PPP2CA-T-WNT3A	8306	15391	15440	22058	43691	FZD5-WNT1-WNT3A	46539	42443	44834	49091	30828
TCF7L1-WNT1-WNT3A	47046	10502	49803	53053	33064	FOSL1-NLK-WNT3A	43309	33771	50006	38500	4467
FOSL1-JUN-WNT3A	10579	5753	10670	19639	21636	BCL9-FGF4-WNT3A	48960	21173	56013	55763	6132
CCND3-FOXN1-WNT3A	53912	11334	52192	32549	47236	TLE2-WIF1-WNT3A	33475	13433	36234	29978	9382
AES-SLC9A3R1-WNT3A	25865	22510	7109	28361	27321	FZD7-NKD1-WNT3A	56393	1785	42882	38968	851
CCND3-FGF4-WNT3A	2964	34278	17730	11836	49760	DKK1-PYGO1-WNT3A	49429	22863	28934	47297	24196
FZD5-FGF4-WNT3A	4616	7975	9759	18730	22965	DVL2-FGF4-WNT3A	28299	7239	25133	17514	55735
FBXW4-WNT3A-WNT4	17016	30005	5680	6177	53510	CXXC4-WIF1-WNT3A	54553	44801	48557	52030	1570
FZD6-WNT1-WNT3A	56029	34810	37658	39310	933	PPP2R1A-WNT3-WNT3A	36443	18940	41310	53135	2959
CTBP1-FGF4-WNT3A	8200	460	13684	26877	18621	CCND3-SFRP1-WNT3A	14356	25266	26873	23467	26717
BTRC-GSK3A-WNT3A	5197	2769	4826	638	44313	FZD7-NLK-WNT3A	56722	52305	45867	39848	966
CCND3-NKD1-WNT3A	17921	19886	26294	22858	34282	TCF7L1-WIF1-WNT3A	50706	10131	45130	48883	856
NKD1-WIF1-WNT3A	37352	21808	33337	55217	6162	KREMEN1-FBXW4-WNT3A	45167	47280	56590	48968	2663
FZD7-T-WNT3A	57116	45706	31412	38082	48517	PITX2-WNT3-WNT3A	1072	29636	4611	11649	49643
CCND1-WIF1-WNT3A	30286	43921	47521	55757	2241	DVL1-FOXN1-WNT3A	47581	4764	35882	37697	32002
FSHB-T-WNT3A	38613	13069	34339	29636	16201	FSHB-FZD2-WNT3A	39818	41432	46903	36007	7232
CCND3-FZD2-WNT3A	21930	38957	21806	22322	45824	FZD6-PORCN-WNT3A	56095	49583	38183	45187	10584
FBXW11-FOXN1-WNT3A	37771	37458	34204	47681	8870	AXIN1-MYC-WNT3A	55143	55018	52203	52922	5932
CTNNB1-FOXN1-WNT3A	14432	17654	10067	1699	34508	BCL9-JUN-WNT3A	1664	30352	8333	8059	41645
FOSL1-WNT1-WNT3A	15630	39992	11099	5546	48850	DVL2-FBXW4-WNT3A	14577	48454	4103	4489	48405
DKK1-GSK3A-WNT3A	4570	55680	19251	18539	47694	FBXW11-FGF4-WNT3A	22277	1832	26256	5894	41316
LRP5-WNT1-WNT3A	51115	46900	55604	39495	9121	KREMEN1-NKD1-WNT3A	3850	55089	612	11917	55918
CSNK1D-WNT3-WNT3A	36262	46174	50463	43303	12247	CXXC4-WNT1-WNT3A	46602	51045	38468	51607	4562
CSNK1D-JUN-WNT3A	41685	14518	29055	33675	22133	CCND2-LRP6-WNT3A	4596	45720	404	249	56846
KREMEN1-WIF1-WNT3A	36608	31863	33558	56397	51574	KREMEN1-WNT3-WNT3A	46697	24784	33813	55605	41537
CXXC4-FOXN1-WNT3A	51263	50390	30984	42574	46666	CCND3-LRP6-WNT3A	34677	8954	29468	44307	23310
DKK1-FOXN1-WNT3A	50685	32463	50243	48254	12211	CCND3-CSNK1A1-WNT3A	2952	56510	305	26398	49052
DVL2-PYGO1-WNT3A	35451	32587	46161	49351	14826	FRAT1-FBXW4-WNT3A	42074	26045	31970	33331	9797
CCND3-GSK3A-WNT3A	24268	44070	28374	18849	40260	PPP2R1A-WNT1-WNT3A	44486	25983	55160	38768	876
DKK1-PORCN-WNT3A	50877	8870	41126	42802	14055	FZD5-CCND2-WNT3A	44151	8669	39209	29947	3499
DKK1-FBXW4-WNT3A	43840	46055	39740	42266	18236	FZD5-GSK3A-WNT3A	4921	4098	4925	5427	49194
CXXC4-DVL2-WNT3A	17336	51748	14847	23229	36228	FRZB-WNT1-WNT3A	47750	57036	42232	37002	55623
FZD7-WIF1-WNT3A	462	1898	24495	17586	7553	FRAT1-WIF1-WNT3A	38203	56268	35949	38506	8834
LEF1-PYGO1-WNT3A	40621	17131	45161	29919	31440	PPP2CA-TCF7-WNT3A	53743	13986	53761	54445	6921
KREMEN1-MYC-WNT3A	53432	44377	45039	45412	2524	FBXW11-JUN-WNT3A	29118	54401	45309	57041	2430
CCND3-PYGO1-WNT3A	51433	27320	30354	36390	39641	NKD1-WNT2B-WNT3A	4519	50837	9924	21240	36721
CCND3-PITX2-WNT3A	34394	29164	30661	48295	16862	CCND3-T-WNT3A	20183	39370	25828	26415	52435
CTBP2-T-WNT3A	15847	17322	7068	4880	31616	SFRP1-WNT3-WNT3A	44625	19927	40999	39830	7659
DIXDC1-JUN-WNT3A	642	31777	12679	15634	45593	CCND3-MYC-WNT3A	36632	24224	28942	30557	27130
KREMEN1-SLC9A3R1-WNT3A	7391	2325	5102	8894	56781	FZD6-GSK3A-WNT3A	26209	37042	19572	17832	42767
FZD7-PYGO1-WNT3A	1165	50482	26897	25768	53340	LRP5-WNT3-WNT3A	50760	41203	55018	45994	3924
CSNK1G1-FOXN1-WNT3A	18175	14967	2698	926	50456	BTRC-WNT2-WNT3A	7977	19933	27864	6975	11980
CSNK1D-NLK-WNT3A	15647	31281	25207	25693	26652	CSNK1G1-WNT1-WNT3A	10811	5687	16886	21507	41231
BCL9-WNT3-WNT3A	5547	41916	2456	22916	32645	DAAM1-FGF4-WNT3A	20174	3824	15389	9232	44937
CSNK1G1-JUN-WNT3A	23983	11639	7142	6023	49316	APC-GSK3A-WNT3A	9483	20303	24414	16874	26548
FOSL1-PORCN-WNT3A	9807	26119	20412	9520	38142	SEN2-WNT1-WNT3A	34690	19702	55187	53391	16705
FBXW11-PYGO1-WNT3A	39947	53781	36004	52889	15695	FOSL1-FRAT1-WNT3A	46128	6025	54699	53346	1957

Table 12. Rankings of WNT3A-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez.

RANKING @ t _i USING SOBOL - MARTINEZ												
3rd order comb.	t ₁	t ₃	t ₆	t ₁₂	t ₂₄	3rd order comb.	t ₁	t ₃	t ₆	t ₁₂	t ₂₄	
FZD8-FBXW4-WNT3A	7056	31842	46739	40238	36501	SENP2-FBXW4-WNT3A	16928	95	53827	44450	47650	
DKK1-JUN-WNT3A	8769	37818	1990	21743	36662	AES-AXIN1-WNT3A	15056	5283	10347	52124	50110	
DVL2-JUN-WNT3A	48177	29325	2623	32807	56119	TLE1-WIF1-WNT3A	54823	52	43313	24834	36086	
AES-DVL1-WNT3A	18127	17367	7052	33366	29321	CCND1-FGF4-WNT3A	24534	56753	10107	10064	31195	
FBXW2-WNT3A-WNT4	6270	53231	8071	37859	6097	JUN-PYGO1-WNT3A	8462	12690	54986	11759	6706	
CTNNBIP1-WIF1-WNT3A	53630	42083	719	36277	23420	DAAM1-FBXW4-WNT3A	43505	31829	4759	12231	34937	
PPP2CA-WNT1-WNT3A	51242	1279	28051	1456	15170	FZD7-PORCN-WNT3A	601	7936	6391	14753	43442	
FZD7-WNT1-WNT3A	4926	33896	22789	22507	2977	CCND1-PYGO1-WNT3A	37702	16739	21907	35980	8685	
TLE1-WNT1-WNT3A	44592	1282	36683	33143	36702	CXXC4-FGF4-WNT3A	10179	2559	53194	27467	11706	
AXIN1-DVL1-WNT3A	14409	55064	39765	11792	2235	SFRP4-WNT1-WNT3A	48735	26194	4852	2971	25528	
FBXW11-FBXW4-WNT3A	46644	43402	40481	41505	18213	FRAT1-NLK-WNT3A	39223	41587	3411	8849	50359	
KREMEN1-PYGO1-WNT3A	30698	50067	9324	3950	37622	CTNNBIP1-JUN-WNT3A	56225	30611	13354	42578	38675	
DKK1-FGF4-WNT3A	38951	18571	8036	23562	36040	CCND2-WNT1-WNT3A	38052	26165	56279	42744	11694	
FBXW2-PYGO1-WNT3A	12666	21939	42752	33609	33918	FZD7-JUN-WNT3A	2485	10637	49466	56154	32099	
FBXW11-LRP6-WNT3A	47024	25495	14415	41987	42918	EP300-WNT1-WNT3A	35049	51879	24918	13081	9432	
KREMEN1-PORCN-WNT3A	5432	49056	32287	41650	15766	CXXC4-FRAT1-WNT3A	36507	46562	51863	10238	16814	
PPP2CA-T-WNT3A	21205	15120	48258	46762	44219	FZD5-WNT1-WNT3A	39449	21065	43152	2693	25098	
TCF7L1-WNT1-WNT3A	43995	1480	24915	310	42232	FOSL1-NLK-WNT3A	14627	8003	43826	49427	54343	
FOSL1-JUN-WNT3A	50101	9229	37322	47023	17545	BCL9-FGF4-WNT3A	31619	40699	44336	20997	15869	
CCND3-FOXN1-WNT3A	50053	45004	31016	1520	12027	TLE2-WIF1-WNT3A	30043	1060	49500	49207	34907	
AES-SLC9A3R1-WNT3A	35103	11272	35582	44847	511	FZD7-NKD1-WNT3A	55002	31493	37129	54525	25394	
CCND3-FGF4-WNT3A	47238	8745	57087	20189	23245	DKK1-PYGO1-WNT3A	8005	22192	47473	28811	30935	
FZD5-FGF4-WNT3A	35834	31214	55640	55595	48928	DVL2-FGF4-WNT3A	3244	49248	45177	22542	44953	
FBXW4-WNT3A-WNT4	17207	4496	54748	47713	9359	CXXC4-WIF1-WNT3A	52245	44345	37185	10089	25395	
FZD6-WNT1-WNT3A	36284	56172	25948	12051	29929	PPP2R1A-WNT3-WNT3A	23525	2536	27665	46568	52987	
CTBP1-FGF4-WNT3A	14617	27725	34149	29830	49970	CCND3-SFRP1-WNT3A	31217	11519	24926	33838	1219	
BTRC-GSK3A-WNT3A	2575	13354	10047	4920	37543	FZD7-NLK-WNT3A	56916	32082	34420	55311	39594	
CCND3-NKD1-WNT3A	28743	22048	30991	7266	33090	TCF7L1-WIF1-WNT3A	25144	47879	2878	6546	54575	
NKD1-WIF1-WNT3A	37743	54707	30419	4236	24113	KREMEN1-FBXW4-WNT3A	8418	46509	36118	39983	9062	
FZD7-T-WNT3A	56831	34653	1481	35573	32001	PITX2-WNT3-WNT3A	27307	12715	32115	33802	9431	
CCND1-WIF1-WNT3A	9447	44577	2811	36770	20781	DVL1-FOXN1-WNT3A	9700	3070	20612	38587	40675	
FSHB-T-WNT3A	43678	43564	11912	21619	8516	FSHB-FZD2-WNT3A	30517	55741	54	3890	8435	
CCND3-FZD2-WNT3A	19066	50273	13095	30891	8586	FZD6-PORCN-WNT3A	41626	8812	22868	9411	30030	
FBXW11-FOXN1-WNT3A	50107	43006	674	2226	51894	AXIN1-MYC-WNT3A	55509	54145	33050	21592	28724	
CTNNB1-FOXN1-WNT3A	29714	13205	18603	30325	36637	BCL9-JUN-WNT3A	20867	49964	56086	28204	902	
FOSL1-WNT1-WNT3A	14387	17574	45609	36527	7338	FOSL1-FBXW4-WNT3A	49578	2041	33911	51137	47259	
DKK1-GSK3A-WNT3A	16553	5928	12331	29149	25073	FBXW11-FGF4-WNT3A	36175	21078	38299	4053	1712	
LRP5-WNT1-WNT3A	33593	55868	17391	9767	11455	KREMEN1-NKD1-WNT3A	47109	46468	16075	12688	6199	
CSNK1D-WNT3-WNT3A	11520	29889	44430	29706	9625	CXXC4-WNT1-WNT3A	47935	18433	28000	8963	43231	
CSNK1D-JUN-WNT3A	49779	33157	919	18538	52334	CCND2-LRP6-WNT3A	42816	24556	1873	50134	35053	
KREMEN1-WIF1-WNT3A	6067	35361	30834	25461	23532	KREMEN1-WNT3-WNT3A	19008	54560	37296	5287	22527	
CXXC4-FOXN1-WNT3A	50619	41748	8631	29304	47291	CCND3-LRP6-WNT3A	37887	24264	2429	9732	37143	
DKK1-FOXN1-WNT3A	19453	38040	4327	31689	25200	CCND3-CSNK1A1-WNT3A	27407	21026	33109	36618	45870	
DVL2-PYGO1-WNT3A	43701	24035	15691	38022	9753	FRAT1-FBXW4-WNT3A	43009	48789	21342	24484	14792	
CCND3-GSK3A-WNT3A	4963	22340	38422	23675	37620	PPP2R1A-WNT1-WNT3A	43905	2516	24424	44521	46746	
DKK1-PORCN-WNT3A	34106	307	37594	26694	44252	FZD5-CCND2-WNT3A	16479	45535	26663	18173	11136	
DKK1-FBXW4-WNT3A	7254	29039	37142	25000	45687	FZD5-GSK3A-WNT3A	11566	32215	4809	28259	41770	
CXXC4-DVL2-WNT3A	4375	4525	24217	56901	55168	FRZB-WNT1-WNT3A	51243	19304	7397	21580	29759	
FZD7-WIF1-WNT3A	28792	30157	25705	48713	7016	FRAT1-WIF1-WNT3A	41904	51607	5191	8446	11262	
LEF1-PYGO1-WNT3A	5198	45927	54006	20564	20342	PPP2CA-TCF7-WNT3A	33451	27979	41924	1311	22611	
KREMEN1-MYC-WNT3A	25654	54231	30951	12063	16864	FBXW11-JUN-WNT3A	28102	9545	33676	14440	51300	
CCND3-PYGO1-WNT3A	54519	5890	27106	31847	16248	NKD1-WNT2B-WNT3A	22521	5424	29294	6657	45978	
CCND3-PITX2-WNT3A	34871	51188	18237	3845	52805	CCND3-T-WNT3A	11540	3687	49789	37682	39913	
CTBP2-T-WNT3A	39058	14172	22811	5445	35324	SFRP1-WNT3-WNT3A	42574	1365	38582	55618	42196	
DIXDC1-JUN-WNT3A	10815	54602	4233	32407	48637	CCND3-MYC-WNT3A	53240	25317	3867	34661	38919	
KREMEN1-SLC9A3R1-WNT3A	42884	32211	8455	56502	6413	FZD6-GSK3A-WNT3A	9091	40387	20507	10546	40929	
FZD7-PYGO1-WNT3A	9804	27532	53059	23345	3373	LRP5-WNT3-WNT3A	26835	52022	38473	102	8681	
CSNK1G1-FOXN1-WNT3A	8675	49134	21528	19393	15926	BTRC-WNT2-WNT3A	8706	18897	11483	4932	41262	
CSNK1D-NLK-WNT3A	30261	5484	6297	36145	38245	CSNK1G1-WNT1-WNT3A	7756	30860	56406	56754	31743	
BCL9-WNT3-WNT3A	1348	9717	40736	4967	38777	DAAM1-FGF4-WNT3A	1399	4636	21921	48704	14968	
CSNK1G1-JUN-WNT3A	3805	47832	41036	7286	26921	APC-GSK3A-WNT3A	16962	15255	18163	45566	11345	
FOSL1-PORCN-WNT3A	49724	53367	21610	17015	8003	SENP2-WNT1-WNT3A	47421	6035	39529	13763	43324	
FBXW11-PYGO1-WNT3A	50959	38129	6742	53728	35651	FOSL1-FRAT1-WNT3A	11698	1119	38201	37206	48568	

