AN ATLAS OF THE GENETIC VARIATIONS LINKING DYSREGULATION OF AUTOPHAGY TO HUMAN DISEASES: THE MISSING ENVIRONMENTAL LINK

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Abstract

The rising incidence of complex illnesses and their costs have revolutionized basic research, patient management, and societal needs. Between 70 to 90% of the risk of developing a disease is due to the air we breathe, the water we drink, and the surroundings in which we work and live. Visibly polluted, infectious or not, the fact remains that we are more than ever exposed to environmental risks. Air pollution is the fourth most prevalent deadly risk factor worldwide and by far the leading risk factor for hundreds of diseases, including respiratory infections, inflammatory illness, and cancer. Thus, an unhealthy environment can be considered as a pandemic, affecting 280 million people and claiming 12 million deaths every year. Although critical for identifying of the people at risk, the causal environment components (pollutants and/or the microbiome), and the affected physiological mechanisms are not well understood. Herein, we consider the dysregulation of macroautophagy (hereafter referred to as 'autophagy'), as the mechanism at the heart of an immediate response to environmental stress. We discuss the missing link between the autophagy gene variations, and the exposome in the susceptibility, prognosis, and management of complex diseases when embracing personalized medicine.

Keywords

Air pollutants/exposomics, autoimmunity, autophagy, cancers, COPD, environmental diseases, eQTL, infection, inflammatory, polymorphism, prognosis, risk, susceptibility, theragnosis.

Short title

Autophagy Gene SNP — Environmental Interactions in Human Diseases

Abbreviations

ATG, autophagy-related

CD, Crohn disease

eQTL, expression quantitative trait loci

GTEx, genotype-tissue expression

GWAS, genome-wide association studies

LC3-II, phosphatidylethanolamine conjugated to LC3

LD, linkage disequilibrium

LUAD, lung adenocarcinoma

MAF, minor allele frequency

NSCLC, non-small cell lung cancer

OS, overall survival

PtdIns3K CIII, class III phosphatidylinositol 3-kinase

PtdIns3P, phosphatidylinositol-3-phosphate

SNPs, single-nucleotide polymorphisms

sQTL, splicing quantitative trait loci

ULK, unc-51 like autophagy activating kinase

WHO, World Health Organization

Autophagy: an immediate cellular response to environmental challenges

When it comes to environmental stress, we are not equal (**Figure 1**). Accordingly, we reasoned that the efficiency of our inherited "environmental response machinery" may determine our susceptibility to illness. Among the many mechanistic pathways, we focus our attention on autophagy, an immediate adaptive cellular response to environmental injury that ensures cell repair [1]. As suggested by its name (auto = self; phagy = eating), autophagy enables in all eukaryotic cell types the turnover of all organelles and most long-lived proteins by a pathway that begins with the formation of a double-membrane compartment, termed a "phagophore", which captures from the cytosol these components. The phagophore expands into a completed vesicle, an "autophagosome," and subsequently, the autophagosome rapidly fuses with a lysosome to become an "autolysosome" in which the content is finally degraded. Successful completion of autophagy requires the coordinated orchestration of more than 61 different autophagy-related (ATG) proteins and regulators acting at different steps of the process, namely:

(i) ULK (unc-51 like autophagy activating kinase) complex (ULK1, ULK2, ATG13, RB1CC1/FIP200, and ATG101) initiates the induction step;

(ii) Once activated, ULK1 phosphorylates AMBRA1, a component of the class III phosphatidylinositol 3-kinase (PtdIns3K CIII) complex (PIK3C3/VPS34, PIK3R4/VPS15, ATG14, BECN1 and NRBF2), enabling it to relocate from the cytoskeleton to the phagophore.

(iii) Phosphatidylinositol-3-phosphate (PtdIns3P), generated by the PtdIns3K CIII, specifically binds the PtdIns3P effectors WIPI1 (WD repeat domain, phosphoinositide interacting 1) and WIPI2 and catalyzes the ubiquitination-like reactions that regulate phagophore elongation.

(iv) In the first ubiquitination-like reaction, ATG5 and ATG12 are conjugated to each other in the presence of ATG7 and ATG10. Attachment of the fully formed complex containing ATG5, ATG12, and ATG16L1 on the phagophore membrane induces the second complex to covalently conjugate phosphatidylethanolamine to LC3 (LC3-II), which facilitates closure of the phagophore into the autophagosome.

(v) ATG9 (the ATG9-ATG2-WIPI1/Atg18 complex), another factor essential for expansion of the phagophore, cycles between endosomes, the Golgi, and the phagophore, possibly carrying lipid components for membrane expansion.

(vi) ATG4 removes LC3-II from the outer surface of newly formed autophagosomes, and LC3 on the inner surface is eventually degraded when the autophagosome fuses with lysosomes.

(vii) The fusion between an autophagosome and a lysosome involves several proteins, including LAMP, RAB7, and the second complex of PtdIns3K CIII (PIK3R4/VPS15, PIK3C3, UVRAG, and BECN1) resulting in vesicle breakdown and cargo degradation into autolysosomes by lysosomal hydrolases.

(viii) Under both baseline conditions and times of stress, the autophagic receptors SQSTM1/p62, NBR1, CALCOCO2/NDP52, and OPTN recognize and facilitate the selective elimination of ubiquitinated protein aggregates and damaged/dysfunctional organelles by sequestration within autophagosomes; these aggregates and organelles would otherwise accumulate during the life of the cell (**Figure 2**).

Throughout development and life, autophagy is required for the maintenance, self-renewal, and differentiation of stem-like cells, such as in the hematopoietic system. Likewise, such an intracellular 'renewal' (i.e., recycling) process also plays an essential role in determining homeostasis, functionality, and longevity of post-mitotic cells such as cardiomyocytes and neurons. In a state of emergency, exposure of all cell-types to environmental challenges as varied as nutrient starvation, pathogens, and chemical pollutants massively and transiently upregulates the whole autophagy machinery to repair cells and meet their need for energy. Such an intricate interplay between autophagy and the environment is essential for cell/individual adaptation to changing conditions.

The dosage effects of autophagy variants in human disease: Proof-of-principle from transgenic mice

To cope with environmental injury in a timely manner, the expression level of each autophagy component is upregulated to fine-tune the rate of autophagic flux. In support of this, the complete knockout of *Atg7* in mice, and by inference, the inhibition of the entire autophagy pathway, results in early lethality due to the critical survival role of autophagy. In contrast, $Atg7^{+/-}$ heterozygotes are viable through compensation from one wild-type allele, suggesting a dosage effect. Likewise, allelic loss of *Becn1* was demonstrated in mice to predispose to lymphomas, breast, hepatocellular, and lung carcinomas (**Figures S1C, S3C, S4C**). Since then, the mono-allelic deletion of other autophagy genes (*Atg16l1, Irgm1, Atg4c, Atg5, Uvrag, Ambra1,* etc.) has been shown to render cells or mice prone to neurodegeneration, inflammatory disease, and cancer (see for references **Figures S1C-S5C**).

Although these elegant genetic models have undoubtedly linked defects in autophagy to pathologies, these murine models do not reflect sufficiently the natural history of human diseases. The limitations include: *i*) important differences between human and mouse physiologies, and hence, the functions of autophagy may be more or less different and *ii*) similar deletions/loss-of-function *ATG* mutations have been found in humans, but they are not typical of common devastating diseases. In contrast to the monogenic variants identified for Mendelian disorders, most *ATG* variants identified so far through genome-wide association studies (GWAS) and genetic studies are common (see **tables S1-S6**). For instance, the discovery, a decade ago, of the two autophagy genes *ATG16L1* and *IRGM* as Crohn's

disease (CD) susceptibility loci has met some skepticism (**Figures S4**). The high prevalence of the CD risk-variants *ATG16L1* rs2241880 (leading to a T300A conversion, 51%) and *IRGM* rs10065172 (c.313C>T, 10%) in unaffected populations argues against a general deleterious autophagy phenotype as being the cause of inflammatory bowel disease. Strikingly, *Irgm1* null mice develop normally, have no apparent phenotype, and yet they are extremely susceptible to bacterial infections, all dying at 11–16 weeks post-infection. Similarly, the expression of the human ATG16L1^{T300A} variant does not affect constitutive or starvation-induced autophagy, whereas it dramatically impairs the clearance of bacteria by autophagy (i.e., xenophagy). This suggests that the losses of *Irgm1*– and *Atg16l1*– dependent autophagy are dispensable under normal physiological conditions, and instead impair selective xenophagy, upon bacterial challenge (**Figures S4**).

Therefore, we propose that neither exposure to environmental challenge, nor the presence of genetic autophagy variants alone are the direct cause of a disease. However, SNPs that lead to a low degree of autophagy impairment may alter the cell's ability to detoxify damaged organelles and predispose individuals to develop diseases related to aging (such as cancer, infection, neurodegenerative and inflammatory diseases), only upon chronic exposure to a *particular environmental risk*.

The challenge of assigning *ATG* variations to the cause of human disease phenotypes

The picture is even more complicated when considering any given environmental challenge, in which the life-threatening diseases develop in only a small minority of exposed individuals. To resolve this enigma, the current consensus suggests that both environmental and genetic risk factors control susceptibility. Over the last fifteen years, the completion of the human genome project and the remarkable progress of GWAS have identified hundreds of susceptibility loci for complex diseases, some of which concern autophagy-related genes.

In May 2020, a PubMed search of "autophagy AND (susceptibility OR polymorphism OR SNP OR variant OR variation OR mutation)" yielded 7,057 entries. Two hundred and sixteen relevant studies identified 216 common autophagy SNPs with a minor allele frequency (MAF) > 0.05 that are enriched in autoimmune, inflammatory, cardiovascular, neurological and lung diseases, and cancers (**Figure 3, Figures S1-S5**). A comprehensive SNP survey using the dbSNP (https://www.ncbi.nlm.nih.gov /snp/) [2], LitVar (https://www.ncbi.nlm.nih.gov/CBBresearch/Lu/Demo/LitVar/) [3], HaploReg (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php, v4.1) [4], and GTEx (Genotype-Tissue Expression; https://www.gtexportal.org/home/ v8 release) [5] public databases reveal that a huge gap remains between the correlations of *ATG* SNP and disease causality.

In fact, more than 90% of the risk-associated alleles are localized to non-coding genomic regions (intron, intergenic, 5' and 3' untranslated regions [UTRs]), which represents a critical bottleneck for SNP disease correlations (**Figure 4A**). In contrast, the "loss-of-function" mutations (i.e., nonsense, indels, frameshifts, and splice variants) that lead to a truncated protein, as well as missense variations that change the amino acid sequence, are rare (from 0.1 to 10%). By exerting a damaging effect on the corresponding protein, it might be expected that these loss-of-function *ATG* mutations can be harmful, result in severe diseases and may even be lethal, by impairing autophagy and the adaptation to changing environments.

It is noteworthy that 28% of *ATG* SNPs are *regulatory SNPs* also called expression quantitative trait loci (eQTL) that control mRNA transcript abundance by influencing the binding of a *transcription factor*, mRNA *splicing* (sQTL), and *stability* through microRNA. Likewise, most *ATG* SNPs (67%) are located in regions of the genome with linkage disequilibrium (LD) > 0.8, making it difficult to identify causal SNPs and their functional impact [6] (see **Figure 4B** and **supplementary tables**).

With this in mind, we present here a comprehensive atlas of 219 SNPs for 61 autophagy-related genes in 79 disease states (**Figures 4A-5A**, **Figures S1-S5, tables S1-S6**). So far, it should be acknowledged that most studies have focused on a handful of autophagy genes, precluding the establishment of any 'polygenic risk score' (**Figure 4B**). Likewise, only 25 studies have documented 'autophagy gene × environmental' interactions in conditions of bacterial infection (20 studies; 20,600 patients), tobacco usage (2 studies; 2,100 patients), exposures to coal (1 study; 1,400 patients) and air pollution (2 studies; 900 patients) (**Figure 3**).

The missing environmental link.