7.5.1. Examining the Behaviour of JUN-WNT3A-X Combinations

Sato et al. [51] found that the expression levels of AXIN2 and c-JUN activated by WNT3A stimulation in HEK293T cells were also inhibited in the presence of STOCKS2S-26016 (inhibitors of the WNK signalling pathway as reported in Mori et al. [52]). Looking at the tables above, one finds the following combinations for JUN along with WNT3A, to be prominent at 3rd order level - DKK1-JUN-WNT3A, DVL2-JUN-WNT3A, FOSL1-JUN-WNT3A, CSNK1D-JUN-WNT3A, DIXDC1-JUN-WNT3A, CSNK1G1-JUN-WNT3A, JUN-PYGO1-WNT3A, CTNNBIP1-JUN-WNT3A, FZD7-JUN-WNT3A, BCL9-JUN-WNT3A and FBXW11-JUN-WNT3A. Additionally, one also finds the following combinations for AXIN1 along with WNT3A, to be prominent at 3rd order level - AXIN1-DVL1-WNT3A, AES-AXIN1-

WNT3A and AXIN1-MYC-WNT3A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.5.2. Examining the Behaviour of DVL-WNT3A-X Combinations

Zhan et al. [53] state that the WNT canonical pathway is activated upon binding of secreted WNT ligands (for example, WNT3A and WNT1) to FZD receptors and LRP co-receptors. LRP receptors are then phosphorylated by CK1 α and GSK3 β , which recruits Dishevelled (DVL) proteins to the plasma membrane where they polymerize and are activated as observed in Metcalfe et al. [54]. Looking at the tables above, one finds the following combinations for members of DVL family along with WNT3A, to be prominent at 3rd order level - DVL2-JUN-WNT3A, AES-DVL1-WNT3A, AXIN1-DVL1-WNT3A, DVL2-PYGO1-WNT3A, CXXC4-DVL2-WNT3A, DVL2-FGF4-WNT3A and DVL1-FOXN1-WNT3A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.5.3. Examining the Behaviour of TCF-WNT3A-X Combinations

The TCF/Lef family of transcription factors utilise β -catenin as a transcriptional co-activator, and instigate target gene expression in WNT signaling pathway. In order to assess whether a list of 90 differentially expressed genes (DEGs) had been previously identified as direct targets of β -catenin/TCF-/Lef in other cell types, Szemes et al. [55] compared the gene list with published target genes of canonical WNT signalling, based on using ChIPseq in U87 glioma cells in Zhang et al. [56], HEK293, and the colorectal cancer cell line LS174T in Schuijers et al. [57]. 53 out of the 90 DEGs were identified as having β -catenin and/or TCF7L2/TCF4 bound to their promoters in one or more of these three data sets. Looking at the tables above, one finds the following combinations for members of TCF family along with WNT3A, to be prominent at 3rd order level - TCF7L1-WNT1-WNT3A, TCF7L1-WIF1-WNT3A and PPP2CA-TCF7-WNT3A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.5.4. Examining the Behaviour of FZD / LRP / CCND / FOSL1 / PITX2 -WNT3A-X Combinations

Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative disease characterized by progressive degeneration of the motor neurons in the cortex, brainstem, and spinal cord. Yu et al. [58] identified differentially regulated WNT signaling molecules by comparing the transcription profiles of spinal cord from ALS and wild-type mice at different stages. Among the different WNT molecules, WNT3A was found to be up-regulated at 95 days. Frizzled receptors including FZD1 to FZD8 and coreceptor LRP5 were all up-regulated at 122 days. In this study, they found that CCND-1/2/3, FOSL1 and PITX2, target genes of canonical WNT signaling pathway, were upregulated in the spinal cord of ALS mice at the end stage. Looking at the tables above, one finds the following combinations for members of • FZD family along with WNT3A, to be prominent at 3rd order level - FZD8-FBXW4-WNT3A, FZD7-WNT1-WNT3A, FZD5-FGF4-WNT3A, FZD6-WNT1-WNT3A, FZD7-T-WNT3A, CCND3-FZD2-WNT3A, FZD7-WIF1-WNT3A, FZD7-PYGO1-WNT3A, FZD7-PORCN-WNT3A, FZD7-JUN-WNT3A, FZD5-WNT1-WNT3A, FZD7-NKD1-WNT3A, FZD7-NLK-WNT3A, FSHB-FZD2-WNT3A, FZD6-PORCN-WNT3A, FZD5-CCND2-WNT3A, FZD5-GSK3A-WNT3A and FZD6-GSK3A-WNT3A;

- LRP family along with WNT3A, to be prominent at 3rd order level - FBXW11-LRP6-WNT3A, LRP5-WNT1-WNT3A, CCND2-LRP6-WNT3A, CCND3-LRP6-WNT3A and LRP5-WNT3-WNT3A;

- CCND family along with WNT3A, to be prominent at 3rd order level - CCND3-FOXN1-WNT3A, CCND3-FGF4-WNT3A, CCND3-NKD1-WNT3A, CCND1-WIF1-WNT3A, CCND3-FZD2-WNT3A, CCND3-GSK3A-WNT3A, CCND3-PYGO1-WNT3A, CCND3-PITX2-WNT3A, CCND1-FGF4-WNT3A, CCND1-PYGO1-WNT3A, CCND2-WNT1-WNT3A, CCND3-SFRP1-WNT3A, CCND2-LRP6-WNT3A, CCND3-LRP6-WNT3A, CCND3-CSNK1A1-WNT3A, FZD5-CCND2-WNT3A, CCND3-T-WNT3A and CCND3-MYC-WNT3A;

- FOSL1 along with WNT3A, to be prominent at 3rd order level - FOSL1-JUN-WNT3A, FOSL1-WNT1-WNT3A, FOSL1-PORCN-WNT3A, FOSL1-NLK-WNT3A, FOSL1-FBXW4-WNT3A and FOSL1-FRAT1-WNT3A;

• PITX2 along with WNT3A, to be prominent at 3rd order level - CCND3-PITX2-WNT3A and PITX2-WNT3-WNT3A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.6. Conserved Machine Learning Rankings for Tested WNT4-X-X Combinations

A total of 2415, 3rd order combinations involving WNT4 were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 14, 15 and 16 show the rankings for the same combinations as in table 13, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

Table 13. Rankings of WNT4-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear.

RANKING @ t_i USING HSIC - LINEAR												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CXXC4-PORCN-WNT4	49	6186	19448	20672	51388	FZD5-JUN-WNT4	79	8704	42294	52216	15657	
CCND3-PORCN-WNT4	91	42809	21302	8841	38191	CSNK1D-FGF4-WNT4	98	6482	43663	41124	12062	
LRP5-NLK-WNT4	173	5427	19931	576	56700	PITX2-PORCN-WNT4	177	16891	32175	32123	27627	
FSHB-FZD2-WNT4	180	18252	43713	35344	29882	AXIN1-WNT1-WNT4	201	580	3510	9905	54684	
DVL2-JUN-WNT4	203	51324	39998	14159	3459	FZD7-PORCN-WNT4	242	40498	12752	9577	22443	
DVL1-EP300-WNT4	272	18110	37869	41167	44769	FSHB-T-WNT4	285	39661	52682	15922	9372	
APC-PORCN-WNT4	310	33562	14239	15555	28291	DKK1-JUN-WNT4	316	926	46570	28834	28365	
CSNK1G1-NLK-WNT4	321	20710	3312	50831	31403	CCND2-WNT1-WNT4	361	1435	7615	22032	3874	
FOSL1-FRAT1-WNT4	372	34237	49971	11736	48629	FOSL1-NLK-WNT4	378	3397	2566	2260	40025	
FZD6-PORCN-WNT4	394	39861	46523	785	6046	CTBP2-CTNNB1-WNT4	396	52514	33751	11681	23262	
CSNK2A1-MYC-WNT4	398	40617	54219	12588	16421	CCND1-WIF1-WNT4	439	23377	41096	38262	34292	
FOSL1-PORCN-WNT4	455	37570	20729	10105	38487	CXXC4-NLK-WNT4	491	167	4767	2069	15953	
FBXW2-PORCN-WNT4	531	21565	4445	36629	31422	FBXW2-WNT3A-WNT4	532	33676	31112	1276	53531	
FRAT1-NLK-WNT4	534	1131	4271	13789	39755	DAAM1-FBXW4-WNT4	549	34728	19596	34657	49060	
APC-PITX2-WNT4	634	38339	50192	23301	18227	CCND2-LRP6-WNT4	644	11567	19405	22272	4341	
FZD5-PORCN-WNT4	646	40380	25866	12816	56710	TCF7L1-WNT1-WNT4	655	2370	4483	13462	55477	
TLE1-WNT1-WNT4	667	32528	3738	7043	51569	DIXDC1-PORCN-WNT4	690	39847	12582	10499	56262	
KREMEN1-PORCN-WNT4	693	6753	23243	1864	44869	DKK1-PORCN-WNT4	724	36114	54617	3866	55268	
FZD5-WNT1-WNT4	761	4701	2943	19535	17810	FBXW11-FBXW4-WNT4	765	28721	5152	19772	46420	
CSNK1A1-FBXW4-WNT4	789	26748	5104	45626	10949	FBXW2-JUN-WNT4	806	26430	56620	37987	55952	
DKK1-FGF4-WNT4	819	18185	27937	20093	36539	FBXW2-WNT1-WNT4	837	13006	10579	22224	30630	
SEN2-WNT1-WNT4	879	37625	2401	4412	29111	FBXW2-PYGO1-WNT4	880	37565	28874	6673	56916	
DKK1-WNT1-WNT4	937	35081	20751	8986	41364	SEN2-FBXW4-WNT4	962	28442	9419	12651	42095	
FBXW2-FGF4-WNT4	1113	26433	56296	28240	20430	TLE1-WIF1-WNT4	1157	30379	12684	11265	1014	
CCND1-FGF4-WNT4	1178	54535	37077	23589	34951	RHO-WNT1-WNT4	1198	602	1780	21941	43967	
DVL1-WNT1-WNT4	1231	29200	3177	8357	51345	DIXDC1-WNT3-WNT4	1279	51438	14477	19803	17251	
KREMEN1-WNT1-WNT4	1280	5994	3234	2746	2189	BTRC-FOXN1-WNT4	1304	7824	14183	18230	50189	
PPP2R1A-WNT1-WNT4	1345	13482	18287	10132	56367	FBXW11-FOXN1-WNT4	1404	854	7156	11739	28714	
LRP6-SC9A3R1-WNT4	1405	13327	19284	40124	55720	FZD8-PORCN-WNT4	1416	27491	15836	9789	36903	
FBXW11-PORCN-WNT4	1417	38911	18306	23726	35310	FBXW11-WNT1-WNT4	1484	28114	9144	7266	48038	
DIXDC1-NKD1-WNT4	1536	13509	3143	4994	28564	FRZB-WNT1-WNT4	1551	27936	3165	17377	26548	
DIXDC1-FZD2-WNT4	1576	35367	3250	12254	41951	CTNNBIP1-JUN-WNT4	1605	6379	54822	28948	10594	
BTRC-PPP2CA-WNT4	1638	35087	32587	22025	51750	PPP2CA-WNT1-WNT4	1668	20515	14866	23920	21265	
FZD5-FOXN1-WNT4	1669	270	8162	13262	25359	FBXW4-WNT3A-WNT4	1716	50053	13154	14680	40891	
NLK-PORCN-WNT4	1742	49908	50644	30880	6042	CXXC4-FGF4-WNT4	1747	5857	34419	49599	54246	
FRZB-PORCN-WNT4	1770	28522	21808	15299	35164	CTBP1-PYGO1-WNT4	1792	40412	9281	9970	26271	
DAAM1-FOXN1-WNT4	1844	38681	28928	7957	40811	FZD6-WNT1-WNT4	1853	43209	40276	6172	38442	
AES-WNT1-WNT4	1876	46650	9370	48199	39204	FZD5-CTNNBIP1-WNT4	1879	27376	31789	10709	11495	
FZD8-FBXW4-WNT4	1891	19368	8364	46765	38967	GSK3B-PORCN-WNT4	1893	29701	28162	8296	19073	
CSNK1G1-FZD2-WNT4	1942	1607	11956	46269	29169	APC-FZD6-WNT4	1977	32504	20425	49267	54999	
FRAT1-PORCN-WNT4	1985	2835	18017	16053	23730	APC-WNT1-WNT4	2022	10916	5447	12675	23929	
FGF4-NLK-WNT4	2033	3044	4724	33423	28154	FBXW2-FOXN1-WNT4	2046	1696	16595	16816	51258	
DIXDC1-FOXN1-WNT4	2069	18260	5558	10405	1210	FSHB-LEF1-WNT4	2075	48049	40576	21210	20847	
DIXDC1-LRP5-WNT4	2098	56736	1699	4505	8233	BCL9-FGF4-WNT4	2106	2510	45259	52055	40966	
SFRP4-WNT1-WNT4	2127	95	2835	6120	22533	DIXDC1-NLK-WNT4	2128	13920	3978	2846	15403	
DIXDC1-WNT1-WNT4	2134	8527	1926	11050	9192	DIXDC1-GSK3A-WNT4	2177	45494	1826	20781	48238	
TCF7L1-WIF1-WNT4	2218	10007	38673	37345	36797	LRP5-WNT1-WNT4	2229	1395	5749	39655	44313	
DVL1-JUN-WNT4	2301	47974	51855	14133	54580	FBXW11-JUN-WNT4	2347	31775	43178	32762	53196	
CTBP1-FOXN1-WNT4	2367	462	7335	11158	57077	CCND1-CTNNBIP1-WNT4	2383	54600	49609	27061	54370	
DAAM1-FZD8-WNT4	2390	46444	31977	2001	38168	PPP2R1A-WNT3-WNT4	2411	43365	6520	45456	48427	
CSNK2A1-CTNNB1-WNT4	2414	44132	33116	25592	4111	FRZB-GSK3A-WNT4	2431	25702	4279	5062	13670	
SFRP4-T-WNT4	2447	3345	9321	27672	38136	DVL2-FZD1-WNT4	2449	52236	54182	3759	6336	
RHO-SC9A3R1-WNT4	2468	14726	19963	23342	24539	FRZB-NLK-WNT4	2520	1556	5592	7221	22356	
CSNK1G1-WIF1-WNT4	2582	628	24563	33380	53761	FOSL1-WNT1-WNT4	2598	5807	2371	11336	21308	
FBXW11-FGF4-WNT4	2617	29162	50590	39482	9423	FZD5-NKD1-WNT4	2642	3099	2732	32040	47167	
RHO-SFRP1-WNT4	2662	39129	39941	42257	16102	CXXC4-JUN-WNT4	2688	13375	46722	2824	3108	
DVL1-MYC-WNT4	2694	44421	6906	30604	49682	BTRC-CCND3-WNT4	2710	41552	34711	18962	45323	
APC-FZD2-WNT4	2724	12296	23481	31460	50621	CSNK1D-NLK-WNT4	2750	2726	9906	45186	25621	
CTBP1-FRAT1-WNT4	2821	37523	56525	1417	51685	DIXDC1-SFRP1-WNT4	2827	56975	50212	3166	44324	
FBXW2-WIF1-WNT4	2836	2416	50951	26493	30178	DVL2-FGF4-WNT4	2852	47290	41994	24840	42923	
LEF1-WNT1-WNT4	2885	69	3884	19634	31692	PPP2R1A-TLE1-WNT4	2902	4217	52852	23987	31073	
FOSL1-FOXN1-WNT4	2926	19268	4984	7030	42733	CSNK1G1-JUN-WNT4	2974	622	48857	6464	4596	
FZD5-PYGO1-WNT4	2980	4229	8238	13260	24709	NKD1-WIF1-WNT4	2997	2461	45561	55000	34857	

Table 14. Rankings of WNT4-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf.

RANKING @ t_i USING HSIC - RBF											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CXXC4-PORCN-WNT4	12492	2278	24920	46755	55842	FZD5-JUN-WNT4	28544	6905	45357	25315	15393
CCND3-PORCN-WNT4	32692	49112	4162	52578	21791	CSNK1D-FGF4-WNT4	2044	17655	11902	17351	48590
LRP5-NLK-WNT4	34513	16387	35220	5468	37281	PITX2-PORCN-WNT4	9247	2492	36647	13332	52478
FSHB-FZD2-WNT4	6816	11813	3438	4079	43595	AXIN1-WNT1-WNT4	20694	6087	43073	4	31972
DVL2-JUN-WNT4	21779	49475	22727	20132	5205	FZD7-PORCN-WNT4	13920	49151	38523	48943	22793
DVL1-EP300-WNT4	44214	8987	34040	43683	919	FSHB-T-WNT4	34987	32997	6654	22504	22222
APC-PORCN-WNT4	3592	12533	35169	40131	56018	DKK1-JUN-WNT4	8806	34	14859	3085	9371
CSNK1G1-NLK-WNT4	37117	32429	26444	1650	27288	CCND2-WNT1-WNT4	2977	14277	27528	561	23008
FOSL1-FRAT1-WNT4	29015	37923	40684	6763	23547	FOSL1-NLK-WNT4	46914	7268	50547	1274	44200
FZD6-PORCN-WNT4	49	30454	13795	53236	50505	CTBP2-CTNNB1-WNT4	18111	52326	3249	37949	49979
CSNK2A1-MYC-WNT4	4376	38940	46395	33447	19179	CCND1-WIF1-WNT4	29821	25068	12712	33994	6600
FOSL1-PORCN-WNT4	1429	25705	30547	51837	52319	CXXC4-NLK-WNT4	22955	3089	37410	121	47163
FBXW2-PORCN-WNT4	26557	1122	13989	31473	19951	FBXW2-WNT3A-WNT4	41397	25061	14067	24192	5301
FRAT1-NLK-WNT4	32436	4345	56234	697	36071	DAAM1-FBXW4-WNT4	16555	49037	31781	12281	4527
APC-PITX2-WNT4	6441	34135	28508	16023	43494	CCND2-LRP6-WNT4	4422	3548	30464	14515	38111
FZD5-PORCN-WNT4	21655	38004	30699	16505	55082	TCF7L1-WNT1-WNT4	2999	2222	48449	1665	32919
TLE1-WNT1-WNT4	11603	13045	36391	33	21812	DIXDC1-PORCN-WNT4	25202	25146	26100	53862	33842
KREMEN1-PORCN-WNT4	4572	591	18551	4045	46258	DKK1-PORCN-WNT4	9761	29610	8470	23618	51513
FZD5-WNT1-WNT4	953	2772	39511	2938	32504	FBXW11-FBXW4-WNT4	5686	23921	16351	38242	5248
CSNK1A1-FBXW4-WNT4	40830	22049	52381	8977	9106	FBXW2-JUN-WNT4	49067	9843	17416	10298	1111
DKK1-FGF4-WNT4	961	9858	8764	7787	53958	FBXW2-WNT1-WNT4	11293	2661	26185	11977	4635
SEN2-WNT1-WNT4	595	42309	31627	659	12885	FBXW2-PYGO1-WNT4	7669	38818	19627	43015	3643
DKK1-WNT1-WNT4	3280	26528	35802	8296	26214	SEN2-FBXW4-WNT4	7957	13325	39354	38785	4122
FBXW2-FGF4-WNT4	1543	18666	8503	7844	19295	TLE1-WIF1-WNT4	40180	37225	30537	13365	9063
CCND1-FGF4-WNT4	18589	53668	21926	37718	3049	RHO-WNT1-WNT4	751	1923	30562	18071	6917
DVL1-WNT1-WNT4	6554	24157	44308	144	3395	DIXDC1-WNT3-WNT4	23687	55063	42305	53552	6689
KREMEN1-WNT1-WNT4	2412	6480	36977	30144	18633	BTRC-FOXN1-WNT4	5283	22892	41659	11506	604
PPP2R1A-WNT1-WNT4	13056	3776	48355	444	25289	FBXW11-FOXN1-WNT4	740	5464	41361	27962	1025
LRP6-SLC9A3R1-WNT4	38478	36365	36922	14399	11194	FZD8-PORCN-WNT4	3177	7307	28634	31520	31714
FBXW11-PORCN-WNT4	6702	42970	13553	51464	33227	FBXW11-WNT1-WNT4	981	22983	17188	12039	8862
DIXDC1-NKD1-WNT4	28297	20930	51455	19765	821	FRZB-WNT1-WNT4	2247	16822	45170	603	48278
DIXDC1-FZD2-WNT4	16200	33727	42194	2888	3723	CTNNBIP1-JUN-WNT4	39260	388	36889	17634	53412
BTRC-PPP2CA-WNT4	13782	33555	41012	5416	5243	PPP2CA-WNT1-WNT4	1316	18383	42717	1659	16550
FZD5-FOXN1-WNT4	2386	974	55938	4772	34091	FBXW4-WNT3A-WNT4	12835	41912	3061	4307	23428
NLK-PORCN-WNT4	33383	45823	7542	34942	49961	CXXC4-FGF4-WNT4	299	4403	10799	6662	56255
LRP6-PORCN-WNT4	9103	50017	36210	40277	54561	CTBP1-PYGO1-WNT4	22742	44655	41099	39815	48059
DAAM1-FOXN1-WNT4	811	33511	38613	3022	2531	FZD6-WNT1-WNT4	2093	43237	30056	300	18080
AES-WNT1-WNT4	41018	46572	36752	8655	32178	FZD5-CTNNBIP1-WNT4	32042	29652	35862	13833	2270
FZD8-FBXW4-WNT4	3885	12298	49972	12596	630	GSK3B-PORCN-WNT4	7755	14164	10378	27077	53726
CSNK1G1-FZD2-WNT4	13040	11367	14247	4325	36477	APC-FZD6-WNT4	22646	35186	53398	4621	55392
FRAT1-PORCN-WNT4	6345	412	40450	45568	49626	APC-WNT1-WNT4	3183	2118	45782	4710	30780
FGF4-NLK-WNT4	4835	2733	36815	3654	11745	FBXW2-FOXN1-WNT4	946	9458	49198	27879	3575
DIXDC1-FOXN1-WNT4	3943	26131	55172	7688	2054	FSHB-LEF1-WNT4	41497	39387	3625	9699	38711
DIXDC1-LRP5-WNT4	7502	57090	41500	5927	3494	BCL9-FGF4-WNT4	14849	5543	52613	25505	49301
SFRP4-WNT1-WNT4	19664	2692	41573	2007	32211	DIXDC1-NLK-WNT4	5010	8900	42377	1999	3181
DIXDC1-WNT1-WNT4	8940	3055	44478	355	3113	DIXDC1-GSK3A-WNT4	1408	54188	56943	11999	14706
TCF7L1-WIF1-WNT4	13995	23515	42960	42008	36503	LRP5-WNT1-WNT4	17296	2208	27685	2301	15486
DVL1-JUN-WNT4	40299	42142	50777	23893	513	FBXW11-JUN-WNT4	9431	23186	8566	40722	2169
CTBP1-FOXN1-WNT4	2074	2430	52419	14266	42088	CCND1-CTNNBIP1-WNT4	13603	54435	23381	23986	7616
DAAM1-FZD8-WNT4	23906	46096	10699	2772	21704	PPP2R1A-WNT3-WNT4	6466	47384	44643	26384	8285
CSNK2A1-CTNNB1-WNT4	28908	47468	40425	46495	27403	FRZB-GSK3A-WNT4	2291	17308	55967	6138	44450
SFRP4-T-WNT4	4187	24391	50059	54870	31074	DVL2-FZD1-WNT4	4477	45535	34276	13472	9855
RHO-SLC9A3R1-WNT4	4823	12213	14742	31515	1411	FRZB-NLK-WNT4	6001	9443	53325	4130	50442
CSNK1G1-WIF1-WNT4	16896	27273	7830	48279	26589	FOSL1-WNT1-WNT4	4799	4228	46889	440	32783
FBXW11-FGF4-WNT4	1226	24078	8845	42304	9442	FZD5-NKD1-WNT4	12678	521	57060	25537	26670
RHO-SFRP1-WNT4	1469	25767	11493	33127	20094	CXXC4-JUN-WNT4	4946	4363	31447	4600	32510
DVL1-MYC-WNT4	9095	41629	54957	29293	11521	BTRC-CCND3-WNT4	19497	48624	44461	7332	36428
APC-FZD2-WNT4	2232	6396	27501	267	29444	CSNK1D-NLK-WNT4	1538	21775	47534	6449	28873
CTBP1-FRAT1-WNT4	18976	14759	42598	7813	23120	DIXDC1-SFRP1-WNT4	33874	55995	36243	38745	9587
FBXW2-WIF1-WNT4	20440	27918	8101	14377	2991	DVL2-FGF4-WNT4	3899	36296	7736	29132	49144
LEF1-WNT1-WNT4	8880	7636	44357	23	28028	PPP2R1A-TLE1-WNT4	34919	1417	25861	8678	8293
FOSL1-FOXN1-WNT4	2275	8743	50316	14275	47768	CSNK1G1-JUN-WNT4	3575	5	23478	28885	6190
FZD5-PYGO1-WNT4	12619	9688	49504	15069	50337	NKD1-WIF1-WNT4	20047	23652	20170	17000	48569

Table 15. Rankings of WNT4-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002.