It has been estimated that environmental factors contribute to at least 70% of all diseases [7], which are, thus, considered avoidable. Because of the long latency period, exposures to a causal agent typically occur years to decades before disease diagnosis [8] (**Figure 5B**). Rather than a single-environment stress paradigm, it should be emphasized that we are exposed in the 'real world' to low but chronic exposure to a large variety of chemicals and stressors. At the cellular level, both pollutants and the microbiome virulence factors target autophagy [9,10]. Of interest, epidemiological studies have left no doubt that the etiology of auto-inflammatory or autoimmune disorders are more complicated than the binary 'environment x gene' interaction previously anticipated. Indeed, the incidences of CD are the highest in Europe and North America, where air pollution may encourage the spreading of certain viruses and bacteria. Evidence for this complex relationship is supported by mouse experiments demonstrating that co-infection with 'asymptomatic' virus and commensal bacteria sensitizes the *ATG16L1*^{T300A} mice to Crohn disease [11] ('virus-bacteria-susceptibility allele' relationship). Another concern is that during

our lifetime, we accumulate in our body long-lived and hydrophobic chemicals resulting from different routes and times of exposure. The totality of these components is called the exposome [8,12] (**Figure 2**). However, only a very limited number of widespread pollutants are currently monitored by the agencies that measure the quality of air, water, and food. As a result, this 'short' monitoring significantly underestimates past and current exposures.

To tackle the complex mixture of contaminants, we propose to stimulate interdisciplinary research to develop, test, validate, and compare internal and external biomarkers that could provide more accurate estimates of the environmental exposures relevant to chronic environmental diseases. The impacts of the environment on human health should be reconstructed through a combination of questionnaires, air quality measurements, dispersion model simulations, and exposomics (i.e., the totality of the chemicals and their metabolites in the blood and tissues).

PERSPECTIVES: The *ATG* GENE x EXPOSOME relationships as a road map for the future

At this stage, it should be stressed that previous efforts have missed investigating the impact of environmental pollutants on the expression of eQTL *ATG* variants. *ATG* eQTL are associated with a difference in transcript abundance between the homozygote of the referent allele, the heterozygote, and the alternate homozygote in the general population. While informative at the tissue level, it is not clear which cell types are affected by the *ATG* variants. Attention should be paid to gene regulation and thus eQTL variant expression, which is highly specific for an environmental cue. However, there is no information about the type of environmental exposures (external and internal exposomes, latency periods) of the investigated population-case cohorts. Solving this intricate exposome/microbiome/ autophagy eQTL relationship is particularly critical to understanding the rapid spread of the novel coronavirus SARS-CoV-2 and the high inter-individual vulnerability to COVID-19. [13]

In the next decade, we will find ourselves at a challenging crossroads encountering an unprecedented wealth of GENOMICS and EXPOSOMICS ("GENEXPOSOMICS") data, which will extend our understanding into defects in autophagy that are related to disease development. Elucidating the consequence by which ATG variants contribute to the inter-individual clinical variability upon environmental challenge is an essential step to translate the wealth of information of epidemiological, environmental, and genetic studies into precision medicine.

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No competing interests:

The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Figure 1: Global challenges linking environmental factors to health Issues.

92% of the world population breathes toxic air. An unhealthy environment can be considered as a pandemic, affecting 280 million people and claiming 12 million deaths every year, which is, more than deaths due to wars, famine, AIDS, tuberculosis, and, recently, COVID-19, all combined. The related annual financial losses of $4.6 trillion are equally massive — deaths and economic costs that are all preventable. In response to this public health emergency, 155 countries around the world now recognize the legal right to a healthy environment.

Figure 2: Overview of the Autophagy Pathway in response to environmental challenges.

Schematic depiction illustrating the molecular machinery of autophagy with the major autophagy-related proteins and complexes. Associations of *ATG* polymorphisms with cancers (red) and non-cancer diseases (blue). Upper, 'autophagy gene × environmental' interactions in conditions of bacterial infection, tobacco usage, exposures to coal and air pollution.

Figure 3: Atlas of the studies linking autophagy-related gene polymorphism to human diseases.

Upper, Number of studies, totaling the number of patients, *ATG* genes, and SNP per Europe, United States, and Asia. Note that whereas 70 to 90% of the risk of developing a disease is due to the environment, only 13% of studies on autophagy gene SNPs have included the environment as a trigger or exacerbating factor. Likewise, air pollution is the fourth most prevalent deadly risk factor worldwide and, so far, most of the studies focused on infections. Related to:


Europe


United States


Asia


Air pollution


Bacterial infection


Smoking

Lower, Workflow for identifying the common autophagy-related gene polymorphisms and their interaction with environmental factors in the susceptibility of complex human diseases.

Figure 4: Landscape of *ATG* polymorphism in human diseases

A. Distribution (in percentage, *left*) and predicted functional consequences (*right*) of 219 coding and non-coding regulatory *ATG* SNPs.
B. Limitations of the studies carried so far. *Left*, a handful of studied *ATG* SNPs. The number of diseases per gene as a function of the number of SNPs. *Right*, *ATG* SNP linkage disequilibrium.

Figure 5: Biomarkers of exposure and, ultimately, of risk assessment and clinical outcome.

A. Number of *ATG* polymorphisms in percentage for 79 diseases (cardiovascular, neurodegenerative, autoimmune diseases, and cancer). These variations have a significant impact on theragnosis, prognosis, and risk, particularly in cancer.

B. The concept of the exposome. Because of the long latency period, exposures to a causal agent/mixture typically occur years to decades before the diagnosis of cancer. The exposome is a unique marker that characterizes the totality of trace chemicals resulting from different routes (internal and external) and times of exposure over the lifetime of an individual. Shifts in endogenous metabolites and signaling molecules (OMICS) are meaningful.

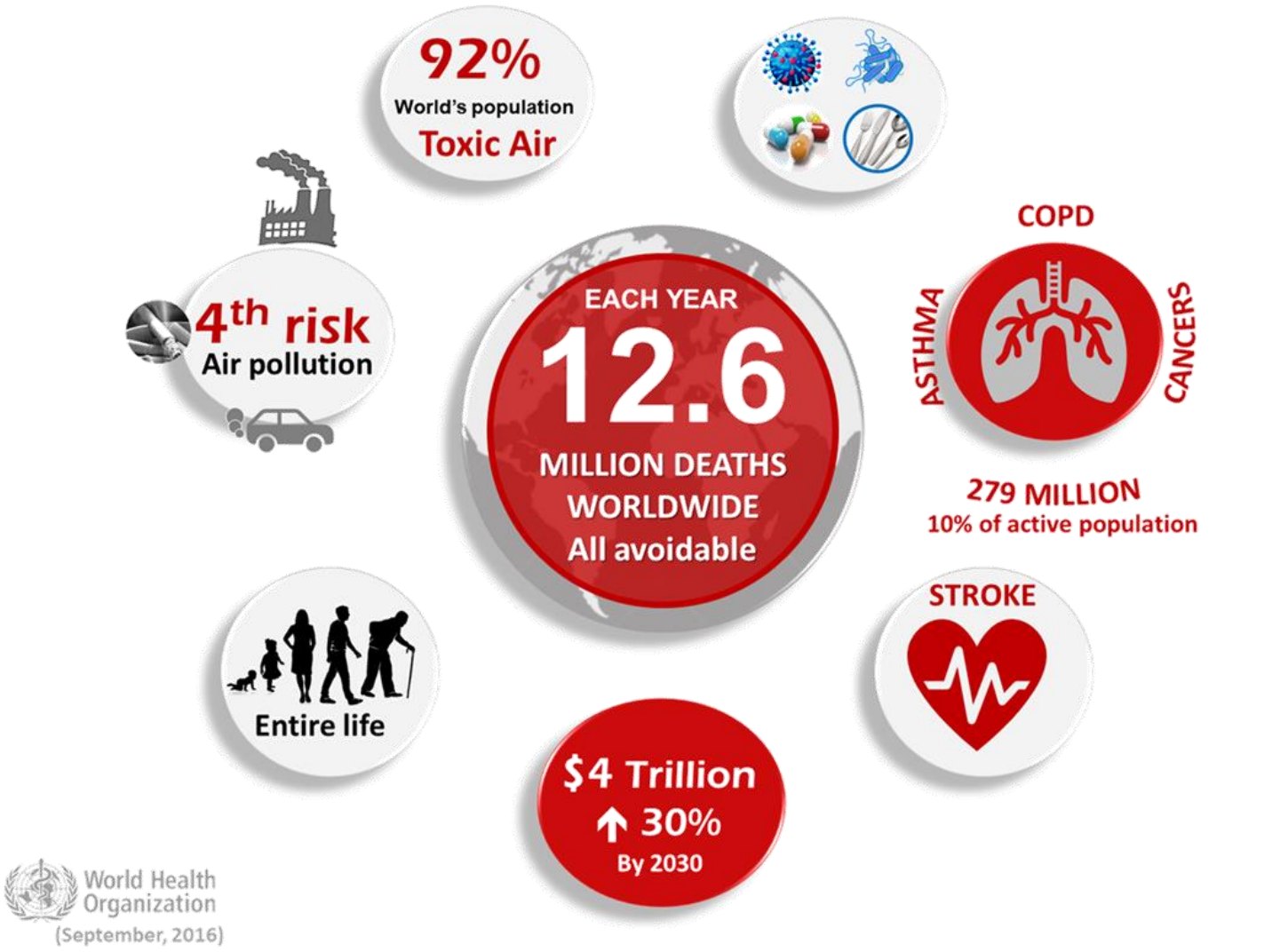
References

1. Yin Z, Pascual C, Klionsky D. Autophagy: machinery and regulation. Microb Cell [Internet] 2016; 3:588–96. Available from: http://microbialcell.com/researcharticles/autophagy-machinery-and-regulation/
2. Smigielski EM, Sirotkin K, Ward M, Sherry ST. dbSNP: a database of single nucleotide polymorphisms. Nucleic Acids Res [Internet] 2000; 28:352–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10592272
3. Allot A, Peng Y, Wei C-H, Lee K, Phan L, Lu Z. LitVar: a semantic search engine for linking genomic variant data in PubMed and PMC. Nucleic Acids Res [Internet] 2018; 46:W530–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29762787
4. Ward LD, Kellis M. HaploReg v4: systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease. Nucleic Acids Res [Internet] 2016; 44:D877-81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26657631
5. Carithers LJ, Ardlie K, Barcus M, Branton PA, Britton A, Buia SA, Compton CC, DeLuca DS, Peter-Demchok J, Gelfand ET, et al. A Novel Approach to High-Quality Postmortem Tissue Procurement: The GTEx Project. Biopreserv Biobank [Internet] 2015; 13:311–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26484571
6. Schaid DJ, Chen W, Larson NB. From genome-wide associations to candidate causal variants by statistical fine-mapping. Nat Rev Genet [Internet] 2018; 19:491–504. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29844615
7. Rappaport SM, Smith MT. Epidemiology. Environment and disease risks. Science [Internet] 2010; 330:460–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20966241
8. Wild CP, Scalbert A, Herceg Z. Measuring the exposome: a powerful basis for evaluating environmental exposures and cancer risk. Environ Mol Mutagen [Internet] 2013; 54:480–99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23681765
9. He B, Wang X, Yang C, Zhu J, Jin Y, Fu Z. The regulation of autophagy in the pesticide-induced toxicity: Angel or demon? Chemosphere [Internet] 2020; 242:125138. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31670000
10. Larabi A, Barnich N, Nguyen HTT. New insights into the interplay between autophagy, gut microbiota and inflammatory responses in IBD. Autophagy [Internet] 2020; 16:38–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31286804
11. Cadwell K, Patel KK, Maloney NS, Liu T-C, Ng ACY, Storer CE, Head RD, Xavier R, Stappenbeck TS, Virgin HW. Virus-Plus-Susceptibility Gene Interaction Determines Crohn's Disease Gene

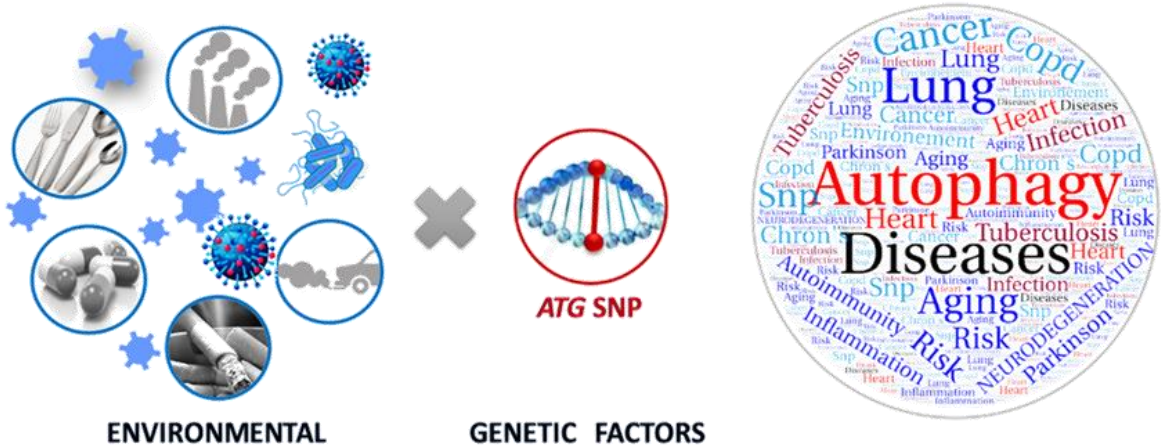
Atg16L1 Phenotypes in Intestine. Cell [Internet] 2010; 141:1135–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867410005453

12. Wild CP. The exposome: from concept to utility. Int J Epidemiol [Internet] 2012; 41:24–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22296988

13. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res [Internet] 2020; 24:91–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2090123220300540

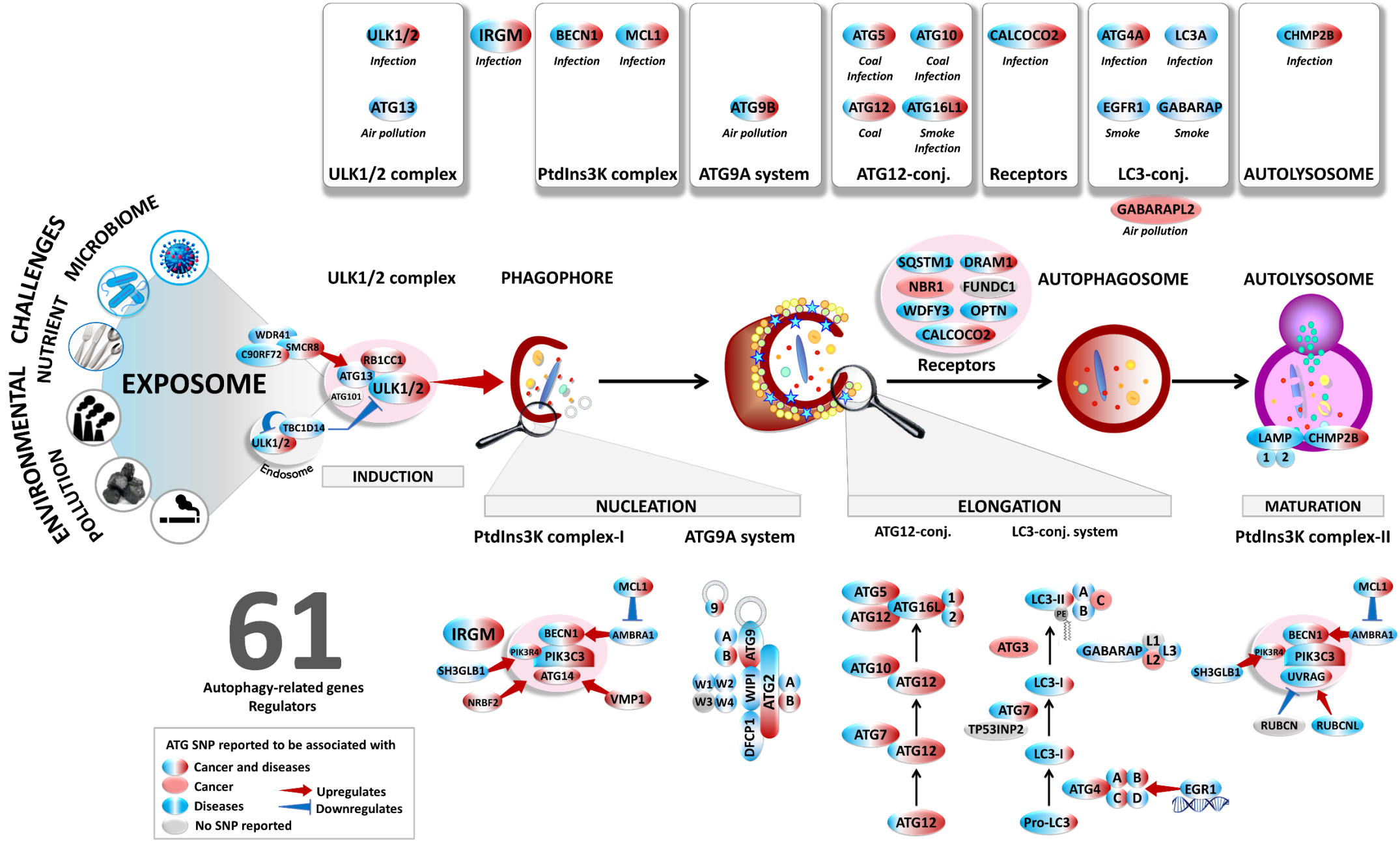


The basic, clinical and societal needs



▶ Definition of a population at risk

Figure 1_Iris GROSJEAN and Barnabé ROMÉO et al.



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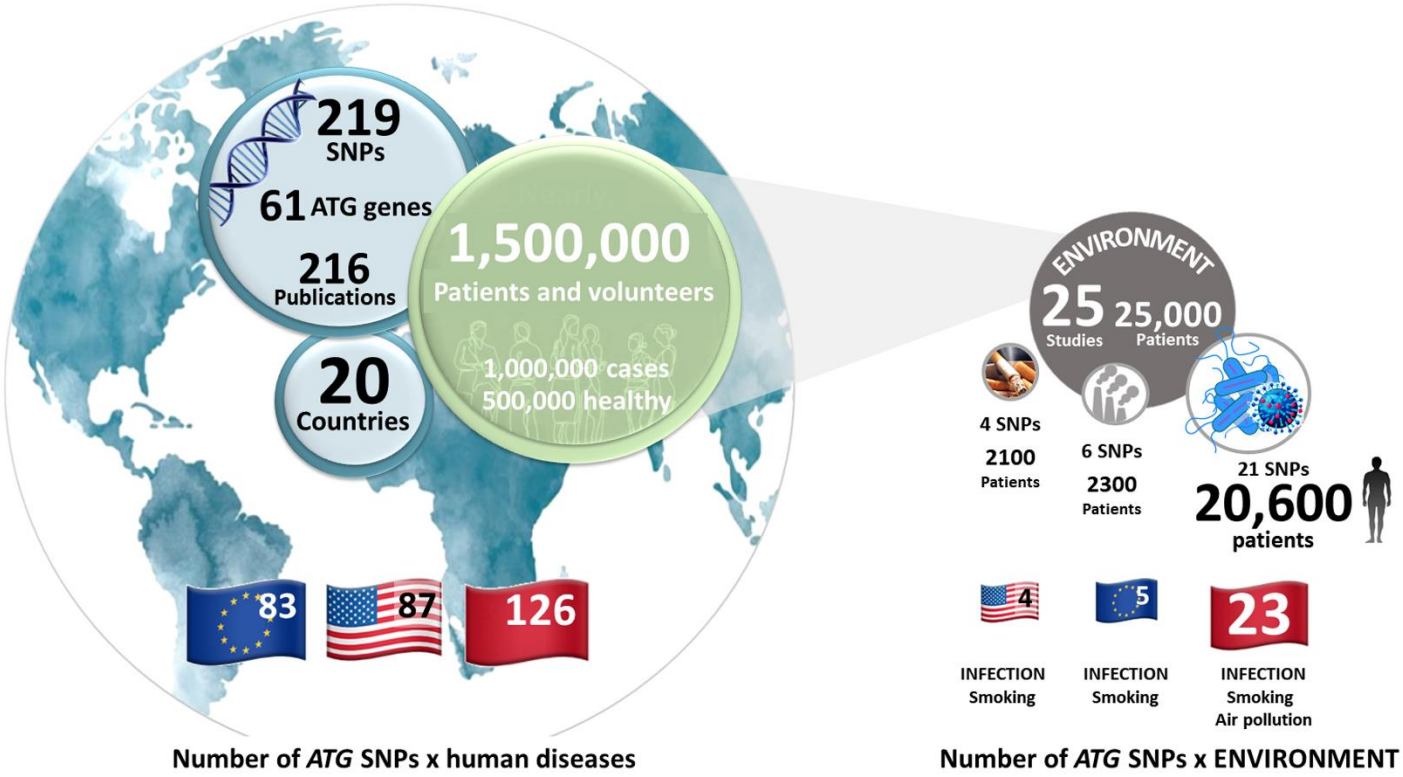