RANKING @ t_i USING SOBOL - 2002											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CXXC4-PORCN-WNT4	9600	4879	1294	6463	37839	FZD5-JUN-WNT4	10431	52363	25511	23980	54325
CCND3-PORCN-WNT4	18880	48655	24219	6338	25351	CSNK1D-FGF4-WNT4	31095	19365	29428	42965	30788
LRP5-NLK-WNT4	48309	18357	56155	51944	12470	PITX2-PORCN-WNT4	38340	23219	45866	44679	30684
FSHB-FZD2-WNT4	25678	24971	11443	1797	54089	AXIN1-WNT1-WNT4	8437	50165	25379	13519	26376
DVL2-JUN-WNT4	16345	10299	13394	21121	55056	FZD7-PORCN-WNT4	36181	33007	32383	51098	7850
DVL1-EP300-WNT4	6957	41307	26582	26171	51444	FSHB-T-WNT4	11538	4148	13011	9461	56946
APC-PORCN-WNT4	14017	20902	10996	23651	3554	DKK1-JUN-WNT4	2160	6260	8008	12977	38088
CSNK1G1-NLK-WNT4	7646	8437	104	10192	43063	CCND2-WNT1-WNT4	37427	5486	57083	52869	12235
FOSL1-FRAT1-WNT4	11661	37114	3277	931	53168	FOSL1-NLK-WNT4	11701	13725	13502	3308	41595
FZD6-PORCN-WNT4	12889	17968	25060	5439	42744	CTBP2-CTNNB1-WNT4	28071	5456	9291	4192	36316
CSNK2A1-MYC-WNT4	21742	34401	488	7129	23829	DKK1-WIF1-WNT4	4841	13848	2511	11475	50379
FOSL1-PORCN-WNT4	47380	31804	36756	47696	19151	CXXC4-NLK-WNT4	53246	51233	55370	49749	15337
FBXW2-PORCN-WNT4	22459	33611	12168	3597	56281	FBXW2-WNT3A-WNT4	645	48140	5748	27685	37510
FRAT1-NLK-WNT4	35248	26254	44997	50913	4522	DAAMI-FBXW4-WNT4	21407	40391	21448	21180	23111
APC-PITX2-WNT4	24477	25329	3199	26367	36930	CCND2-LRP6-WNT4	52554	11512	56752	56906	311
FZD5-PORCN-WNT4	9207	29406	23871	11381	42466	TCF7L1-WNT1-WNT4	6797	53924	5514	15758	36704
TLE1-WNT1-WNT4	11578	46284	18979	24705	42168	DIXDC1-PORCN-WNT4	52700	17940	45762	56841	2056
KREMEN1-PORCN-WNT4	2994	1634	5445	11732	52786	DKK1-PORCN-WNT4	10378	26852	12688	21000	45686
FZD5-WNT1-WNT4	5854	22531	7374	3906	26585	FBXW11-FBXW4-WNT4	19278	48904	26377	292	23146
CSNK1A1-FBXW4-WNT4	17150	33308	23879	17349	39381	FBXW2-JUN-WNT4	6945	6699	21970	13741	36379
DKK1-FGF4-WNT4	53981	45053	34733	49147	46685	FBXW2-WNT1-WNT4	19904	7193	17462	26313	34455
SENK2-WNT1-WNT4	27482	37862	8657	159	32055	FBXW2-PYGO1-WNT4	6048	35274	8914	13383	40180
DKK1-WNT1-WNT4	14034	47678	15738	28358	36674	SENK2-FBXW4-WNT4	14841	33195	5632	25971	23429
FBXW2-FGF4-WNT4	32626	57091	46949	54803	17638	TLE1-WIF1-WNT4	24611	48165	2574	1753	54527
CCND1-FGF4-WNT4	44482	33581	40853	49384	6582	RHO-WNT1-WNT4	11749	31988	13883	25949	25686
DVL1-WNT1-WNT4	26875	9515	14492	15387	33351	DIXDC1-WNT3-WNT4	46662	7426	56710	34574	35761
KREMEN1-WNT1-WNT4	15955	22656	18139	572	9093	BTRC-FOXN1-WNT4	9396	56292	5649	9293	40497
PPP2R1A-WNT1-WNT4	11965	38223	20939	13880	37473	FBXW11-FOXN1-WNT4	17360	35949	3866	7278	42454
LRP6-SLC9A3R1-WNT4	978	55109	7830	12485	54244	FBXW2-PORCN-WNT4	4950	13451	24888	5374	42530
FBXW11-PORCN-WNT4	16540	28739	25012	3970	46428	FBXW11-WNT1-WNT4	26765	21608	22134	8381	42819
DIXDC1-NKD1-WNT4	4313	56293	22786	21278	56181	FRZB-WNT1-WNT4	3817	9962	13664	27247	1304
DIXDC1-FZD2-WNT4	230	13998	10061	1865	31112	RHO-WNT1-WNT4	18138	13025	5771	2388	39991
BTRC-PPP2CA-WNT4	44520	22084	53956	47933	11904	PPP2CA-WNT1-WNT4	8831	44953	16654	15477	52783
FZD5-FOXN1-WNT4	14164	41400	10203	708	30386	FBXW4-WNT3A-WNT4	17016	30005	5680	6177	53510
NLK-PORCN-WNT4	3277	2846	7185	12509	42889	CXXC4-FGF4-WNT4	49638	56741	41820	32756	8361
FRZB-PORCN-WNT4	10841	20110	18202	7735	48889	CTBP1-PYGO1-WNT4	27649	26968	22166	2301	29150
DAAMI-FOXN1-WNT4	11332	36244	24535	26243	31947	FZD6-WNT1-WNT4	2254	41747	26122	12348	47338
AES-WNT1-WNT4	27010	28528	10812	21640	40683	FZD5-CTNNBIP1-WNT4	4920	1396	20389	19102	1872
FZD8-FBXW4-WNT4	849	2213	15601	22758	30762	GSK3B-PORCN-WNT4	1508	45949	15059	14068	43601
CSNK1G1-FZD2-WNT4	7022	898	12245	15373	35027	APC-FZD6-WNT4	36082	48689	32517	31725	4788
FRAT1-PORCN-WNT4	26095	16695	23293	12549	25899	APC-WNT1-WNT4	21833	42532	14975	17983	28168
FGF4-NLK-WNT4	41389	35281	52350	41017	19285	FBXW2-FOXN1-WNT4	23806	8597	6054	457	48803
DIXDC1-FOXN1-WNT4	56220	46188	42283	53911	12529	FSHB-LEF1-WNT4	8288	8012	27212	12914	53835
DIXDC1-LRP5-WNT4	22389	29687	26166	18602	8466	BCL9-FGF4-WNT4	9320	38833	24029	11932	50562
SFRP4-WNT1-WNT4	37496	17229	52547	42549	9682	DIXDC1-NLK-WNT4	16250	51618	16235	15399	35237
DIXDC1-WNT1-WNT4	45923	10872	37922	33117	17030	DIXDC1-GSK3A-WNT4	1153	10495	17804	9290	36662
TCF7L1-WIF1-WNT4	11430	37104	6438	4338	54134	LRP5-WNT1-WNT4	6306	53328	564	3576	53083
DVL1-JUN-WNT4	2826	32287	18281	21611	46629	FBXW11-JUN-WNT4	26374	10075	23918	26885	48050
CTBP1-FOXN1-WNT4	8543	5972	26453	9572	32267	CCND1-CTNNBIP1-WNT4	6347	11299	16755	27884	40777
DAAMI-FZD8-WNT4	25405	25396	11540	1480	50873	PPP2R1A-WNT3-WNT4	16616	40261	2791	2571	54999
CSNK2A1-CTNNB1-WNT4	8106	6970	4829	17083	49554	FRZB-GSK3A-WNT4	40759	56843	32408	29292	35226
SFRP4-T-WNT4	13895	50711	4389	7713	42416	DVL2-FZD1-WNT4	28356	49141	14197	11764	48922
RHO-SLC9A3R1-WNT4	49419	19737	53037	53877	5239	FRZB-NLK-WNT4	36879	4793	38330	40342	8139
CSNK1G1-WIF1-WNT4	53996	12035	47320	37468	7141	FOSL1-WNT1-WNT4	41560	17077	46101	51615	8307
FBXW11-FGF4-WNT4	34938	55322	30926	51258	15887	FZD5-NKD1-WNT4	56303	4227	51100	48739	7738
RHO-SFRP1-WNT4	37727	26597	31742	40770	45055	CXXC4-JUN-WNT4	11461	1911	4636	18755	45271
DVL1-MYC-WNT4	19795	16372	8113	21232	36075	BTRC-CCND3-WNT4	5431	8557	4996	27798	44486
APC-FZD2-WNT4	36871	19270	43340	35088	3005	CSNK1D-NLK-WNT4	41521	25413	31966	31421	31114
CTBP1-FRAT1-WNT4	45752	29806	46733	42589	25329	DIXDC1-SFRP1-WNT4	182	13057	19225	8756	34550
FBXW2-WIF1-WNT4	1570	2869	13912	18127	41471	DVL2-FGF4-WNT4	28866	49995	31976	39651	1428
LEF1-WNT1-WNT4	3003	50013	24760	22408	35262	PPP2R1A-TLE1-WNT4	50847	17197	51184	35836	4656
FOSL1-FOXN1-WNT4	53448	12	54578	41681	9465	CSNK1G1-JUN-WNT4	33107	46065	50016	51102	7862
FZD5-PYGO1-WNT4	15278	10463	12217	3358	53540	NKD1-WIF1-WNT4	27161	54046	639	3320	54064

Table 16. Rankings of WNT4-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez.

RANKING @ t _i USING SOBOL - MARTINEZ												
3rd order comb.	t ₁	t ₃	t ₆	t ₁₂	t ₂₄	3rd order comb.	t ₁	t ₃	t ₆	t ₁₂	t ₂₄	
CXXC4-PORCN-WNT4	4276	14596	42774	57022		45130	FZD5-JUN-WNT4	19865	9292	48700	121386	52601
CCND3-PORCN-WNT4	26806	19860	18309	28843	27352	CSNK1D-FGF4-WNT4	30931	24624	1645	40905	44453	
LRP5-NLK-WNT4	11875	29409	39497	6717	14614	PITX2-PORCN-WNT4	9395	23474	32883	37297	24846	
FSHB-FZD2-WNT4	2021	57140	14789	29295	53443	AXIN1-WNT1-WNT4	2778	38952	44497	24969	214	
DVL2-JUN-WNT4	12922	5091	28902	26178	19271	FZD7-PORCN-WNT4	5819	17955	1724	40196	33807	
DVL1-EP300-WNT4	25389	12501	1599	51389	44362	FSHB-T-WNT4	40510	47251	23497	18487	55763	
APC-PORCN-WNT4	22457	14933	19953	27502	33252	DKK1-JUN-WNT4	292	3863	10616	27487	47309	
CSNK1G1-NLK-WNT4	9882	34667	14911	20141	31237	CCND2-WNT1-WNT4	56311	32819	51920	32545	37821	
FOSL1-FRAT1-WNT4	40993	13521	5723	19915	17592	FOSL1-NLK-WNT4	45098	10285	6164	24489	8061	
FZD6-PORCN-WNT4	199	7166	3089	14140	1367	CTBP2-CTNNB1-WNT4	34634	28678	15747	18697	28122	
CSNK2A1-MYC-WNT4	19871	31001	13262	3506	6248	CCND1-WIFI-WNT4	19090	34087	44892	9619	637	
FOSL1-PORCN-WNT4	7917	37593	48481	35640	51574	CXXC4-NLK-WNT4	55944	14516	7372	46062	23888	
FBXW2-PORCN-WNT4	46672	28991	8289	11846	43257	FBXW2-WNT3A-WNT4	6270	53231	8071	37859	6097	
FRAT1-NLK-WNT4	25990	49738	661	19315	9889	DAAM1-FBXW4-WNT4	9541	3985	22660	40797	34016	
APC-PITX2-WNT4	33809	3550	4717	20161	40028	CCND2-LRP6-WNT4	37728	13104	27207	45558	52678	
FZD5-PORCN-WNT4	8507	37632	48747	30800	4942	TCF7L1-WNT1-WNT4	32094	40529	21150	6996	1659	
TLE1-WNT1-WNT4	36555	15670	21408	7024	45023	DIXDC1-PORCN-WNT4	12247	40184	4921	27175	55522	
KREMEN1-PORCN-WNT4	25014	55908	56360	6264	40529	DKK1-PORCN-WNT4	25947	40656	8698	44050	26641	
FZD5-WNT1-WNT4	47089	43274	11221	47423	52439	FBXW11-FBXW4-WNT4	11236	5133	55151	49822	27142	
CSNK1A1-FBXW4-WNT4	21502	52930	8543	32700	10282	FBXW2-JUN-WNT4	35429	42647	44788	43088	49776	
6 DKK1-FGF4-WNT4	15805	32746	7014	37963	19923	FBXW2-WNT1-WNT4	12354	12266	47167	24853	6316	
SEN2-WNT1-WNT4	23302	15994	3637	19774	7442	FBXW2-PYGO1-WNT4	52436	10894	44161	20796	21790	
DKK1-WNT1-WNT4	4150	8692	11857	26791	3627	SEN2-FBXW4-WNT4	30943	9589	56816	22982	2735	
FBXW2-FGF4-WNT4	35089	12142	7048	18433	30806	TLE1-WIFI-WNT4	13417	53175	11985	6640	5468	
CCND1-FGF4-WNT4	45423	56248	37480	20853	10917	RHO-WNT1-WNT4	14697	29770	55730	10370	1690	
DVL1-WNT1-WNT4	17136	51482	9987	16743	1726	DIXDC1-WNT3-WNT4	7590	21662	40072	54760	19415	
KREMEN1-WNT1-WNT4	2199	38104	48857	13973	4782	BTRC-FOXXN1-WNT4	46136	7354	21239	41736	23521	
PPP2R1A-WNT1-WNT4	37092	5843	25053	14666	48915	FBXW11-FOXXN1-WNT4	15807	8100	17793	26530	5575	
LRP6-SLC9A3R1-WNT4	36806	29083	35933	3613	8254	FZD8-PORCN-WNT4	16866	18194	19414	12569	12962	
FBXW11-PORCN-WNT4	20159	34969	20626	54364	6425	FBXW11-WNT1-WNT4	11180	25231	49052	48653	18382	
DIXDC1-NKD1-WNT4	46229	42232	4694	26610	37481	FRZB-WNT1-WNT4	6698	54817	3429	48430	7937	
DIXDC1-FZD2-WNT4	50281	20232	28903	8355	45251	CTNNB1P1-JUN-WNT4	8571	16635	1790	9191	55418	
BTRC-PPP2CA-WNT4	18544	53592	12219	41275	6887	PPP2CA-WNT1-WNT4	45922	51703	31831	5639	9	
FZD5-FOXXN1-WNT4	396	43921	5362	42075	4967	FBXW4-WNT3A-WNT4	17207	4496	54748	47713	9359	
NLK-PORCN-WNT4	839	35865	37133	52537	3763	CXXC4-FGF4-WNT4	53473	50248	53015	47741	53510	
FRZB-PORCN-WNT4	36039	40997	30705	7328	55361	CTBP1-PYGO1-WNT4	31272	3069	22436	8609	40251	
DAAM1-FOXXN1-WNT4	42073	49218	33120	29009	300	FZD6-WNT1-WNT4	7233	45016	15516	10015	3188	
AES-WNT1-WNT4	35587	7864	26131	9828	43837	FZD5-CTNNB1P1-WNT4	37790	17996	35360	13627	69	
FZD8-FBXW4-WNT4	15999	27058	54943	26395	226	GSK3B-PORCN-WNT4	30196	41020	21974	56816	40470	
CSNK1G1-FZD2-WNT4	10410	34283	49819	8764	3839	APC-FZD6-WNT4	37397	53670	39026	39666	36556	
FRAT1-PORCN-WNT4	1204	15349	9265	36000	46519	APC-WNT1-WNT4	917	11941	13711	9897	48253	
FGF4-NLK-WNT4	7085	8398	45782	12210	41629	FBXW2-FOXXN1-WNT4	39561	25779	15329	28673	6746	
DIXDC1-FOXXN1-WNT4	32682	1731	13063	29733	30817	FSHB-LEF1-WNT4	15442	25307	14632	33427	52184	
DIXDC1-LRP5-WNT4	1097	14539	41487	34988	44516	BCL9-FGF4-WNT4	4313	55037	11369	13920	5299	
SFRP4-WNT1-WNT4	27168	3150	38903	887	56174	DIXDC1-NLK-WNT4	1935	7729	30708	20858	4426	
DIXDC1-WNT1-WNT4	31540	9049	855	15412	43794	DIXDC1-GSK3A-WNT4	33583	29470	10959	48219	48401	
TCF7L1-WIFI-WNT4	16671	56895	12326	3087	5863	LRP5-WNT1-WNT4	38582	11835	11954	12770	51873	
DVL1-JUN-WNT4	37828	11537	12122	28401	10081	FBXW11-JUN-WNT4	37910	15788	21334	3785	16647	
CTBP1-FOXXN1-WNT4	43275	38868	21797	19991	39467	CCND1-CTNNB1P1-WNT4	33341	37082	32687	33491	887	
DAAM1-FZD8-WNT4	834	52586	22406	43223	34981	PPP2R1A-WNT3-WNT4	38925	6831	8673	22959	7896	
CSNK2A1-CTNNB1-WNT4	1302	27956	45071	49285	9763	FRZB-GSK3A-WNT4	51688	50258	8762	4281	16089	
SFRP4-T-WNT4	37649	20378	3687	1979	51544	DVL2-FZD1-WNT4	17536	52315	14707	9854	19061	
RHO-SLC9A3R1-WNT4	52925	62	40274	23424	10431	FRZB-NLK-WNT4	20535	24126	28511	55751	12292	
CSNK1G1-WIFI-WNT4	56789	43140	52845	54585	19132	FOSL1-WNT1-WNT4	40112	4912	51361	40583	39621	
FBXW11-FGF4-WNT4	44736	39342	39578	319	36586	FZD5-NKD1-WNT4	50883	36657	40818	51578	32742	
RHO-SFRP1-WNT4	37322	9276	39470	33165	21606	CXXC4-JUN-WNT4	8214	33327	19909	4326	55524	
DVL1-MYC-WNT4	39413	5460	14296	33480	49353	BTRC-CCND3-WNT4	40306	33905	50218	23253	472	
APC-FZD2-WNT4	55887	29000	17998	44736	23788	CSNK1D-NLK-WNT4	55088	4562	19617	29935	54873	
CTBP1-FRAT1-WNT4	42916	92	41662	39172	18130	DIXDC1-SFRP1-WNT4	5295	28151	32604	54855	40585	
FBXW2-WIFI-WNT4	29533	55498	12217	29219	42911	DVL2-FGF4-WNT4	18376	48270	11104	49246	35704	
LEF1-WNT1-WNT4	2712	26579	51004	53571	711	PPP2R1A-TLE1-WNT4	51244	380	10001	46733	50906	
FOSL1-FOXXN1-WNT4	20287	2448	37360	25562	16564	CSNK1G1-JUN-WNT4	7327	52583	35808	38813	18150	
FZD5-PYGO1-WNT4	33763	36551	23826	53334	40907	NKD1-WIFI-WNT4	29254	43808	28256	8965	5464	