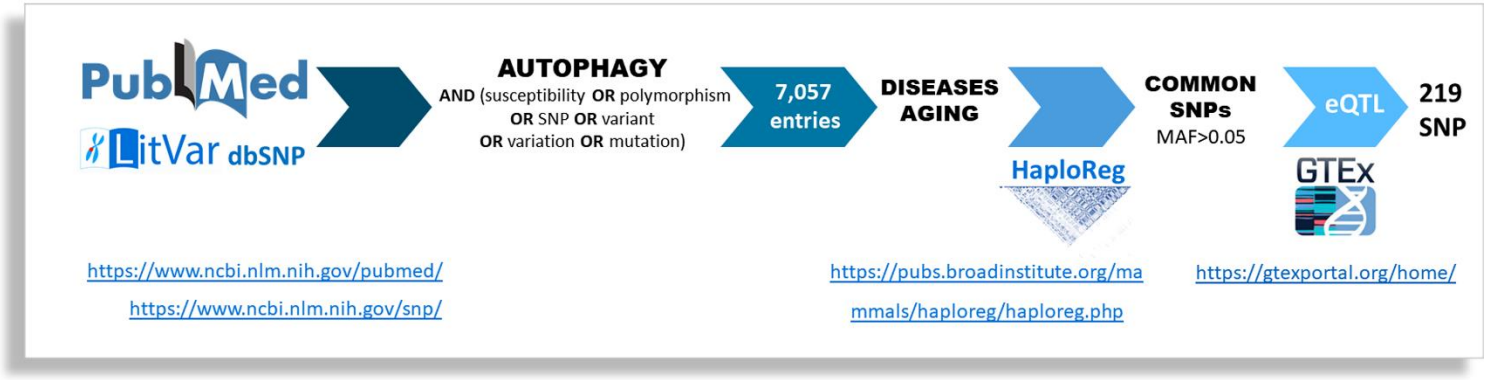

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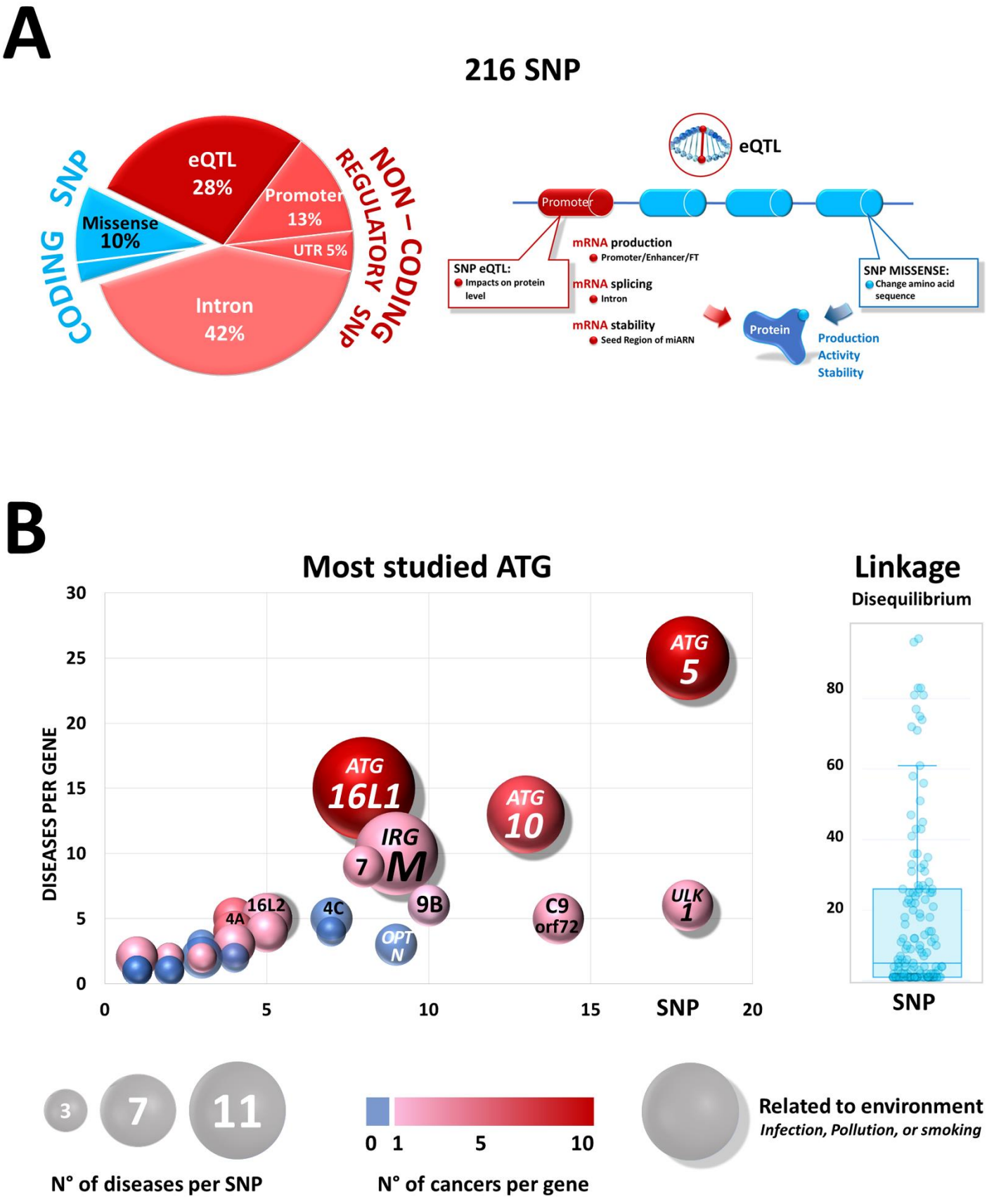
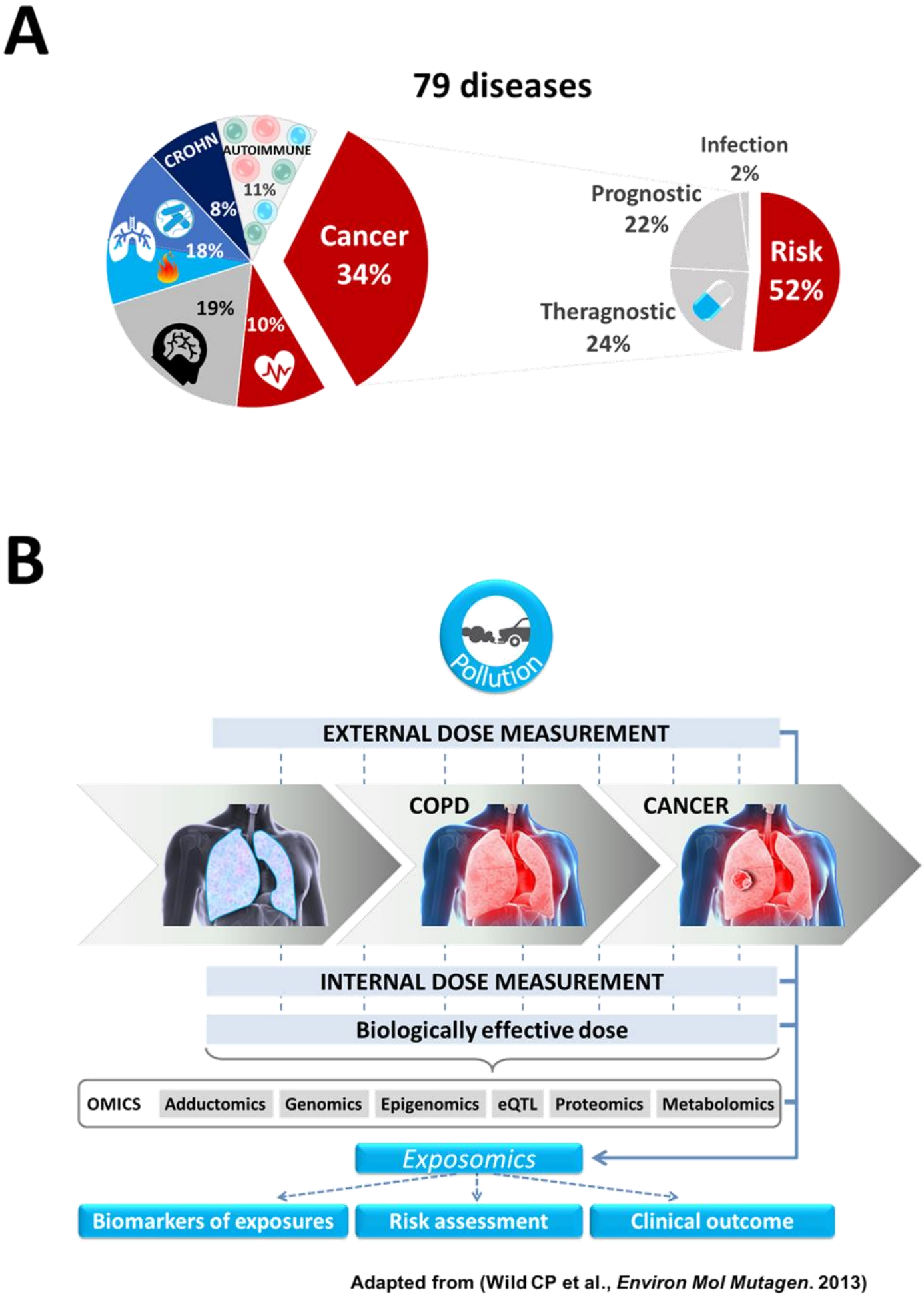


Figure 4_Iris GROSJEAN and Barnabé ROMÉO *et al.*



Adapted from (Wild CP et al., *Environ Mol Mutagen*. 2013)

Figure 5_Iris GROSJEAN and Barnabé ROMÉO *et al.*

Supplemental Information

An atlas of the genetic variations linking dysregulation of autophagy to human diseases: the missing environmental link

Iris Grosjean and Barnabé Roméo *et al.*

Supplementary list of autophagy-related genes and regulators investigated in this study

I. ULK1/2 complex
- ULK1
- ULK2
- RB1CC1
- ATG13
- ATG101
- TBC1D14
- SMCR8
- C9orf72
- WDR41
- IRGM

II. PtdIns3K complex
- BECN1
- PIK3C3/Vps34
- PIK3R4/VPs15
- AMBRA1
- ATG14
- NRBF2
- UVRAG
- RUBCN
- RUBCNL
- SH3GLB1/BIF-1
- MCL1
- VMP1

III. ATG9 complex
- ATG2A
- ATG2B
- ATG9A
- ATG9B
- WIPI1
- WIPI2
- WDR45B
- WDR45
- ZFYVE1/DFCP1

IV. ATG12 conj
- ATG5
- ATG7
- ATG10
- ATG12
- ATG16L1
- ATG16L2
- TP53INP2

V. LC3 conjugation system
- EGR1
- MAP1LC3A
- MAP1LC3B
- MAP1LC3C
- GABARAP
- GABARAPL1
- GABARAPL2
- GABARAPL3
- ATG3
- ATG4A
- ATG4B
- ATG4C
- ATG4D

VI. Autophagy receptors
- SQSTM1
- NBR1
- CALCOCO2
- WDFY3
- OPTN
- FUNDC1

- LAMP1
- LAMP2
- CHMP2B

Supplementary Figures

Figure S1. Autophagy deficiency in human lung diseases.

Figure S2. Autophagy deficiency in human cardiovascular diseases.

Figure S3. Autophagy deficiency in breast and urogenital diseases.

Figure S4. Autophagy deficiency in human gastrointestinal disorders.

Figure S5. Autophagy deficiency in human central nervous system diseases.

A. Summary of autophagy-related gene variations.

B. Steps of the autophagy pathway affected by SNPs.

C. Phenotypes of autophagy-deficient mouse models.

A

LUNG DISEASES

ASTHMA

ULK1 rs7487166, rs9652059, rs11616018, rs10902472 **RISK**

ATG5 rs573775, rs12201458_ rs12212740 >G rs633724 **RISK**
ATG5 rs510432> A ↑ exp (promoter)
ATG7 rs2594971>GG, rs1375206>CC **RISK**

MAP1LC3B rs8051218, rs7204722 **RISK**

TUBERCULOSIS

ULK1 rs7300908 **RISK**, rs12297124>T ↓ **RISK** x INFECTION
ULK1 rs7138581 3'-UTR>C ↓ >CG ↓ **RISK**, ↑ Severity
ULK1 rs9481 3'-UTR >A ↑ **RISK**

IRGM rs4958843>C, rs4958846> C (eQTL prom) ↓ **RISK** ↓ exp
IRGM rs10065172>T (eQTL miR-196) ↓ **RISK** ↓ exp
IRGM rs10059011 ↓ RISK, rs10052068
IRGM rs13361189 , rs9637876
MCL1 rs961581226
ATG4C rs11208029

ATG10 rs1864183, rs3734114

LAMP1 rs9577229

LUNG FIBROSIS

ATG5 rs510432 > T **RISK** x COAL
ATG10 rs1864182> GT ↓ **RISK** x COAL
ATG12 rs26538>T ↓ exp ↓ **RISK** x COAL

COPD

ATG16L1 rs2241880 >A ↑ **RISK** x SMOKING
ERG1 rs7729723 >G ↑ **RISK**

NICOTINE DEPENDENCE

GABARAP rs222843 **RISK**
GABARAP rs17710

LUNG CANCER

ULK1 rs7953348>A, rs12303764 >C **THERAGNOSTIC** (platinum)

MCL1 rs3831987 (non-smoker Protective)

BECN1 rs11552193

ATG14 rs17742719>A, rs8003279>G,
rs10099647>A **THERAGNOSTIC** (platinum)

ATG5 rs2245214>C **RISK**
ATG5 rs688810>C **RISK**, BAD **PROGNOSIS** (gefitinib)
ATG5 rs510432 PROTECTIVE, GOOD **PROGNOSIS** (gefitinib)

ATG7 rs8154>T (EGFR*) PROTECTIVE

ATG10 rs10036653>T **RISK** of brain metastasis
ATG10 rs1864183, rs1864182 rs10514231 **RISK**
ATG10 rs1864183 **THERAGNOSIS** (platinum)
ATG10 rs10036653 GOOD **PROGNOSIS** (gefitinib)
ATG10 rs1864182>T GOOD **THERAGNOSIS** (gefitinib)

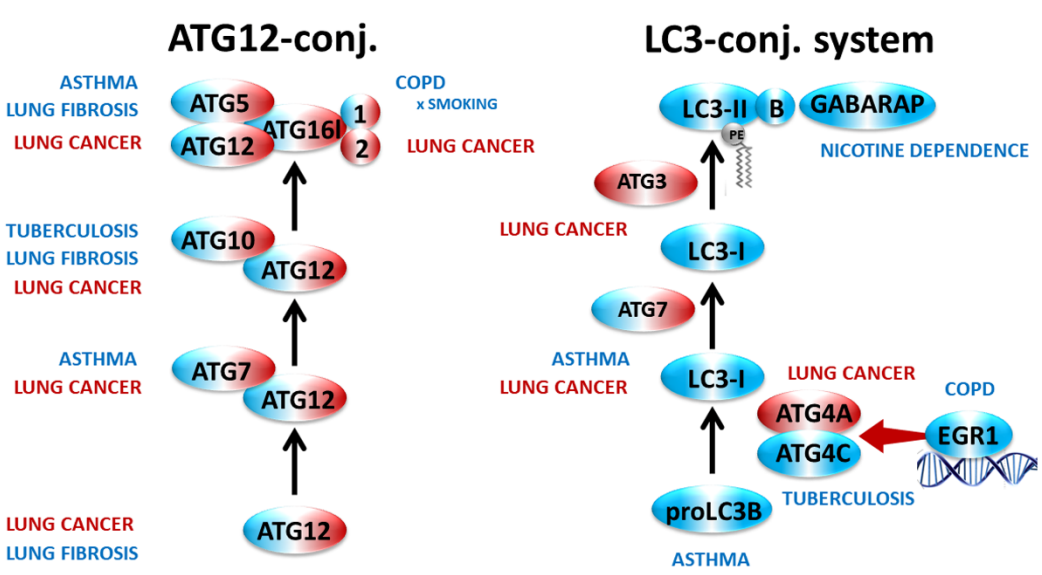
ATG12 rs26532>AA **RISK** of brain metastasis
ATG12 rs26538>T RISK, BAD **THERAGNOSIS** (gefitinib)
ATG12 rs1058600

ATG16L1 rs2241880 NSCLC >G ↓ RISK of brain metastasis
ATG16L1 rs2241880 (E GFR*) >G **RISK**
ATG16L2 rs11235604 >T BAD **THERAGNOSIS** (gefitinib)
ATG16L2 rs10898880>C **THERAGNOSIS** (radiotherapy) ↑ exp

ATG3 rs13082005>A **THERAGNOSIS** (platinum)
ATG4A rs807185 **RISK**

DRAM rs7955890>A and rs17032060>A **THERAGNOSIS**

B



C

Ulk1/2 $^{-/-}$ (DKO)	**RESPIRATORY distress** [1] Death within 24 h of birth
Atg5 $^{-/-}$	
Atg4b $^{-/-}$	**IDIOPATHIC PULMONARY FIBROSIS** (IPF) [2] (tunicamycin) ↑ inflammation
	LUNG FIBROSIS [3] (bleomycin) ↑ inflammation (neutrophil infiltration)
Atg5 ^{flox} Or ***Atg7*** ^{flox} *Myeloid Cell-Specific*	**FIBROSIS LUNG x INFLAMMATION** [4] ↑ IL18 (bleomycin)
Egr1 KO	**smoke-induced COPD** [5] *Egr1* KO ↓ Atg4B expression ↓ LC3B conversion
Map1lc3b $^{-/-}$	**smoke-induced COPD** [6]
	LUNG FIBROSIS [7] upon aging (bleomycin)
Becn1 $^{-/-}$ *Lung-Specific, Conditional*	**LETHAL RESPIRATORY INSUFFICIENCY** [8] ↓ Lung development (branching)
Silencing ***Fundc1***	**smoke-induced COPD** [9] cigarette smoke (CSE) COPD mice ↑ FUNDC1. Silencing *Fundc1* → ↓IL6 TNF ↓ CSE-induced mitophagy cell apoptosis. ↑ COPD lung function
Becn1 $^{+/-}$	**LUNG ADENOCARCINOMAS** [10,11]
Sh3glb1 $^{-/-}$	**SMALL CELL LUNG CARCINOMAS** [12]

Figure S1_Iris GROSJEAN and Barnabé ROMÉO et al.