7.6.1. Examining the Behaviour of PORCN-WNT4-X Combinations

Zhang et al. [59] observe that palmitoylation of WNT4 is required for its binding to FZD1, but this is not essential for its secretion. Rao et al. [60] found that WNT4 secretion was PORCN-independent, and the secreted WNT4 did not exhibit paracrine activity but had a cell-autonomous activity, which indirectly proves the necessity of WNT4 palmitoylation. Zhu et al. [61] showed that low level of a natural health supplement, 3,3'-diindolylmethane (DIM) promoted gastric cancer progression by inducing the PORCN-dependent secretion of WNT4 and the activation of β -catenin signaling. Looking at the tables above, one finds the following combinations for PORCN along with WNT4, to be prominent at 3rd order level - CXXC4-PORCN-WNT4, CCND3-PORCN-WNT4, APC-PORCN-WNT4, FZD6-PORCN-WNT4, FOSL1-PORCN-WNT4, FBXW2-PORCN-WNT4, FZD5-PORCN-WNT4, KREMEN1-PORCN-WNT4, FBXW11-PORCN-WNT4, NLK-PORCN-WNT4, FRZB-PORCN-WNT4, FRAT1-PORCN-WNT4, PITX2-PORCN-WNT4, FZD7-PORCN-WNT4, DIXDC1-PORCN-WNT4, DKK1-PORCN-WNT4, FZD8-

PORCN-WNT4 and GSK3B-PORCN-WNT4. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.6.2. Examining the Behaviour of FZD-WNT4-X Combinations

Ring et al. [62] observe that WNT4/FZD10 and WNT5a/FZD4 in combination with LRP6 show strong specific signal. Lyons et al. [63] found that Madin–Darby Canine Kidney (MDCK) cells express the FZD6 receptor and that WNT4 forms a biochemical complex with the FZD6 CRD. Acute myocardial infarction (AMI)-induced excessive myocardial fibrosis exaggerates cardiac dysfunction. Yin et al. [64] showed that in vitro, hypoxia enhanced the secretion and expression of WNT-2/4 in neonatal rat cardiac myocytes (NRCMs) or fibroblasts (NRCFs). In cultured NRCFs, FZD-2/4 proteins or mRNAs were increased by WNT-2/4 treatment and WNT-2/4 activated NF- κ B to promote cardiac fibrosis by FZD-4/2 receptor signaling. Looking at the tables above, one finds the following combinations for member of FZD family along with WNT4, to be prominent at 3rd order level - FSHB-FZD2-WNT4, FZD6-PORCN-WNT4, FZD5-PORCN-WNT4, FZD5-WNT1-WNT4, DIXDC1-FZD2-WNT4, FZD5-FOXN1-WNT4, FZD8-FBXW4-WNT4, CSNK1G1-FZD2-WNT4, DAAM1-FZD8-WNT4, APC-FZD2-WNT4, FZD5-PYGO1-WNT4, FZD5-JUN-WNT4, FZD7-PORCN-WNT4, FZD8-PORCN-WNT4, FZD6-WNT1-WNT4, FZD5-CTNNBIP1-WNT4, APC-FZD6-WNT4, DVL2-FZD1-WNT4 and FZD5-NKD1-WNT4. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.6.3. Examining the Behaviour of FOSL1-WNT4-X Combinations

Yu et al. [58] observed upregulation of WNT4 and FOSL1 in spinal cords of neurodegenerative disease amyotrophic lateral sclerosis (ALS) transgenic SOD1^{G93A} mice. Looking at the tables above, one finds the following combinations for FOSL1 along with WNT4, to be prominent at 3rd order level - FOSL1-FRAT1-WNT4, FOSL1-PORCN-WNT4, FOSL1-FOXN1-WNT4, FOSL1-NLK-WNT4 and FOSL1-WNT1-WNT4. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.6.4. Examining the Behaviour of NLK-WNT4-X Combinations

Nemo-like kinase (NLK) is an evolutionarily conserved protein kinase involved in WNT/ β -catenin signalling. Ota et al. [65] demonstrate that NLK functions downstream of Dishevelled (DVL) in the WNT/ β -catenin signalling pathway. Swann et al. [66] observe that NLK has previously been demonstrated to either enhance or suppress Wnt signaling in a context-dependent manner; however, the defective migration of the thymic lobes, parathyroids or thyroid was preserved in NLK-deficient, WNT4-transgenic embryos, indicating that NLK is not required to mediate the WNT4-induced signaling pathway that disrupts organ morphogenesis. Yu et al. [67] observed that recombinant WNT4 proteins (rWNT4) stimulation induced the formation of the TAK1-TAB2-NLK complex. Looking at the tables above, one finds the following combinations for NLK along with WNT4, to be prominent at 3rd order level - LRP5-NLK-WNT4, CSNK1G1-NLK-WNT4, FRAT1-NLK-WNT4, NLK-PORCN-WNT4, FGF4-NLK-WNT4, FOSL1-NLK-WNT4, CXXC4-NLK-WNT4, DIXDC1-NLK-WNT4, FRZB-NLK-WNT4 and CSNK1D-NLK-WNT4. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.6.5. Examining the Behaviour of DVL-WNT4-X Combinations

Sikora et al. [68] observed that WNT4 did not activate β -catenin-dependent transcription in HT1080 cells despite inducing phosphorylation of the DVL-2/3 WNT signaling molecules in HT1080. Emodin, an anthraquinone with multiple physiological activities, has been reported to inhibit proliferation of vascular smooth muscle cells (VSMCs) that might cause intimal arterial thickening. Emodin relieved injury-induced artery intimal thickness. To assess the downstream signal of WNT4 that mediates emodin-induced prevention of artery stenosis, Hua et al. [69] examined levels of DVL-1 and β -catenin in injured arteries and found that expression of both proteins was activated by vascular

balloon injury, but was inhibited in rats administered emodin. Looking at the tables above, one finds the following combinations for members of DVL family along with WNT4, to be prominent at 3rd order level - DVL2-JUN-WNT4, DVL1-EP300-WNT4, DVL1-WNT1-WNT4, DVL1-JUN-WNT4, DVL1-MYC-WNT4, DVL2-FZD1-WNT4 and DVL2-FGF4-WNT4. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.7. Conserved Machine Learning Rankings for Tested WNT5A-X-X Combinations

A total of 2415, 3rd order combinations involving WNT5A were obtained from a full set of ${}^{71}C_3 = 57155$ combinations. Further, from this selected set, using the above criteria for conserved rankings, I report/tabulate the meaningful combinations that might be working synergistically. Tables 18, 19 and 20 show the rankings for the same combinations as in table 17, but using rbf kernel for HSIC, 2002 implementation for SOBOL and martinez implementation for SOBOL, respectively. As one tallies the rankings of across these tables for a particular combination, one finds that the role of the combination of interest is conserved. This conservation points to the existence of the biological synergy, whether the combination has been tested or unexplored/untested.

7.7.1. Examining the Behaviour of WIF1-WNT5A-X Combinations

Surmann-Schmitt et al. [70] report that WIF1 is highly expressed at cartilage-mesenchyme interfaces of the early developing skeleton and in fetal and postnatal skeletal development, WIF1 is expressed in a sharply restricted zone in the upper hyaline layer of epiphyseal and articular cartilage and in trabecular bone. They found that recombinant WIF1 and WNT factors show specific binding of the former to WNT3A, WNT4, WNT5A, WNT7A, WNT9A and WNT11. Chondrosarcoma (CS) is a rare cancer and Liu et al. [71] in their study, found promoter methylated WIF1 in both CS cell lines (CS-1 and SW1353) and tumor tissues. They confirmed loss of WIF1 expression and activation of Wnt pathway proteins (WNT5-A/B, LRP6, and DVL2) and an inverse correlation between the expression of WNT5-A/B and WIF1. Taken together, their results support the hypothesis that WIF1 restoration could attenuate the activity of WNT pathway and impedes the transmission of WNT signal. Skaria et al. [72] investigated the antagonistic effect of the RYK specific secreted WIF1 on WNT5A-mediated activation/inactivation of LIMK/CFL, and adherens junction disruption in human vascular endothelial cells (VECs). They found that in human coronary artery endothelial cells (HCAEC), treatment with WNT5A enhanced the phosphorylation of LIMK and CFL that was significantly prevented by WIF1. The presence of WIF1 suppressed WNT5A-mediated disruption of β -catenin and VE-cadherin adherens junctions in HCAEC, thereby preventing barrier dysfunction caused by WNT5A. Vassallo et al. [73] show that loss of WIF1 enhanced the migratory potential of glioblastoma through WNT5A that activated the WNT/ Ca^{2+} pathway and metastasis-associated lung adenocarcinoma transcript 1 (MALAT1). Gujral and MacBeath [1] record the activity of WIF1 and WNT5A and it shows that in time, the expression levels of WIF1 are much higher than WNT5A, indicating that WIF1 might be attenuating WNT5A expression. Looking at the tables above, one finds the following combinations for WIF1 along with WNT5A, to be prominent at 3rd order level - CTNNBIP1-WIF1-WNT5A, TLE1-WIF1-WNT5A, JUN-WIF1-WNT5A, CCND1-WIF1-WNT5A, TCF7L1-WIF1-WNT5A and PYGO1-WIF1-WNT5A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.7.2. Examining the Behaviour of FZD-WNT5A-X Combinations

Kurayoshi et al. [74] show that the binding of WNT5A to the extracellular domain of FZD5 required palmitoylation of WNT5A but not required for its secretion. Kumawat et al. [75] show that silencing of the noncanonical WNT5A receptors FZD8 and RYK attenuated TGF- β -induced extracellular matrix (ECM) expression. Traumatic brain injury (TBI) can dramatically increase levels of intracellular calcium (Ca^{2+}). In mammalian nerve cells, Niu et al. [76] study the association between WNT5A-FZD2 signaling and Ca^{2+} cellular homeostasis and demonstrated that the WNT5A-FZD2 signaling pathway contributed to increasing intracellular Ca^{2+} in nerve cells under physiological and

pathological conditions. Chen et al. [77] observe that endocytosis of FZD4 in human embryonic kidney 293 cells was dependent on added WNT5A protein and was accomplished by the multifunctional adaptor protein beta-arrestin 2 (betaarr2), which was recruited to FZD4 by binding to phosphorylated DVL2. Kawasaki et al. [78] concluded that WNT5A is a natural ligand of FZD3 that triggers the PI3K/AKT signal and promotes adhesion of human dermal fibroblasts. About half of all melanomas harbor a mutation that results in a constitutively active BRAF kinase mutant (BRAF^{V600E/K}) that can be selectively inhibited by targeted BRAF inhibitors (BRAFi). Anastas et al. [79] suggest that chronic BRAF inhibition elevates WNT5A expression, which promotes AKT signaling through FZD7 and RYK, leading to increased growth and therapeutic resistance. Looking at the tables above, one finds the following combinations for members of FZD family along with WNT5A, to be prominent at 3rd order level - FZD5-JUN-WNT5A, APC-FZD6-WNT5A, FZD6-PORCN-WNT5A, FZD5-PPP2R1A-WNT5A, CSNK1G1-FZD2-WNT5A, APC-FZD2-WNT5A, FRZB-FZD2-WNT5A, FZD1-SFRP1-WNT5A, FZD2-WNT1-WNT5A, FZD5-FGF4-WNT5A, FSHB-FZD2-WNT5A, FZD5-FOXN1-WNT5A, FZD6-WNT1-WNT5A, FZD6-PORCN-WNT5A, FZD5-SFRP1-WNT5A, FZD8-WNT1-WNT5A, FZD5-NKD1-WNT5A, FZD1-NLK-WNT5A, FZD7-NKD1-WNT5A, FZD5-FZD2-WNT5A, FZD5-CSNK1D-WNT5A, FZD8-GSK3A-WNT5A, FZD1-T-WNT5A, AXIN1-FZD2-WNT5A and EP300-FZD2-WNT5A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.7.3. Examining the Behaviour of FGF4-WNT5A-X Combinations

The apical ectodermal ridge (AER) has a vital role in directing embryonic limb development. Allen [80] demonstrate that FGF4 from the AER activates a distal gradient of WNT5A expression in the limb. They observe that when the FGF4 bead is implanted closer to the limb bud, endogenous WNT5A is expressed more strongly, indicating that elevated levels of WNT5A are expressed with increasing FGF4 concentration. Looking at the tables above, one finds the following combinations for FGF4 along with WNT5A, to be prominent at 3rd order level - CSNK1D-FGF4-WNT5A, DIXDC1-FGF4-WNT5A, CCND1-FGF4-WNT5A, DKK1-FGF4-WNT5A, DVL2-FGF4-WNT5A, CTBP1-FGF4-WNT5A, CXXC4-FGF4-WNT5A, FZD5-FGF4-WNT5A, FBXW2-FGF4-WNT5A, CSNK1A1-FGF4-WNT5A, FBXW11-FGF4-WNT5A and CTNNBIP1-FGF4-WNT5A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

7.7.4. Examining the Behaviour of FOXN1-WNT5A-X Combinations

Epithelial–mesenchymal interactions are key to skin morphogenesis and homeostasis. Through functional rescue experiments Hu et al. [81] establish WNT5A as an essential downstream mediator of Notch–CSL signaling, impinging on expression in the keratinocyte compartment of FOXN1, a gene with a key hair follicle regulatory function. Their immunofluorescence analysis confirmed that WNT5A treatment caused a significant increase of FOXN1 expression in hair follicles of cultured (ColI-Cre * RBP-J^{loxP/loxP}) skin. Looking at the tables above, one finds the following combinations for FOXN1 along with WNT5A, to be prominent at 3rd order level - DVL1-FOXN1-WNT5A, DIXDC1-FOXN1-WNT5A, DKK1-FOXN1-WNT5A, FZD5-FOXN1-WNT5A, FOSL1-FOXN1-WNT5A, FBXW11-FOXN1-WNT5A, CXXC4-FOXN1-WNT5A, BTRC-FOXN1-WNT5A, CSNK1G1-FOXN1-WNT5A, APC-FOXN1-WNT5A, and FBXW2-FOXN1-WNT5A. All these combinations indicate possible existence of a synergy when they take a higher rank in the list of combinations.

Table 17. Rankings of WNT5A-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - linear.

RANKING @ t_i USING HSIC - LINEAR											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CSNK1D-FGF4-WNT5A	59	12095	43366	47094	42796	FSHB-T-WNT5A	122	29061	57139	24091	2613
CTNNBIP1-WIF1-WNT5A	128	2117	50325	55816	30661	CCND1-FGF4-WNT5A	165	47269	47793	37145	12904
FZD5-JUN-WNT5A	284	6962	43259	53869	10481	CCND2-LRP6-WNT5A	407	16539	8597	20565	13858
PITX2-PORCN-WNT5A	460	36097	17787	53210	23094	CXXC4-PORCN-WNT5A	535	15961	16253	55679	46631
LEF1-T-WNT5A	536	18912	30178	32688	1901	DKK1-FGF4-WNT5A	647	20327	35056	40689	45318
CCND2-WNT1-WNT5A	649	4100	17754	49943	24216	DVL2-FGF4-WNT5A	704	40017	53884	26198	56433
CTNNBIP1-FRAT1-WNT5A	734	14176	29898	41568	9680	CTBP1-FGF4-WNT5A	828	15379	39203	43512	39680
CTNNBIP1-NLK-WNT5A	840	10869	21909	56571	16909	DVL2-JUN-WNT5A	871	37929	52159	30056	48277
TCF7L1-WNT1-WNT5A	951	10419	14748	50321	56416	CXXC4-FGF4-WNT5A	957	4552	41511	51712	55041
CSNK1D-PPP2R1A-WNT5A	992	931	1207	30631	56811	FZD5-FGF4-WNT5A	1112	9925	43559	46683	36390
CCND3-WNT1-WNT5A	1130	34700	23749	48106	39841	FSHB-NKD1-WNT5A	1146	8921	29165	19619	2206
LEF1-WIF1-WNT5A	1188	23457	43932	51409	21021	FSHB-FZD2-WNT5A	1190	10906	56570	47332	4072
LRP6-TCF7-WNT5A	1209	36573	40965	49762	7878	FBXW2-FGF4-WNT5A	1216	14837	41991	48331	9404
AES-EP300-WNT5A	1232	50236	54302	23216	39305	DKK1-FOXN1-WNT5A	1346	18310	46663	16625	23963
APC-FZD6-WNT5A	1498	16910	1630	41699	21038	FZD5-FOXN1-WNT5A	1560	2664	23846	23386	12164
LRP6-SLC9A3R1-WNT5A	1593	9653	35688	33506	34192	CSNK1A1-FGF4-WNT5A	1597	15092	35949	31672	40613
DVL1-FOXN1-WNT5A	1611	44292	19025	17511	32923	LEF1-MYC-WNT5A	1622	11652	19069	1638	12533
FBXW11-LRP6-WNT5A	1633	9564	30602	20103	19149	EP300-WNT1-WNT5A	1667	20162	16144	44114	26527
PITX2-WNT3-WNT5A	1726	32979	5136	41370	17012	CCND2-TCF7-WNT5A	1728	3936	34730	44523	52026
CXXC4-FOSL1-WNT5A	1800	15338	42242	52718	32578	FBXW11-FGF4-WNT5A	1812	8275	53849	49534	26193
DIXDC1-NKD1-WNT5A	1830	5103	33835	49403	2232	CSNK2A1-MYC-WNT5A	1924	52368	38656	2374	28977
BCL9-PORCN-WNT5A	1929	7488	5825	56273	34499	LRP5-SFRP1-WNT5A	1931	37754	47154	35962	19209
LEF1-WNT1-WNT5A	1934	1735	16448	40349	48415	FZD6-WNT1-WNT5A	2012	42767	35693	43649	25350
NLK-SFRP1-WNT5A	2032	55480	32725	47613	26430	FOSL1-FOXN1-WNT5A	2034	6923	6744	9847	23516
LEF1-WNT1-WNT5A	2164	2916	24333	52522	19459	FZD6-PORCN-WNT5A	2165	41983	26329	43017	27185
FZD6-PORCN-WNT5A	2165	41983	26329	43017	27185	CCND1-WIF1-WNT5A	2206	17920	56231	50097	15244
CCND1-CTBP1-WNT5A	2219	47772	29829	51047	3738	FBXW11-FOXN1-WNT5A	2226	594	18962	23786	9557
FZD5-PPP2R1A-WNT5A	2239	9275	9172	22179	32268	CTNNBIP1-FGF4-WNT5A	2261	20092	46938	34699	41410
CCND3-PORCN-WNT5A	2270	38617	15634	39601	37699	JUN-PYGO1-WNT5A	2273	30941	1607	4887	6388
LRP6-RHOU-WNT5A	2371	52871	42173	56381	27277	FZD5-SFRP1-WNT5A	2397	37105	25747	56833	14943
DVL2-SFRP1-WNT5A	2494	52098	6476	40859	55468	FBXW11-SLC9A3R1-WNT5A	2545	22242	54164	19587	2861
PITX2-WNT1-WNT5A	2609	5926	14837	51671	5692	FZD8-WNT1-WNT5A	2653	3688	15335	41914	55425
BCL9-WNT3-WNT5A	2722	18035	5750	39690	6184	CSNK1G1-PORCN-WNT5A	2747	5935	22657	45224	29673
CTNNBIP1-WNT1-WNT5A	2892	2340	17541	31012	32743	CSNK1D-PORCN-WNT5A	2899	17376	34214	55252	32946
DVL1-EP300-WNT5A	2981	45215	32109	50904	36947	FZD5-NKD1-WNT5A	3021	6206	35575	52940	2092
CSNK2A1-CTNNB1-WNT5A	3035	55445	26243	38266	23130	LRP5-PORCN-WNT5A	3051	25077	6874	53519	30711
CSNK1G1-JUN-WNT5A	3068	8191	56989	38952	10438	CXXC4-FOXN1-WNT5A	3109	8816	13105	18798	36097
PPP2CA-WNT1-WNT5A	3127	17958	20275	50785	22700	FZD1-NLK-WNT5A	3220	14961	17555	36449	16975
APC-WNT1-WNT5A	3260	5882	29068	48459	44398	LRP5-NLK-WNT5A	3296	15243	30086	6594	47805
CSNK1G1-FZD2-WNT5A	3333	14640	38705	56952	5899	FZD7-NKD1-WNT5A	3371	2073	37837	34079	40424
DIXDC1-FGF4-WNT5A	3402	30477	40511	46509	49117	FZD5-FZD2-WNT5A	3441	11100	36263	56497	6341
CSNK1A1-CTBP2-WNT5A	3469	3917	28636	35088	16423	FOSL1-PORCN-WNT5A	3631	16428	9587	43895	35656
CSNK2A1-T-WNT5A	3660	45233	45887	26671	1396	BTRC-FOXN1-WNT5A	3687	8784	26520	30828	49695
DKK1-GSK3A-WNT5A	3713	18916	49874	56725	48396	CSNK1G1-FOXN1-WNT5A	3844	2053	5432	27959	8766
DIXDC1-FOXN1-WNT5A	3863	7743	18318	21775	11741	FOSL1-SFRP1-WNT5A	3880	20546	15812	56341	45565
DIXDC1-PORCN-WNT5A	3885	26867	8379	47688	52084	DVL1-SLC9A3R1-WNT5A	3901	42878	40021	40175	11848
FOSL1-WNT1-WNT5A	3911	934	9883	39216	24538	FZD5-CSNK1D-WNT5A	3923	32577	23307	47873	6444
CXXC4-NLK-WNT5A	3932	2627	16679	25816	15722	FZD8-GSK3A-WNT5A	3951	39522	29545	46470	37762
CSNK1D-SFRP1-WNT5A	3998	16473	29590	51130	13720	TCF7L1-WIF1-WNT5A	4007	25712	49240	53231	50932
LRP5-WNT1-WNT5A	4047	7108	21074	49106	36111	DAAM1-GSK3A-WNT5A	4051	49629	42474	35216	41411
DKK1-WNT1-WNT5A	4068	35503	45563	48503	45432	APC-FOXN1-WNT5A	4076	5465	27067	17582	33273
APC-FZD2-WNT5A	4079	13021	38909	56003	5306	KREMEN1-WNT1-WNT5A	4086	1014	15715	19712	13437
AXIN1-EP300-WNT5A	4180	9970	29920	45061	25015	FZD1-T-WNT5A	4216	53465	32743	41156	8347
APC-GSK3A-WNT5A	4225	14825	31576	32622	52407	AXIN1-FZD2-WNT5A	4330	36177	46404	56433	4476
SFRP4-T-WNT5A	4355	4858	31246	35810	3883	LRP5-WNT3-WNT5A	4490	38334	13435	16356	15034
CXXC4-SFRP1-WNT5A	4494	13816	11726	55305	20868	DKK1-PPP2R1A-WNT5A	4534	3478	36759	50853	55700
FBXW4-WNT1-WNT5A	4581	30084	19370	45293	28364	FSHB-GSK3A-WNT5A	4722	7262	52632	23091	38927
JUN-WIF1-WNT5A	4730	23210	50885	51206	36664	EP300-FZD2-WNT5A	4742	6196	44889	55869	24808
CCND3-CSNK1D-WNT5A	4753	43030	22446	46977	51854	FBXW2-FOXN1-WNT5A	4762	1838	37770	29635	12817
FRZB-FZD2-WNT5A	4769	13108	38666	56335	37688	LEF1-NKD1-WNT5A	4811	14924	45796	29502	2694
BTRC-GSK3A-WNT5A	4818	34238	56433	32265	47742	PYGO1-WIF1-WNT5A	4948	8911	30428	21376	24898
FZD1-SFRP1-WNT5A	4968	39398	12863	44772	6780	DIXDC1-GSK3A-WNT5A	4971	24828	27305	38034	51261
FZD2-WNT1-WNT5A	4992	34448	12933	13131	24695	CCND1-FRAT1-WNT5A	5062	46569	3187	54041	12710

Table 18. Rankings of WNT5A-X-X. A list of approximately first 126 combinations with rankings below 10,000 out of 57,155. SA - HSIC; Kernel - rbf.