A

HEART DISEASES

STROKE
ATG9B rs3800787, rs11769158, rs6464119, rs3918220, rs3763486 (attributed to NOS3)
GABARAPL1 rs3803539

CORONARY ARTERY disease
TBC1D14 rs10804990
ATG9B rs2373929
MAP1LC3 rs2424994, rs6088521

BLOOD PRESSURE and heart rate
ATG9B rs7830 **x AIR POLLUTION** urban **elderly**

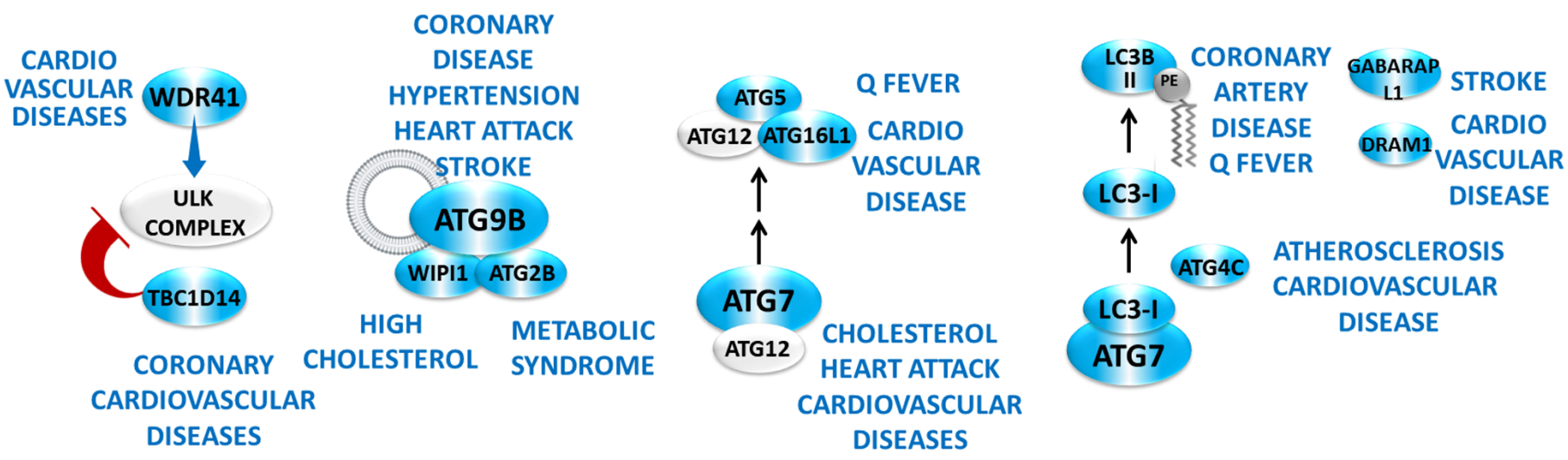
Q FEVER x *C. burnetii* infection
ATG5 rs2245214 Protective
MAP1LC3A rs1040747

CARDIOVASCULAR DISEASE
ATG4C rs6683832 _ **ATHEROSCLEROSIS**
ATG4C rs6587988
ATG4D rs10439163
ATG7 rs2594975_ **INFARCTION**
ATG7 rs7635838, rs2447607
ATG9B rs13307588 **INFARCTION**
ATG16L1 rs2241880 RISK ♀
DRAM1 rs77694286_Aging
WDR41 rs335632

METABOLIC syndrome
ATG2B rs4905480
AMBRA1 rs110389913

HDL cholesterol level
ATG7 rs2606736, rs7635838
WIPI1 rs2909207 eQTL

B



C

Atg13 $^{-/-}$	**HEART defect** [13] embryonic lethality
Rb1cc1 $^{-/-}$	**HEART defect** [14] embryonic lethality
Atg5 $^{Fl/Fl}$ *Cardiac-Specific*	**age-related CARDIOMYOPATHY** [15] ↑ left ventricular dimension ↓ fractional shortening
Uvrag $^{-/-}$	**age-related CARDIOMYOPATHY** [16] ↑ inflammation
Fbxo32/Atrogin1 $^{-/-}$	**CARDIOMYOPATHY** [17] myocardial remodeling, ↓diastolic function, arrhythmias ➔ fails to degrade CHMP2B, resulting in autophagy impairment

Figure S2_Iris GROSJEAN and Barnabé ROMÉO et al.

A

MENOPAUSE

ATG10 rs9447453 C>A **Delayed age**

CANCER

BREAST CANCER

SMCR8 rs1563634 **RISK**

MCL1 rs3831987 **RISK**
NRBF2 rs10995190 **RISK**
NRBF2 rs10509168 **RISK**
VMP1 rs1295925 **RISK**

ATG10 rs1864182 C>A **RISK**
ATG10 rs10514231 C>T **RISK**
ATG10 rs7707921 T>A **RISK**
ATG10 rs73134739 T>C **RISK**

ATG7 rs8154 T>C **PROGNOSIS**

ATG5 rs473543 G>A **THERAGNOSIS**
(Anthracycline and/or taxane)

NBR1 rs17599948 G>C **RISK**

OVARIAN CANCER

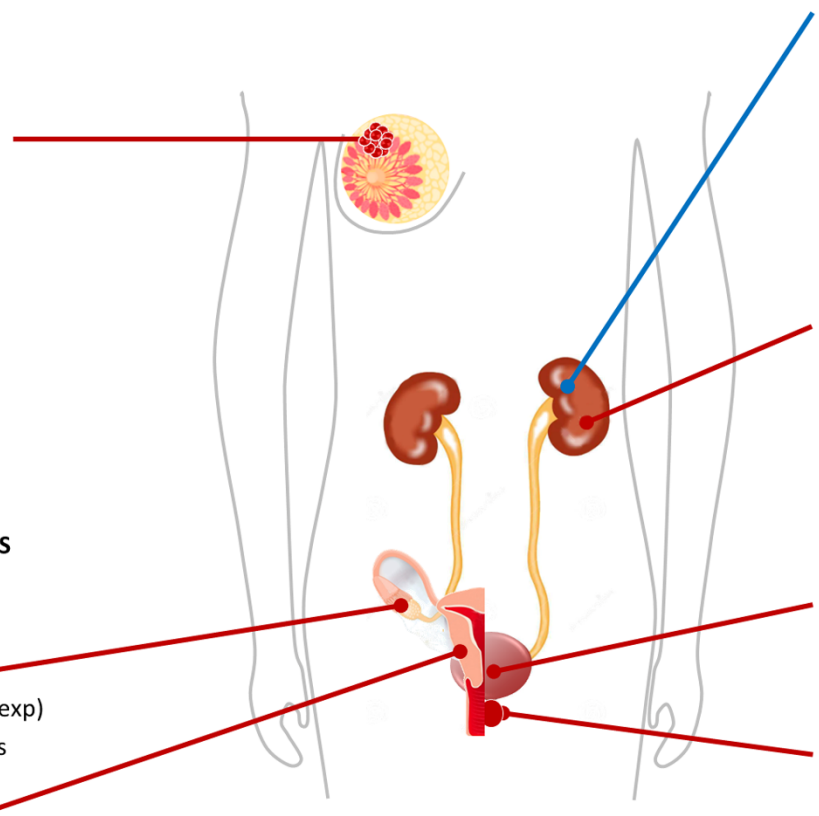
ATG4A rs5973822 (eQTL, miRNA, ↑exp)
SMCR8 rs921986, rs12952556 eQTLs

CERVICAL CANCER

ATG4A rs5973822 (eQTL, miRNA, ↑)
ATG4A rs807181, rs807182 x **HPV INFECTION** RISK
ATG4A rs807183 (eQTL, ↓ exp) x **HPV** RISK

UTERINE LEIOMYOMAS

MAP1LC3C rs1776161 G>A



DISEASES

KIDNEY DISEASE

ATG2A rs188780113 G>A **RISK** of hyperuricemia
Missense rare

ATG16L1 rs2241880 MISSENSE T300A
UROPATHOGENIC E. coli Protection
Protective

ccRCC

ATG4A rs7880351 G>C **THERAGNOSIS** (Pazopanib) ↑ OS PFS
ATG4C rs6683832 G>A rs6670694 G>A
THERAGNOSIS (Pazopanib) ↑ PFS

ATG5 rs490010 A>G **THERAGNOSIS** (Pazopanib) ↓ PFS

ATG16L2 rs10751215 T>C ↓ Metastases

IRGM rs10059011 A>C **RISK** and patient outcome

BLADDER CANCER

ATG2B rs3759601 G>C BAD **THERAGNOSIS** (BCG immunotherapy)

ATG5 rs2245214 C>G BAD **THERAGNOSIS** (BCG immunotherapy)

PROSTATE CANCER

ATG4B rs3771570 C>T

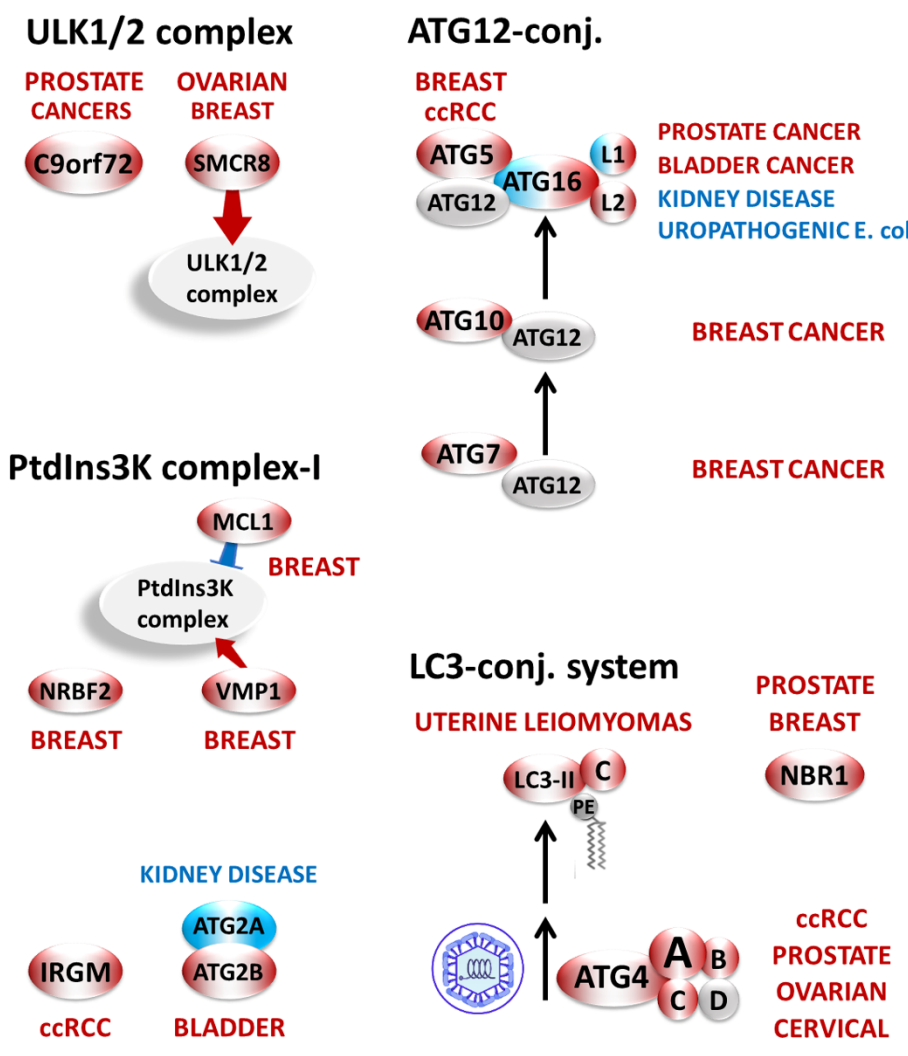
ATG16L1 rs78835907 G>A BAD prognosis

C9orf72 rs774359 T>C, rs3849942 T>C
*rs*10122902 G>A, rs10757665 T>C

ATG14 rs8015211 T>C aggressivity eQTL

NBR1 rs17599948 G>C BAD **THERAGNOSIS** (radiotherapy)
attributed to BRCA1

B



C

Atg5 $^{-/-}$ *Kidney Specific*	**ACUTE KIDNEY INJURY** [18,19] Cisplatin- and ischemia-reperfusion-induced
Atg7 $^{-/-}$	
Atg5 $^{f/f}$	**KIDNEY DISEASE AND AGING** [20]
Atg16l1	**URINARY TRACT INFECTION** [21]
Atg16l1 T300A	**URINARY TRACT UPEC INFECTION** [21] Protection: ↑ vesicle trafficking, ↓ infection. Independent of autophagy or proinflammatory cytokine responses. ↑ expression of RAB33B, which interacts with ATG16L1, as RAB27B and RAB11A → UPEC exocytosis
Optn $^{-/-}$	***E. Coli*-INDUCED PERITONITIS** [22]
Becn1 $^{+/-}$ Or ***Atg7*** $^{-/-}$ *Ovary Specific*	**REDUCED FERTILITY** [23]
Atg16l1 $^{f/F}$ *Uterus Specific*	**REDUCED FERTILITY**[258] [24] Endometrial Decidualization
Sqstm1 shRNA	**ccRCC growth** [25] addictive to *SQSTM1* gene gain and overexpression *(in vitro* and *in vivo)*[259]
Atg7 $^{f/f}$ ***Pten*** $^{f/f}$ *Inducible Prostate-Specific*	**PROSTATE CANCER** [26] *Atg7* KO delays *Pten*-deficient prostate tumor progression (evidence of ER stress)
Becn1 $^{+/-}$ ***Becn1*** ^{F121A} ***(KI/KI)***	**BREAST CANCER** [10,27-29] ↑ ERBB2/HER2-driven tumorigenesis ERBB2/HER2 interacts with BECN1 and inhibits autophagy Somatic Allelic loss of *BECN1* is observed in over 50% of human breast cancers
Rb1cc1 $^{-/-}$ ***Rb1cc1*** $^{f/+}$ *Breast-Specific*	**BREAST CANCER** [30]
Rb1cc1 $^{f/f}$	**OVARIAN CANCER** [31,32] hyperplasia of epidermis (acanthosis)
Becn1 $^{+/-}$	**EARLY OVARIAN TUMORS** [33]

Figure S3_Iris GROSJEAN and Barnabé ROMÉO et al.

A

INFLAMMATORY DISEASES

TYPE 2 DIABETES

ATG13 rs35619591 G>A, insulin processing
BECN1 rs10512488 G>A
SH3GLB1 rs263436 G>A
DRAM1 rs77694286 A>G

ATROPHIC GASTRITIS

CHMP2B rs1002765 G>A ↑ RISK precancerous

FATTY LIVER DISEASE

IRGM rs13361189 T>C

INFLAMMATORY BOWEL DISEASE

ATG9A rs2382817 A>C

CROHN DISEASE

ULK1 rs3088051 T>C **COMPLICATION,**
ULK1 rs7488085 T>G, rs10902469 G>C Protective
ULK1 rs12303764 T>G, rs11616018 C>T, rs7953348 C>T

IRGM rs4958843, ***r***s4958847 G>A
IRGM rs10065172 C>T - eQTL miR-196 ↑ exp ↑ inflammation
IRGM rs13361189 T>C - eQTL prom - ↓ exp

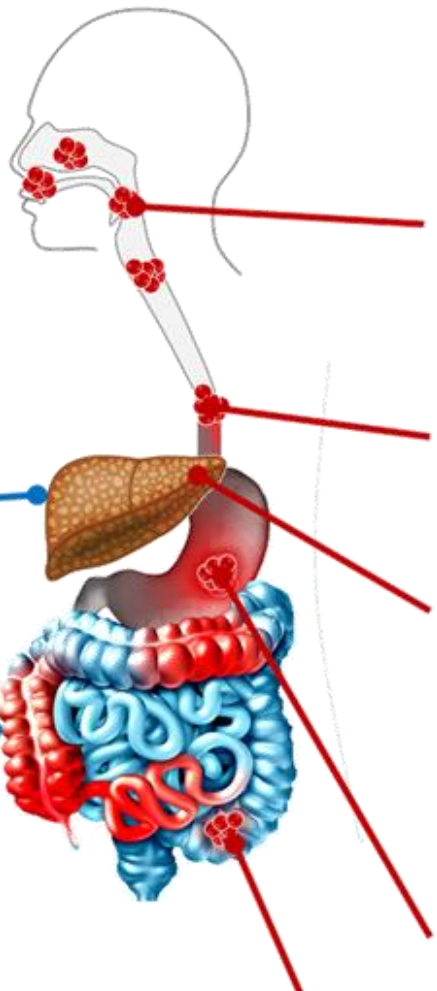
ATG2A rs17146441 C>T Granulomas

ATG4A rs5973822 A>G - eQTL, miRNA, ↑ exp
ATG4B rs35320439 T>C
ATG4D rs2304165 C>T, rs10439163 A>G – Granulomas

ATG5 rs506027 T>C, rs510432 T>C Theragnosis (anti-TNF) ↑ OS
ATG5 rs9373839 T>C Theragnosis (anti-TNF)

ATG16L1 rs2289476 G>A **x SMOKING**
ATG16L1 rs2241880 A>G **COMPLICATION x SMOKING**
ATG16L1 rs6754677 G>A
ATG16L2 rs11235604 C>T Protective ↓ ATG16L2

CALCOCO2 rs2303015 T>C



CANCERS

HEAD AND NECK CANCERS

MCL1 rs9803935 T>G, rs3738485 C>G,
ATG2B rs3759601 G>C ↑ Pharynx RISK
ATG10 rs1864183 C>T, rs4703533, C>G, rs10514231 C>T
Nasopharynx RISK Bad Theragnosis (Radiotherapy)
ATG12 rs26537 T>C
ATG16L1 rs4663402 A>T, rs2241880 A>G

ESOPHAGEAL CARCINOMA

PI3KC3 rs52911 G>A protective

LIVER CANCERS

ATG5 rs510432 T>C, rs548234 C>T, **HEPATITIS B**
ATG5 rs17067724 A>G, Protective
ATG10 rs1864183 C>T, rs10514231 C>T
ATG12 rs26537 T>C
ATG16L1 rs4663402 A>T, rs2241880 A>G

GASTRIC CANCERS

PI3KC3 rs2162440 A>G, rs7235755 A>G
TELOMERE LENGTH
IRGM rs13361189 T>C Protective x ***H. pylori***
IRGM rs4958847 G>A Protective eQTL ↓ exp
ATG16L1 rs2241880 A>G x ***H. pylori***
CHMP2B rs1002765 G>A x ***H. pylori***

COLORECTAL CANCER

PIK3R4 rs10934954 C>T
ATG16L1 rs2241880 A>G ↓ type I IFN
RB1CC1 rs1129660 A>G **THERAGNOSIS** (anti-VEGF)

B

ULK1/2 complex

ULK1 FIP200 — CROHN, COLORECTAL

IRGM

FATTY LIVER DISEASE
CROHN
GASTRIC CANCER

PtdIns3K complex

T2 DIABETES — CANCERS
BECN1, MCL1, SH3GLB1, PIK3C3, PIK3R4
HNSCC
ESOPHAGEAL
GASTRIC
COLORECTAL

ATG9A system

ATG2 A/B — CROHN, HNSCC
ATG9A — INFLAMMATORY BOWEL DISEASE

ATG12-conj.

CROHN
ATG5, ATG12, ATG16 L1/L2
HNSCC
LIVER

HNSCC
LIVER
GASTRIC
COLORECTAL

ATG10
ATG4 A/B/C/D
CROHN DISEASE

DRAM1 — T2 DIABETES
CALCOCO2 — CROHN

MATURATION

CHMP2B
ATROPHIC GASTRITIS
GASTRIC CANCER

C

Atg7$^{f/f}$ *liver specific*	**STEATOSIS** [34,35] hepatomegaly and benign tumors (adenomas), but not HCCs *Via* SQSTM1/p62-KEAP1-NFE2L2/Nrf2
	HEPATOCELLULAR CARCINOMAS [36] via YY1AP1 autophagy degradation
Sh3glb1/Bif1$^{-/-}$	**HEPATOCELLULAR CARCINOMAS** [12]
Becn1$^{+/-}$	**HEPATOCELLULAR CARCINOMAS** [10,11] Spontaneous and HBV carcinogenesis
Atg16l1$^{f/f}$ *Hematopoietic cells or intestinal epithelium*	**CROHN DISEASE** [37,38] ↑INFLAMMATION ↓Paneth cell granule exocytosis
Atg16l1^{HM}	*Virus + susceptibility gene + commensal bacteria* [39] → ↓ Paneth cell granule secretion UVRAG
	↓Secretory autophagy of lysozyme in Paneth cell [40]
Atg16l1$^{T300A/T300A}$	x **Smoking**, a major CD environmental risk factor [41] ↑Paneth cell apoptosis, metabolic dysregulation, ↓PPARγ pathway (Apoptosis rescued by PPARγ agonist rosiglitazone) CD patients and mice
Irgm2/Lrg47$^{-/-}$	**CROHN DISEASE** [42] ↑ INFLAMMATION ↓Paneth cell granule exocytosis
Optn$^{-/-}$	**bacteria-driven COLITIS** [23] and peritonitis: ↓TNF ↓ Neutrophil recruitment
Atg4b$^{-/-}$	**COLITIS CROHN DISEASE** [43] Paneth cell abnormalities ↑INFLAMMATION
Uvrag^{FS}	**COLORECTAL CANCER** (CRC) [44] Frameshift *UVRAG* mutation → UVRAG^{FS} (truncated) in gastric cancer and CRC; UVRAG^{FS} acts as a dominant-negative mutant
	↑ **age-related TUMORIGENESIS** [45] (CTNNB1/β-catenin stabilization)
	↑ INFLAMMATION in **SEPSIS COLITIS** and colitis-associated cancer development
Sh3glb1/Bif1$^{-/-}$	**DUODENAL ADENOCARCINOMAS** **ESOPHAGEAL SQUAMOUS CELL CARCINOMAS** [12]

Figure S4_Iris GROSJEAN and Barnabé ROMÉO et al.

A

NEURODEGENERATIVE DISEASES

DEMENTIA

C9orf72 rs2282241, rs774359, rs2814707, rs3849942
C9orf72 rs10812615, rs10812616, rs17769294

CHMP2B rs63751048, rs63750652
CHMP2B rs63750653

ALZHEIMER DISEASE

PIK3C3 rs1941526
ATG10 rs4703879, rs891159, rs1485587
WDFY3 rs76117213, rs17009220
DFCP1 rs7155380
RUBCNL rs1408184
SQSTM1 rs104893941

HUNTINGTON DISEASE

ATG7 rs36117895 earlier onset

PARKINSON DISEASE

ULK2 rs281357
ATG7 rs1375206
LAMP1 rs12871648

SPINOCEREBELLAR ATAXIA TYPE 3

BECN1 rs60221525 C>A ↓ BECN1, earlier onset. more severe disease.
BECN1 rs116943570 A>C ↑ BECN1. Neuroprotective effects.