RANKING @ t_i USING HSIC - RBF												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1D-FGF4-WNT5A	16991	26760	1497	11585	17580	FSHB-T-WNT5A	38699	15943	1093	25527	28563	
CTNNBIP1-WIF1-WNT5A	23143	5998	4289	37385	52573	CCND1-FGF4-WNT5A	19418	46790	4933	16199	11823	
FZD5-JUN-WNT5A	8780	13834	37545	56636	50500	CCND2-LRP6-WNT5A	10166	22129	20505	51209	15333	
PITX2-PORCN-WNT5A	11335	32674	6548	15458	54809	CXXC4-PORCN-WNT5A	24704	5412	10695	26556	50085	
LEF1-T-WNT5A	8574	24318	38907	16551	20657	DKK1-FGF4-WNT5A	9621	8732	17015	38900	28750	
CCND2-WNT1-WNT5A	2628	30300	41874	37956	39959	DVL2-FGF4-WNT5A	5059	21998	33434	16256	19267	
CTNNBIP1-FRAT1-WNT5A	14700	16677	7050	19562	51259	CTBP1-FGF4-WNT5A	12798	10433	7187	48929	22701	
CTNNBIP1-NLK-WNT5A	43965	11033	40662	17048	49376	DVL2-JUN-WNT5A	16054	35608	35930	17120	44512	
TCF7L1-WNT1-WNT5A	4746	24167	45178	15067	34701	CXXC4-FGF4-WNT5A	6438	9457	13415	42775	42269	
CSNK1D-PPP2R1A-WNT5A	27528	4279	14277	4265	42405	FZD5-FGF4-WNT5A	6337	27591	19612	53409	31870	
CCND3-WNT1-WNT5A	3522	45126	4446	40031	11792	FSHB-NKD1-WNT5A	45339	3228	1592	43013	28219	
TLE1-WIF1-WNT5A	40747	33211	3589	52410	46132	FSHB-FZD2-WNT5A	4908	10915	532	36402	27866	
LRP6-TCF7-WNT5A	3378	28609	32749	45029	28221	FBXW2-FGF4-WNT5A	5739	17796	19310	37639	2729	
AES-EP300-WNT5A	40140	51612	23938	4009	35408	DKK1-FOXN1-WNT5A	6288	34859	41852	39340	54131	
APC-FZD6-WNT5A	9031	23346	51525	51644	24946	FZD5-FOXN1-WNT5A	3489	12125	37214	51686	53948	
LRP6-SLC9A3R1-WNT5A	50636	8388	7361	48711	37589	CSNK1A1-FGF4-WNT5A	8952	17873	1108	36340	28004	
DVL1-FOXN1-WNT5A	4912	51197	23796	43594	44907	LEF1-MYC-WNT5A	9292	1889	50136	33084	16897	
FBXW11-LRP6-WNT5A	5244	4673	9444	17231	20722	EP300-WNT1-WNT5A	2374	24154	16830	20295	34795	
PITX2-WNT3-WNT5A	50071	36976	3198	23809	43096	CCND2-TCF7-WNT5A	36497	1031	22725	50349	37229	
CXXC4-FOSL1-WNT5A	53822	4385	5771	55698	30961	FBXW11-FGF4-WNT5A	6302	7098	2714	7045	9820	
DIXDC1-NKD1-WNT5A	50477	15744	20410	52735	35648	CSNK2A1-MYC-WNT5A	4208	45258	25000	47595	27580	
BCL9-PORCN-WNT5A	8717	4136	14582	10861	40557	LRP5-SFRP1-WNT5A	3834	45289	12470	27179	43165	
TLE2-WNT1-WNT5A	6864	5968	35981	23184	14484	FZD6-WNT1-WNT5A	4137	47371	40981	23375	28715	
NLK-SFRP1-WNT5A	22263	52123	16817	33554	46452	FOSL1-FOXN1-WNT5A	5307	14590	45152	44826	55367	
LEF1-WNT1-WNT5A	9745	8583	36041	23307	26376	FZD6-PORCN-WNT5A	88	50478	30280	17366	51000	
FZD6-PORCN-WNT5A	88	50478	30280	17366	51000	CCND1-WIF1-WNT5A	37414	8236	3639	32526	9840	
CCND1-CTBP1-WNT5A	45138	36969	4022	32791	11604	FBXW11-FOXN1-WNT5A	1244	5232	21083	25289	44693	
FZD5-PPP2R1A-WNT5A	17060	9682	37942	54060	54700	CTNNBIP1-FGF4-WNT5A	8234	24257	4204	17646	42626	
CCND3-PORCN-WNT5A	12281	45137	3555	19433	30263	JUN-PYGO1-WNT5A	9776	20912	9445	6655	56641	
LRP6-RHOU-WNT5A	25925	53449	10404	18899	8677	FZD5-SFRP1-WNT5A	5145	42699	20854	57127	43347	
DVL2-SFRP1-WNT5A	12899	47430	34465	28971	49671	FBXW11-SLC9A3R1-WNT5A	17699	12088	3043	28403	36673	
PITX2-WNT1-WNT5A	29674	16693	38632	17220	34621	FZD8-WNT1-WNT5A	759	20769	42200	33299	23343	
BCL9-WNT3-WNT5A	9435	28043	21541	40962	35192	CSNK1G1-PORCN-WNT5A	8541	17540	20517	6560	46815	
CTNNBIP1-WNT1-WNT5A	2110	11579	40080	21974	43169	CSNK1D-PORCN-WNT5A	17071	12074	1312	10487	50936	
DVL1-EP300-WNT5A	45556	27855	659	56344	29253	FZD5-NKD1-WNT5A	33749	1909	44565	56409	39882	
CSNK2A1-CTNNB1-WNT5A	34875	52148	5403	46302	46674	LRP5-PORCN-WNT5A	4664	27857	8039	7363	54523	
CSNK1G1-JUN-WNT5A	1627	9471	37716	21278	33763	CXXC4-FOXN1-WNT5A	6575	17827	51655	52301	55304	
PPP2CA-WNT1-WNT5A	1188	16609	32224	18050	32772	FZD1-NLK-WNT5A	28100	15641	23012	14962	49066	
APC-WNT1-WNT5A	4247	4366	51707	29496	46072	LRP5-NLK-WNT5A	33250	14809	24503	18293	46276	
CSNK1G1-FZD2-WNT5A	20419	29433	26502	7708	18760	FZD7-NKD1-WNT5A	53120	6594	44749	54824	2305	
DIXDC1-FGF4-WNT5A	4107	43702	11521	38540	15389	FZD5-FZD2-WNT5A	3403	12239	17878	32444	43130	
CSNK1A1-CTBP2-WNT5A	17747	9071	3307	44304	37334	FOSL1-PORCN-WNT5A	684	10157	3538	9803	48095	
CSNK2A1-T-WNT5A	18871	49162	6434	9546	14718	BTRC-FOXN1-WNT5A	4629	21553	49380	16835	38205	
DKK1-GSK3A-WNT5A	43	19654	49919	41864	44606	CSNK1G1-FOXN1-WNT5A	3727	8535	45722	16807	52197	
DIXDC1-FOXN1-WNT5A	5575	34443	41139	40268	26945	FOSL1-SFRP1-WNT5A	10825	7619	8773	53939	44771	
DIXDC1-PORCN-WNT5A	17412	29192	9192	10144	42283	DVL1-SLC9A3R1-WNT5A	24289	20621	1348	45986	19657	
FOSL1-WNT1-WNT5A	5033	6402	35717	26574	39026	FZD5-CSNK1D-WNT5A	10782	25515	25535	29067	55122	
CXXC4-NLK-WNT5A	46697	2350	52931	39870	42513	FZD8-GSK3A-WNT5A	792	39203	53965	12834	30863	
CSNK1D-SFRP1-WNT5A	7931	18053	3281	19001	33260	TCF7L1-WIF1-WNT5A	19561	51039	4589	44974	51657	
LRP5-WNT1-WNT5A	8985	6457	18102	28743	39412	DAAM1-GSK3A-WNT5A	993	52299	45640	48410	22898	
DKK1-WNT1-WNT5A	7312	29238	24298	21731	36669	APC-FOXN1-WNT5A	4028	22788	53731	48438	52873	
APC-FZD2-WNT5A	4650	34812	32837	41537	24627	KREMEN1-WNT1-WNT5A	4362	35794	22223	40251	36925	
AXIN1-EP300-WNT5A	45393	1954	35430	55047	50435	FZD1-T-WNT5A	23654	53150	5001	19952	35892	
APC-GSK3A-WNT5A	177	33763	56807	53251	34234	AXIN1-FZD2-WNT5A	15305	45673	36309	22018	30853	
SFRP4-T-WNT5A	15711	24455	18874	6541	25978	LRP5-WNT3-WNT5A	28843	53692	4853	26810	40037	
CXXC4-SFRP1-WNT5A	13274	4885	7023	55279	47701	DKK1-PPP2R1A-WNT5A	17268	5548	34963	48461	43857	
FBXW4-WNT1-WNT5A	2762	44748	28649	28672	28184	FSHB-GSK3A-WNT5A	3423	15383	30952	30779	42858	
JUN-WIF1-WNT5A	17879	25683	7574	50125	47128	EP300-FZD2-WNT5A	15423	4753	16468	24781	37279	
CCND3-CSNK1D-WNT5A	26184	41606	8103	12634	19595	FBXW2-FOXN1-WNT5A	1059	14872	50798	40842	34023	
FRZB-FZD2-WNT5A	17706	25689	4179	20867	43661	LEF1-NKD1-WNT5A	19218	16256	39358	48742	17741	
BTRC-GSK3A-WNT5A	1331	34656	55842	14294	39235	PYGO1-WIF1-WNT5A	42194	2788	21830	11541	35248	
FZD1-SFRP1-WNT5A	14778	32523	5788	42552	34576	DIXDC1-GSK3A-WNT5A	1711	34055	53310	43993	38089	
FZD2-WNT1-WNT5A	4025	22760	45461	15274	35474	CCND1-FRAT1-WNT5A	7720	35707	9195	34088	9499	

Table 19. Rankings of WNT5A-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - 2002.

RANKING @ t_i USING SOBOL - 2002											
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}
CSNK1D-FGF4-WNT5A	27276	41074	28302	22360	34593	FSHB-T-WNT5A	45606	52982	44145	47718	206
CTNNBIP1-WIF1-WNT5A	37517	8726	47830	33901	17853	CCND1-FGF4-WNT5A	11036	43537	12003	4568	37363
FZD5-JUN-WNT5A	46652	4870	31639	33192	2907	CCND2-LRP6-WNT5A	4772	13576	13447	14907	37434
PITX2-PORCN-WNT5A	4366	18564	14041	19978	22471	CXXC4-PORCN-WNT5A	47497	52019	55859	50726	19154
LEF1-T-WNT5A	13770	32123	1321	829	46232	DKK1-FGF4-WNT5A	3774	41348	22112	15337	7096
CCND2-WNT1-WNT5A	26348	908	6977	2060	37746	DVL2-FGF4-WNT5A	25909	3076	24938	11478	55213
CTNNBIP1-FRAT1-WNT5A	11059	21534	9005	4048	52412	CTBP1-FGF4-WNT5A	7713	2474	7138	10246	21735
CTNNBIP1-NLK-WNT5A	20035	789	8556	6531	46843	DVL2-JUN-WNT5A	40789	46792	43770	36077	2170
TCF7L1-WNT1-WNT5A	50375	3147	51646	41475	20572	CXXC4-FGF4-WNT5A	4008	46378	14592	16580	56090
CSNK1D-PPP2R1A-WNT5A	26135	44357	28294	20860	36948	FZD5-FGF4-WNT5A	18127	25149	13713	14643	40340
CCND3-WNT1-WNT5A	33845	7291	36752	42568	20426	FSHB-NKD1-WNT5A	37314	18350	48369	53041	3700
TLE1-WIF1-WNT5A	32505	9057	54581	55409	2636	FSHB-FZD2-WNT5A	31407	32496	45697	55367	3033
LRP6-TCF7-WNT5A	867	275	15437	481	42453	FBXW2-FGF4-WNT5A	22402	43589	10843	23182	50271
AES-EP300-WNT5A	29197	43023	38116	41964	4843	DKK1-FOXN1-WNT5A	36811	44788	36126	29818	15014
APC-FZD6-WNT5A	14108	30582	22634	26168	31875	FZD5-FOXN1-WNT5A	42864	15694	46968	56449	26791
LRP6-SLC9A3R1-WNT5A	56177	2075	49249	44624	2897	CSNK1A1-FGF4-WNT5A	19234	7567	25442	12975	45195
DVL1-FOXN1-WNT5A	39198	8747	31422	43031	24076	LEF1-MYC-WNT5A	52016	50835	55336	49992	7038
FBXW11-LRP6-WNT5A	35469	4159	38803	31715	5198	EP300-WNT1-WNT5A	26125	33898	12493	14926	56427
PITX2-WNT3-WNT5A	3631	37403	19670	4320	50237	CCND2-TCF7-WNT5A	22744	2466	10207	4582	38232
CXXC4-FOSL1-WNT5A	45823	54747	52368	41434	48001	FBXW11-FGF4-WNT5A	27801	7146	14256	13536	21447
DIXDC1-NKD1-WNT5A	52842	853	34383	35927	975	CSNK2A1-MYC-WNT5A	35456	22735	56665	49988	33664
BCL9-PORCN-WNT5A	10987	16048	15283	11849	27280	LRP5-SFRP1-WNT5A	2477	17688	15662	22754	16525
TLE2-WNT1-WNT5A	39711	21605	38989	30871	11764	FZD6-WNT1-WNT5A	54919	15489	31019	44772	9818
NLK-SFRP1-WNT5A	7723	23039	14415	17477	48341	FOSL1-FOXN1-WNT5A	8341	10381	8155	9375	49603
LEF1-WNT1-WNT5A	54167	7134	32380	34672	21919	FZD6-PORCN-WNT5A	44224	38925	32092	51688	14427
FZD6-PORCN-WNT5A	44224	38925	32092	51688	14427	CCND1-WIF1-WNT5A	52311	43612	54645	45673	6949
CCND1-CTBP1-WNT5A	4347	14757	26231	13484	42235	FBXW11-FOXN1-WNT5A	39827	21653	53284	49894	14306
FZD5-PPP2R1A-WNT5A	13161	3675	15841	13079	29407	CTNNBIP1-FGF4-WNT5A	19330	4795	13940	11390	41432
CCND3-PORCN-WNT5A	38273	8403	32926	50822	31855	JUN-PYGO1-WNT5A	2460	21997	22687	2953	49677
LRP6-RHOU-WNT5A	1674	54809	6843	11880	53337	FZD5-SFRP1-WNT5A	3648	6975	12983	2806	46950
DVL2-SFRP1-WNT5A	27290	8838	10832	13550	48661	FBXW11-SLC9A3R1-WNT5A	26559	43402	28324	24578	29359
PITX2-WNT1-WNT5A	34	29476	27919	8439	25717	FZD8-WNT1-WNT5A	55340	46156	39368	53203	20930
BCL9-WNT3-WNT5A	3109	27442	229	162	32612	CSNK1G1-PORCN-WNT5A	10356	8876	25975	28454	18185
CTNNBIP1-WNT1-WNT5A	39178	36630	45107	49287	14044	CSNK1D-PORCN-WNT5A	33173	15133	30807	39641	18354
DVL1-EP300-WNT5A	50248	16218	30548	30959	5678	FZD5-NKD1-WNT5A	7463	43025	2190	5552	51516
CSNK2A1-CTNNB1-WNT5A	49018	50110	52351	40046	7587	LRP5-PORCN-WNT5A	52695	9213	43304	43600	2584
CSNK1G1-JUN-WNT5A	21479	39247	6333	24156	52648	CXXC4-FOXN1-WNT5A	45779	49880	48086	39298	56659
PPP2CA-WNT1-WNT5A	48329	11938	40478	41705	4471	FZD1-NLK-WNT5A	26056	2877	20780	17408	38034
APC-WNT1-WNT5A	35340	14411	42165	39241	29207	LRP5-NLK-WNT5A	7424	17108	1077	11334	46700
CSNK1G1-FZD2-WNT5A	50135	56267	44911	41731	22635	FZD7-NKD1-WNT5A	44945	5271	38820	34295	16856
DIXDC1-FGF4-WNT5A	54426	18498	38052	43829	24212	FZD5-FZD2-WNT5A	9680	33164	12121	24460	14076
CSNK1A1-CTBP2-WNT5A	11628	24885	28394	9281	35281	FOSL1-PORCN-WNT5A	17862	53252	383	11834	29054
CSNK2A1-T-WNT5A	23799	14174	1661	753	51344	BTRC-FOXN1-WNT5A	47737	862	51520	47865	16688
DKK1-GSK3A-WNT5A	3254	56641	8807	7141	43235	CSNK1G1-FOXN1-WNT5A	21617	15364	15938	25477	56058
DIXDC1-FOXN1-WNT5A	7919	48369	15784	27764	27632	FOSL1-SFRP1-WNT5A	50217	49176	47672	56091	8412
DIXDC1-PORCN-WNT5A	952	7968	6431	9090	46718	DVL1-SLC9A3R1-WNT5A	13958	50206	15689	28528	49687
FOSL1-WNT1-WNT5A	25484	1744	15300	2521	38727	FZD5-CSNK1D-WNT5A	21298	15129	1430	366	40105
CXXC4-NLK-WNT5A	12448	41748	17765	12599	37639	FZD8-GSK3A-WNT5A	20110	8208	19050	4417	52624
CSNK1D-SFRP1-WNT5A	11269	25479	3686	15976	27188	TCF7L1-WIF1-WNT5A	45712	19992	50710	52827	3045
LRP5-WNT1-WNT5A	50803	3849	56592	53600	4056	DAAM1-GSK3A-WNT5A	25487	825	7891	11618	44798
DKK1-WNT1-WNT5A	43200	9393	41473	28806	20289	APC-FOXN1-WNT5A	29633	44234	48820	31227	29427
APC-FZD2-WNT5A	19978	21918	10502	24010	51341	KREMEN1-WNT1-WNT5A	41161	34326	39043	56585	47900
AXIN1-EP300-WNT5A	47677	47620	52664	49981	17016	FZD1-T-WNT5A	24581	37777	8879	6834	26206
APC-GSK3A-WNT5A	18761	23736	20548	24504	33419	AXIN1-FZD2-WNT5A	4423	32881	5507	12376	25610
SFRP4-T-WNT5A	43270	6351	52763	49463	14811	LRP5-WNT3-WNT5A	40845	31021	41202	39346	3252
CXXC4-SFRP1-WNT5A	14084	3064	9093	9911	43525	DKK1-PPP2R1A-WNT5A	4917	40830	24393	22265	31089
FBXW4-WNT1-WNT5A	36308	26390	55507	53187	11273	FSHB-GSK3A-WNT5A	34115	22730	34862	34229	6583
JUN-WIF1-WNT5A	11573	40788	5006	2485	37662	EP300-FZD2-WNT5A	37476	54071	35212	38568	52547
CCND3-CSNK1D-WNT5A	26753	51792	5466	20864	48578	FBXW2-FOXN1-WNT5A	33411	48436	51071	56698	8436
FRZB-FZD2-WNT5A	17628	21945	16123	924	9969	LEF1-NKD1-WNT5A	22558	37161	4282	14655	50963
BTRC-GSK3A-WNT5A	10037	4468	5019	1007	49446	PYGO1-WIF1-WNT5A	9422	32695	26276	12872	6210
FZD1-SFRP1-WNT5A	5325	3946	27019	13433	49902	DIXDC1-GSK3A-WNT5A	55995	46273	39418	47962	20481
FZD2-WNT1-WNT5A	55233	54207	42446	47868	26353	CCND1-FRAT1-WNT5A	427	45796	15844	19380	29008