SUPRANUCLEAR PALSY

TBC1D14 rs4689558

NEUROMUSCULAR DISEASES

AMYOTROPHIC LATERAL SCLEROSIS

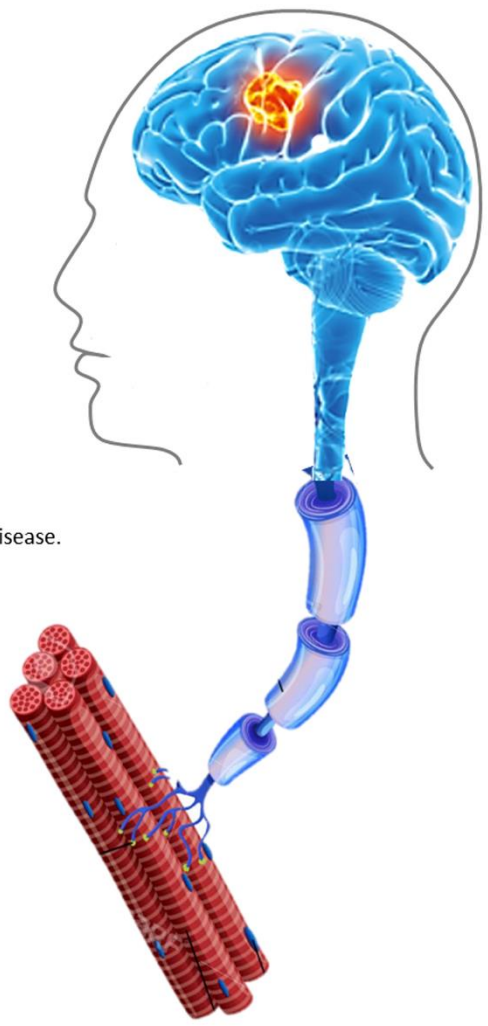
C9orf72 rs774359, rs2814707, rs3849942, rs3849943
C9orf72 rs2282241, rs3849943, rs10122902, rs17769294

CHMP2B rs63751126

RUBCNL rs2478046

MULTIPLE SCLEROSIS

UVRAG rs80191572 A>G, Theragnosis
EGR1 rs4902647



CANCER

GLIOMA

IRGM rs13361189 >CC ↓ exp → ↑ IFNγ
CALCOCO2 rs8074034

NEUROLOGICAL DISORDERS

SCHIZOPHRENIA

ULK1 rs145451295, rs55815560, rs145279005, rs188342389
PIK3C3 rs1046515390 bipolar disorder
AMBRA1 rs11819869, rs12574668, rs7130141, rs7112229
EGR1 rs11743810
C9orf72 rs10967991

NICOTINE DEPENDENCE

GABARAP rs222843, rs17710

NEURODEVELOPMENTAL DISEASES

NEURAL TUBE DEVELOPMENT

SMCR8 rs12939757
WIPI1 rs77156594, rs146357218

CORTICAL DYSPLASIA AND ATROPHY

PIK3R4 A>C (chr3: 130,681,528) intellectual impairment, ataxia, psychomotor delay, muscle wasting, and late-onset epilepsy

CAUDATE VOLUME

WDR41 rs163030, rs163035, rs335636

MEGALENCEPHALIC LEUKOENCEPHALOPATHY

MCL1 rs1258188045

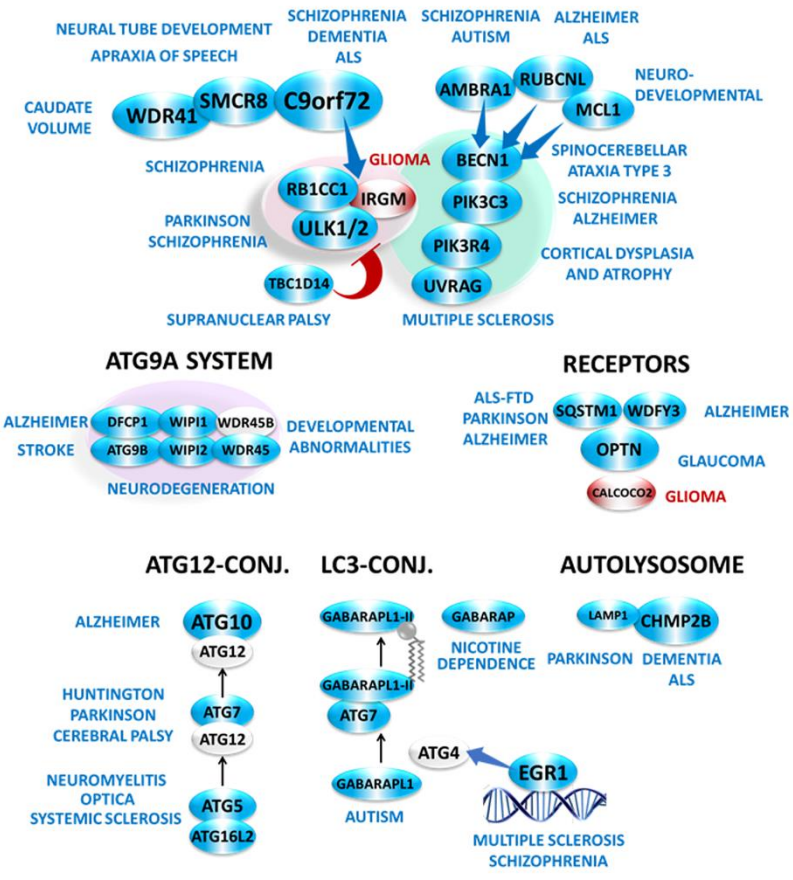
CEREBRAL PALSY

ATG7 rs1470612

AUTISM SYNDROME

AMBRA1 *rs3802890*

B



C

***Atg5*$^{-/-}$** ***Atg7*$^{-/-}$** *Neuron-Specific*	**NEURODEGENERATION** [46,47] deficits in motor function and accumulation of inclusion bodies in neurons
***Becn1*$^{+/-}$**	**ALZHEIMER DISEASE** [48] ↑ Inflammation IL-1b, IL-18
***Sqstm1*$^{-/-}$**	**ALZHEIMER-like phenotype** [49] ↑ anxiety, depression, and loss of working memory that precede the accumulation of tau
***Chmp2b*$^{intron\ 5}$**	**FRONTOTEMPORAL** [50,51] C-terminus truncation (Δ Vps4 binding site)
***Tsc2*$^{+/-}$** ***Atg7* CKO**	♀ **AUTISM SPECTRUM DISORDERS** [52] hyperactivated mTOR and impaired autophagy
***Ambra1*$^{+/-}$**	**NEURODEVELOPMENT AUTISM-SPECTRUM DISORDERS** [53] ↓ AMBRA1 protein brain
***Wdfy3*$^{+/-}$**	**NEURODEVELOPMENTAL delay** [54] (autism/hyperactivity disorder) WDFY3 is required for cerebral cortical size regulation (proper division of neural progenitors) → Wnt-pathway is dysregulated → macrocephaly and deficits in motor coordination and learning.

Figure S5_Iris GROSJEAN and Barnabé ROMÉO et al.

Table S1-S6. Association between common genetic polymorphisms in the autophagy-related genes and human diseases (risk, prognosis, theragnosis). *ATG* SNP (single-nucleotide polymorphism) and their functional annotation (promoter, 5', 3', missense mutations, transcription factor, and miRNA binding sites) were retrieved using PubMed, litvar [58], HaploReg[59,60], and GTEX [61] (eQTLs).

Table S1. **ULK1/2 complex**

Table S2. **PtdIns3K Complex**

Table S3. **ATG9 system**

Table S4. **LC3-conjugation system**

Table S5. **ATG12-conjugation system**

Table S6. **Autophagy receptors**

Related to theragnosis (side effects, toxicity, efficacy), overall survival (OS), and progression-free survival (PFS).

Related to bacterial infection or

viral infection.

Related to air pollution or

coal exposition, or

smoking.

Related to aging

Related to autoimmune and autoinflammatory diseases.

Abbreviations: Alt, alternate allele; Ref, reference allele; exp, expression; (eQTL): eQTL in different tissue of that affected by the disease**;** LD, linkage disequilibrium; MAF, minor allele frequency in European (Eur) or Asian (As) populations; ALS-FTD, amyotrophic lateral sclerosis and frontotemporal degeneration; CD, Crohn disease; ccRCC, clear cell renal cell carcinoma; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; NPC, nasopharyngeal carcinoma; SLE, systemic lupus erythematosus.

Table S1- *ULK1/2* complex - AUTOPHAGY

Gene	SNP (rs)	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ULK1 **NM_003565.1 93 eQTL**	rs9481	A	G	86%	10	**TUBERCULOSIS** [62] Protective	Asian study	3'UTR	(eQTL)
	rs3088051	T	C	29%	1	**CROHN DISEASE** [63] Complications	Oceanian study	3'UTR	(eQTL)
	rs4964879	G	A	10%	1	**ANKYLOSING SPONDYLITIS** [64] Protective	Asian study	Intronic	eQTL- Nerve
	rs7138581	G	C	13%	5	**TUBERCULOSIS** [62] RISK and SEVERITY	Asian study	3'UTR	(eQTL)
	rs7300908	C	T	2% As 8%	1	**TUBERCULOSIS** [65]	Asians	Intronic	(eQTL) ↑ exp[65]
	rs7487166	A	G	81%	12	**ASTHMA** [66]	American study	Intronic	(eQTL)
	rs7953348	C	T			**CROHN DISEASE** [63] Weak association	Oceanian study		
						NON SMALL CELL LUNG CANCER (NSCLC) [67] Theragnostic (Platinum-based chemotherapy)	Asian study		
	rs9652059	T	C			**ANKYLOSING SPONDYLITIS** [64]	Asian study	Intronic	(eQTL)
						ASTHMA [65]	American study		
	rs11616018	C	T			**ASTHMA** [66]	American study	synonymous	eQTL - colon
						CROHN DISEASE [63] Weak association	Oceanian study		
	rs7488085	T	G	6%	23	**CROHN DISEASE** [63] Protective	Oceanian study	Intronic	(eQTL)
	rs10902469	G	C					5' *ULK1*	(eQTL)
	rs10902472	C	T			**ASTHMA** [66]	American study	Intronic	(eQTL)
	rs12297124	G	T	8%	4	**TUBERCULOSIS** [65] Protective	Asians	Intronic	(eQTL) ↑ exp[65]

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ULK1 **NM_003565.1** **93 eQTL**	rs12303764	T	G	36%	1	**CROHN DISEASE** [63,68] **NSCLC** [67] Theragnostic (platinum-based chemotherapy)	European and Oceanian studies Asian study	Intronic	eQTL - colon
	rs55815560	C	T	1%	1	**SCHIZOPHRENIA** [69] A highly heritable psychiatric disorder, combining these 4 SNPs. No variant was individually statistically significant	European study	**MISSENSE** S665L	N/A
	rs145279005	C	T	1%	1			**MISSENSE** A705V	N/A
	rs145451295	C	T	1%	2			**MISSENSE** T242I	N/A
	rs188342389	C	T	0%	6			**Intron** ***MMP17 missense***	N/A
ULK2 **NM_014683** **1450 eQTL**	rs281357	T	C	64%	1	**PARKINSON DISEASE** [70]	American study	Intronic	eQTL-Nerve
	rs281366	C	T	3%	3	**ACUTE LYMPHOBLASTIC LEUKEMIA** [71] Theragnostic (asparaginase-associated pancreatitis)	European study	5' *ULK2*	(eQTL)
TBC1D14 **NM_020773** **746 eQTL**	rs10804990	G	A	62%	1	**CORONARY HEART DISEASE** [72]	American study	Intronic	eQTL- Artery
ATG13 **NM_014741** **4655 eQTL**	rs7484002	A	G	17%	130	**↑ DNA damage** [73]	Asian study	Intronic	eQTL- Skin **↓** exp[73]
	rs35619591	G	A	1%	1	**TYPE 2 DIABETES** [74] Insulin processing	European American study	**MISSENSE** G433R	N/A