Table 20. Rankings of WNT5A-X-X. A list of approximately first 125 combinations with rankings below 10,000 out of 57,155. SA - SOBOL; Implementation - martinez.

RANKING @ t_i USING SOBOL - MARTINEZ												
3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	3rd order comb.	t_1	t_3	t_6	t_{12}	t_{24}	
CSNK1D-FGF4-WNT5A	39875	34325	26022	14242	1408	FSHB-T-WNT5A	56577	45398	1560	25202	8403	
CTNNBIP1-WIF1-WNT5A	28881	38782	26985	15415	14875	CCND1-FGF4-WNT5A	6297	37930	14914	5118	3140	
FZD5-JUN-WNT5A	37922	45149	3248	18094	8459	CCND2-LRP6-WNT5A	23928	33565	7728	24952	7424	
PITX2-PORCN-WNT5A	23589	48950	34402	37236	3755	CXXC4-PORCN-WNT5A	30469	36642	4574	55370	14476	
LEF1-T-WNT5A	49428	14633	28678	580	7231	DKK1-FGF4-WNT5A	38877	17476	11090	25677	46913	
CCND2-WNT1-WNT5A	8935	56664	50350	50391	11278	DVL2-FGF4-WNT5A	37579	21122	32279	30959	6003	
CTNNBIP1-FRAT1-WNT5A	9313	54626	33929	10670	26211	CTBP1-FGF4-WNT5A	2069	20005	8782	7871	28177	
CTNNBIP1-NLK-WNT5A	10769	10715	43199	6383	43941	DVL2-JUN-WNT5A	56096	6903	2980	44469	43199	
TCF7L1-WNT1-WNT5A	44025	2425	32527	20064	38205	CXXC4-FGF4-WNT5A	14261	23219	50216	56128	9682	
CSNK1D-PPP2R1A-WNT5A	34799	46397	27927	38367	6548	FZD5-FGF4-WNT5A	1891	8102	55477	53665	49905	
CCND3-WNT1-WNT5A	43181	44716	14441	14980	34724	FSHB-NKD1-WNT5A	54779	40235	14719	3551	9105	
TLE1-WIF1-WNT5A	13523	477	24572	24146	33247	FSHB-FZD2-WNT5A	22760	56612	24534	7272	7730	
LRP6-TCF7-WNT5A	35245	42533	12463	3947	884	FBXW2-FGF4-WNT5A	27493	53623	25626	34239	3074	
AES-EP300-WNT5A	29498	5467	36624	45146	8858	DKK1-FOXN1-WNT5A	11041	32783	5504	28116	20846	
APC-FZD6-WNT5A	40404	10209	8884	48406	4407	FZD5-FOXN1-WNT5A	14770	8419	1940	49556	36803	
LRP6-SLC9A3R1-WNT5A	53761	48694	17528	9747	26436	CSNK1A1-FGF4-WNT5A	17317	3438	16557	42025	30659	
DVL1-FOXN1-WNT5A	7913	15374	11779	43135	49515	LEF1-MYC-WNT5A	15675	51861	35637	1042	9483	
FBXW11-LRP6-WNT5A	44516	5058	17175	31059	17540	EP300-WNT1-WNT5A	18070	53885	18563	56960	314	
PITX2-WNT3-WNT5A	11058	51240	29498	43821	8108	CCND2-TCF7-WNT5A	5759	24765	29731	14697	7213	
CXXC4-FOSL1-WNT5A	44523	32024	5826	41353	32438	FBXW11-FGF4-WNT5A	34769	3709	29680	9258	5901	
DIXDC1-NKD1-WNT5A	15090	51048	5734	37831	37533	CSNK2A1-MYC-WNT5A	37394	36968	36088	1047	19004	
BCL9-PORCN-WNT5A	34440	9539	51956	35220	5319	LRP5-SFRP1-WNT5A	46626	53919	15587	3017	5879	
TLE2-WNT1-WNT5A	46888	6306	53838	23255	34200	FZD6-WNT1-WNT5A	27585	47847	15634	4486	22587	
NLK-SFRP1-WNT5A	1980	50539	36522	25586	2949	FOSL1-FOXN1-WNT5A	52174	12235	9794	10821	15555	
LEF1-WNT1-WNT5A	24144	51166	47464	53981	30498	FZD6-PORCN-WNT5A	8901	16659	3797	41382	31216	
FZD6-PORCN-WNT5A	8901	16659	3797	41382	31216	CCND1-WIF1-WNT5A	44698	46968	24492	10707	12993	
CCND1-CTBP1-WNT5A	42105	14132	21995	16199	43575	FBXW11-FOXN1-WNT5A	50898	34299	23183	838	55601	
FZD5-PPP2R1A-WNT5A	24265	52942	6115	49206	3338	CTNNBIP1-FGF4-WNT5A	4792	23078	54974	38853	49989	
CCND3-PORCN-WNT5A	39066	29570	4018	3443	56436	JUN-PYGO1-WNT5A	5773	12825	7216	47792	6321	
LRP6-RHOU-WNT5A	29804	56580	34206	18715	801	FZD5-SFRP1-WNT5A	16282	22947	54746	32208	20217	
DVL2-SFRP1-WNT5A	25363	22509	18513	9807	6761	FBXW11-SLC9A3R1-WNT5A	275	14652	20579	7195	42710	
PITX2-WNT1-WNT5A	34426	18511	22931	30346	5013	FZD8-WNT1-WNT5A	55382	28883	536	42970	27045	
BCL9-WNT3-WNT5A	6367	13057	20467	21997	48148	CSNK1G1-PORCN-WNT5A	46413	14655	30449	49521	13435	
CTNNBIP1-WNT1-WNT5A	52693	11674	3169	39076	16576	CSNK1D-PORCN-WNT5A	22402	4216	2288	18135	42734	
DVL1-EP300-WNT5A	18933	25983	3336	33670	35252	FZD5-NKD1-WNT5A	40730	52111	18455	48698	51553	
CSNK2A1-CTNNB1-WNT5A	15912	32149	48221	26938	16715	LRP5-PORCN-WNT5A	14554	31962	47440	55611	32184	
CSNK1G1-JUN-WNT5A	90	18823	34308	8819	39419	CXXC4-FOXN1-WNT5A	55262	11570	2649	39122	29365	
PPP2CA-WNT1-WNT5A	51641	38045	26358	31132	12482	FZD1-NLK-WNT5A	5156	51064	50988	8427	47484	
APC-WNT1-WNT5A	37251	37308	4578	24642	44801	LRP5-NLK-WNT5A	45036	52213	6262	10225	16127	
CSNK1G1-FZD2-WNT5A	47509	40249	19979	4150	23159	FBXW11-NKD1-WNT5A	10258	28094	47222	55721	8269	
DIXDC1-FGF4-WNT5A	21879	5576	19569	19900	43009	FZD5-FZD2-WNT5A	30203	8433	36831	1215	1675	
CSNK1A1-CTBP2-WNT5A	9289	37103	7483	11014	25436	FOSL1-PORCN-WNT5A	51271	54488	32643	20512	3950	
CSNK2A1-T-WNT5A	3889	52194	41219	43938	2464	BTRC-FOXN1-WNT5A	19210	37398	35493	33336	33577	
DKK1-GSK3A-WNT5A	11537	9948	15513	25241	48610	CSNK1G1-FOXN1-WNT5A	6387	29278	22354	7557	5856	
DIXDC1-FOXN1-WNT5A	1445	8496	13536	21503	49118	FOSL1-SFRP1-WNT5A	8800	21398	39607	27982	22951	
DIXDC1-PORCN-WNT5A	16164	11219	7718	36336	22820	DVL1-SLC9A3R1-WNT5A	1145	13814	29450	54395	45479	
FOSL1-WNT1-WNT5A	2153	54808	25487	36688	13369	FZD5-CSNK1D-WNT5A	22240	8729	8905	8361	14874	
CXXC4-NLK-WNT5A	32823	7902	18426	32670	44201	FZD8-GSK3A-WNT5A	4848	28129	11376	48039	45929	
CSNK1D-SFRP1-WNT5A	46232	40726	39677	8395	43436	TCF7L1-WIF1-WNT5A	47869	53134	38896	13270	55762	
LRP5-WNT1-WNT5A	30334	45784	31282	41567	9655	DAAM1-GSK3A-WNT5A	24549	7238	51091	46401	45304	
DKK1-WNT1-WNT5A	7853	29582	28794	6214	37984	APC-FOXN1-WNT5A	36047	8945	28253	35882	15215	
APC-FZD2-WNT5A	14567	9359	10073	34001	26305	KREMEN1-WNT1-WNT5A	8580	19453	28068	44618	42482	
AXIN1-EP300-WNT5A	14220	28915	40087	2321	27392	FZD1-T-WNT5A	22751	44215	45584	36502	24158	
APC-GSK3A-WNT5A	42704	16681	10575	28232	1709	AXIN1-FZD2-WNT5A	32050	29613	22164	9626	30464	
SFRP4-T-WNT5A	29815	18586	46013	35505	49789	LRP5-WNT3-WNT5A	12616	49962	10697	21498	12328	
CXXC4-SFRP1-WNT5A	28284	25901	39210	34131	39373	DKK1-PPP2R1A-WNT5A	50575	2419	39679	15768	20655	
FBXW4-WNT1-WNT5A	39385	854	53445	15372	35604	FSHB-GSK3A-WNT5A	36948	46381	47772	40630	8149	
JUN-WIF1-WNT5A	32685	30228	10807	3557	2870	EP300-FZD2-WNT5A	50365	30389	578	35504	29268	
CCND3-CSNK1D-WNT5A	36336	364	51360	31612	43178	FBXW2-FOXN1-WNT5A	44200	598	33241	28485	56446	
FRZB-FZD2-WNT5A	23085	30981	22715	44817	55133	LEF1-NKD1-WNT5A	10158	48832	41731	2925	35572	
BTRC-GSK3A-WNT5A	30595	22112	8606	29405	28103	PYGO1-WIF1-WNT5A	23700	55503	49268	17706	33207	
FZD1-SFRP1-WNT5A	21330	16151	30093	43189	54496	DIXDC1-GSK3A-WNT5A	35337	25363	3235	35511	45938	
FZD2-WNT1-WNT5A	48674	41210	577	33184	38986	CCND1-FRAT1-WNT5A	29157	12146	55984	49883	9815	

8. Conclusion

This manuscript studies the time behaviour of 3rd order combinations of WNT family members in WNT3A stimulated HEK 293 cells. Based on the established 2nd order combinations of the WNT members, 3rd order combinations emerge using the machine learning based search engine. These 3rd order combinations might be of interest for further wet lab investigations.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on [Preprints.org](https://www.preprints.org).The following files (ending with .txt and can be opened in R or in simple text

processing program) with these names are made available with this manuscript. For every WNT family member, (1) **-3-odr-TP-ranking-linear.txt**, (2) **-3-odr-TP-ranking-rbf.txt**, (3) **-3-odr-TP-ranking-2002.txt**, and (4) **-3-odr-TP-ranking-martinez.txt**, contain rankings for 3rd order combinations across each time point for, HSIC (linear kernel), HSIC (rbf kernel), SOBOL (2002 implementation) and SOBOL (martinez implementation), respectively.

Author Contributions: SS conceived and designed the experiments; wrote the code; performed the experiments; analyzed the data; wrote the manuscript.

Data Availability Statement: Code for time series data available at CERN based Zenodo on <https://zenodo.org/records/14637456>.

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