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
RB1CC1/FIP200 **NM_014781 68 eQTL**	rs1129660	A	G	21%	19	**COLORECTAL CANCER** [75] Bad theragnosis anti-VEGF-toxicity (bevacizumab)	European study	synonymous	N/A
SMCR8 **NM_144775 1,354 eQTL**	rs1563634	T	C	67%	12	**BREAST CANCERS** [76]	European study	5' *SMCR8*	eQTL-Breast
	rs8080966	C	T	31%	81	**CHILDHOOD APRAXIA OF SPEECH** [77]	American study	**MISSENSE** P524L	eQTL- Brain
	rs12939757	A	G			**NEURAL TUBE DEFECTS** [78] Low maternal folate intake	American study	3' *SMCR8*	eQTL- Brain
	rs921986	C	T			**OVARIAN CANCER** [79]	American study	3' *SMCR8*	eQTL- ovary
	rs12952556	T	C					3' *SMCR8*	eQTL- ovary
WDR41 **NM_018268 10007 eQTL** **ULK1 partner**	rs163016	A	T	40%	41	**MYOPIA** [80]	World collaboration	Intronic	(eQTL)
	rs163030	A	C	48%	83	**CAUDATE VOLUME** [81] Brain region implicated in common neurological and psychiatric disorders	American study	Intronic	eQTL - Brain
	rs163035	A	G					Intronic	eQTL - Brain
	rs335636	A	G					Intronic	eQTL - Brain
	rs335632	C	T	1%	1	**HEART DISEASES** [82]	World collaboration	N/A	(eQTL)
	rs33204	C	T	40%	28	**MYOPIA** [80]	World collaboration	**MISSENSE** V326I	(eQTL)
	rs10514104	T	C	18%	14	Age-related **HEARING IMPAIRMENT** [83]	European study	Intronic	eQTL - Brain ↓ exp [83]

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
C9orf72 **NC_000009.12** **6048 eQTL** **ULK1 partner**	rs774359	T	C	27%	81	**ALS** **FTD** [84–86] **PROSTATE CANCER** [87]	Asian and American Word collaboration American study	3'UTR	eQTL - Brain
	rs2814707	C	T			**ALS-FTD** [84–86] **SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)**[88] high serum IFNK (type I IFN)	Asian and American World collaboration American study	5' *C9orf72*	eQTL - Brain
	rs3849942	T	C			**ALS-FTD** [89] **PROSTATE CANCER** [87]	European study American study	3' *C9orf72*	eQTL - Brain
	rs3849943	C	T	75%	1	**ALS** [90]	European study	3' *C9orf72*	eQTL - Brain
	rs2282241	C	A	43%	6	**ALS-FTD** [89]	European study	Intronic	eQTL - Brain
	rs2492816	G	A	42%	8	**SLE** [91]	European study	Intronic	(eQTL)
	rs3849944	T	C	47%	10	**SLE**[88] high serum IFNκ	American study	3' UTR	(eQTL)
	rs10812615	T	C			**FTD** [92]	Oceanian study	Intronic	eQTL- Brain
	rs10812616	T	A					Intronic	eQTL - Brain
	rs10122902	G	A	16%	9	**ALS** [93] **PROSTATE CANCER** [87]	American study American study	synonymous	(eQTL)
	rs10757665	T	C	25%	25	**PROSTATE CANCER** [87]	American study	Intronic	(eQTL)
	rs10967991	C	T			**SCHIZOPHRENIA** [94]	Asian study	5' *C9orf72*	(eQTL)
	rs12686452	T	C	21%	7	**SLE**[88] ♀ high serum IFNK	American study	Intronic	(eQTL)
	rs17769294	T	C	11%	10	**ALS** [93] **FTD** [92]	Oceanian study American study	**MISSENSE** N207S	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
IRGM **NM_001145805 1645 eQTL**	rs4958843	T	C	9%	168	**TUBERCULOSIS & CROHN DISEASE** [95] ↓ RISK	Middle East study	5' *IRGM*	eQTL – Lung ↑ exp[95]
	rs10065172	C	T			**CROHN DISEASE** [96–100] ↓ IRGM mRNA in patient blood and ileum[39], ↑ inflammation	American studies	Synonymous ***MIR196* binding seed** ↑ IRGM [101]	eQTL Lung Colon Blood ↑ exp [96] ↓ exp [97,100,102] = exp [103]
						GRAVE DISEASE [104]	Asian study		
						SEPSIS [102] ↑ mortality	Asian study		
						TUBERCULOSIS [103–106] ↓ RISK in Asians, but not in Africans/African-Americans	Asian study		
	rs11747270	A	G			Severe **PERIODONTITIS** [107]	European study	N/A	(eQTL)
	rs13361189	T	C			**CROHN DISEASE** [96,97,100,108] ↑ inflammation CD colitis (lactoferrin in ileum and TNF in blood) (GTEX) [39]	American study European study	5' *IRGM*	**PROMOTER** eQTL - Lung Colon ↓ mRNA in blood and ileum [97,100]
						GASTRIC CANCER [109] ↓ RISK x ***H. pylori***	Asians Ocean study		
						GLIOMA [110] ↑ IFNG ↑ serum IL4	Asian study		
						GRAVE DISEASE [104]	Asian study		
						LEPROSY [111] ↑ ***Mycobacterium leprae*** ↑ INFG and IL4	Asian study		
						PERIODONTITIS [107]	European study		
						NON-ALCOHOLIC FATTY LIVER DISEASE [112,113]	Asian study American study		
						TUBERCULOSIS [105]	Asian study		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
IRGM **NM_001145805 1645 eQTL**	rs4958846	T	C	13%	51	**TUBERCULOSIS** [95,106,114] ↓ RISK	Middle East and Asian studies	5' *IRGM*	eQTL - Lung ↓ exp [34]
	rs4958847	G	A			**CROHN DISEASE** [108]	European study	Intronic	eQTL - colon
						GASTRIC CANCER [109,115] ↓ RISK (intestinal type)	Asian and European studies		
						GRAVE DISEASE [104]	Asian study		
						PERIODONTITIS [107]	European study		
	rs9637876	C	T	9%	163	**TUBERCULOSIS** [116]	African and European study	5'UTR	eQTL - lung ↑ exp[116]
	rs10052068	T	C	0%	1			Intronic	N/A
	rs10059011	A	C	54%	1	**METASTATIC CLEAR CELL RENAL CELL CARCINOMA ccRCC** [117] RISK and patient outcome	European study	5'UTR	(eQTL)
						TUBERCULOSIS [115]	African and European study		

Table S2 – PtdIns3K Complex AUTOPHAGY_LAP

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
PIK3C3 **Vps34** **NM_002647** **3755 eQTL**	rs52911	G	A	34%	47	**ESOPHAGEAL SQUAMOUS CELL CARCINOMA** [118] Protective	Asian study	Intronic	eQTL - Esophagus
	rs1941526	C	T	20%	83	**ALZHEIMER DISEASE** [119]	American study	Intronic	eQTL - Nerve
	rs2162440	A	G	79%	25	**GASTRIC CANCER** [120,121] (GASTRIC CARDIA ADENOCARCINOMA) associated with shorter telomeres	World collaboration Asian study	3' *PIK3C3* (5' MIR4318)	N/A
	rs7235755	A	G						N/A
PIK3R4 **Vps15** **NM_014602** **263 eQTL**	rs10934954	C	T	20%	176	**COLORECTAL CANCER** [122]	European study	Intronic	eQTL - Colon
	rs2200368	A	G			**AGE-RELATED MACULAR DEGENERATION** [123]	American study	Intronic	(eQTL)
	rs11713445	G	A					Intronic	(eQTL)
BECN1 **NM_003766** **157 eQTL**	rs10512488	G	A	21%	1	**TYPE 2 DIABETES** [124] **NON-HODGKIN LYMPHOMA** [125]	World collaboration American study	Intronic	eQTL - Blood
	rs11552193	C	T	0%	1	**NSCLC** [126]	American and European study	3'UTR	Not found miRNA Target Sites
	rs60221525	C	A	6%	1	**MACHADO-JOSEPH DISEASE/ SPINOCEREBELLAR ATAXIA TYPE 3** [127] Neuroprotective	European study	3' *BECN1*	Not found ↑ exp[127]
	rs116943570	A	C	0%	1			3' *BECN1*	Not found
NRBF2 **NM_030759** **1679 eQTL**	rs10995190	G	A	14%	11	**MAMMOGRAPHIC DENSITY** [128] Putative Enhancer at the 10q21.2 **BREAST CANCER** Risk Locus Regulate NRBF2 Expression	European study	ZNF365 Intronic	N/A
	rs10509168	T	C	52%	4			ZNF365 Intronic	N/A

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
UVRAG **NM_003369 1790 eQTL Autophagosome maturation**	rs80191572	A	G	5%	1	**MULTIPLE SCLEROSIS** [129] Theragnosis (Copaxone)	World collaboration	Intronic	(eQTL)
	rs7933235	A	G	8%	97	**VITILIGO** [130] LD with rs7118567 MISSENSE P10H	Asian study	Intronic	Not found
	rs1458836	C	T					5' *UVRAG*	eQTL - Skin
	rs7116263	C	G	8%	9	**CANCER : Etoposide-induced cytotoxicity** [131]	American study	Intronic	(eQTL)
	rs17134573	G	A	3%	154	**Blood lipid, body mass index** [132]	American study	Intronic	(eQTL)
	rs594826	G	A	6%	3			Intronic	N/A
RUBCNL **NM_025113 2581 eQTL**	rs1408184	C	T	34%	72	**ALZHEIMER DISEASE** [133]	European study	**MISSENSE** G152R	eQTL - Brain
	rs2478046	G	A	14%	61	**ALS** [134]	European study	3' *RUBCNL*	eQTL - Nerve
MCL1 **NM_008562.3 402 eQTL Inhibitor of BECN1**	rs1258188045	C	G, T	0%	1	**MEGALENCEPHALIC LEUKOENCEPHALOPATHY** [135]	European study	**MISSENSE** R84C	Not found
	rs9803935	T	G	56%	36	**HNSCC** [136] **xHPV16-related** oro-pharyngeal type	American study	5' *MCL1*	(eQTL)
	rs3738485	C	G					5' *MCL1*	(eQTL)
	rs961581226	C	A	0%	1	**TUBERCULOSIS** [137]	Asian study	5' *MCL1*	Not found
	rs3831987	CC	21mer	N/A	1	**LUNG CANCER in non-smoker** [138] Protective **BREAST CANCER** [139] Protective	Asian study Asian study	5' *MCL1*	Not found ↑ exp
VMP1 **NM_030938 272 eQTL Partner of PI3K**	rs1295925	T	C	71%	32	**BREAST CANCER** [140] Protective **OSTEOSARCOMA** [141] Protective - TP53 transcriptional binding site	Asian study Asian study	Intronic	eQTL - Breast

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG14 **NM_014924 8192 eQTL**	rs8015211	T	C	35%	53	**PROSTATE CANCER** [142] aggressivity (GWAS) not validated in an independent study	American study	intronic	eQTL Prostate
	rs8003279	A	G			**NSCLC** [67] good Theragnosis (platinum)	Asian study	synonymous	(eQTL)
	rs1009647	G	A	27%	9			3' of TBPL2	(eQTL)
	rs17742719	G	T	18%	8			intronic	eQTL Lung
SH3GLB1/ BIF-1 **NM_016009** ***849 eQTL***	rs263436	G	A	24%	35	**TYPE 2 DIABETES** [143] GWAS	American studies	intronic	N/A
AMBRA1 **NM_017749.3 148 eQTL**	rs11038913	T	C	8%	1	**ARTERY DISEASE** [144] associated with blood proinsulin levels	European study	Intronic	eQTL - Artery
	rs3802890	A	G	31%	1	♀ **AUTISM**[145] protective GWAS	European Study(US and European GWAS)	Intronic ↓ mRNA	(eQTL)
	rs7130141	C	T	17%	113	**SCHIZOPHRENIA**[146]	European Study	Intronic	eQTL - Brain
	rs7112229	C	T					Intronic	eQTL - Brain
	rs11819869	C	T					Intronic	eQTL - Brain

III - ATG9 system AUTOPHAGY

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG2A **NM_015104 16 eQTL**	rs17146441	C	T	23%	2	**CROHN DISEASE** [147] Granulomas	European study	Intronic	(eQTL)
	rs188780113	G	A	0%	1	**KIDNEY DISEASE** [148] RISK of hyperuricemia	Asian study	**MISSENSE** R478C	N/A
ATG2B **NM_018036 318 eQTL**	rs3759601	G	C	42%	27	**BLADDER CANCER** [149] Theragnosis (BCG immunotherapy) ↓ autophagosome formation (macrophages) **HNSCC**[150] ↑ RISK pharyngeal cancer	European study European study	**MISSENSE** Q1383E	(eQTL)
ATG9A **NM_024085 147 eQTL**	rs2382817	A	C	64%	74	**INFLAMMATORY BOWEL DISEASE** [151]	European study	PNKD intron	eQTL – Colon
ATG9B **NM_173681 283 eQTL**  **Attributed to NOS3**	rs7830	G	T	36%	1	**BLOOD PRESSURE** [152] **x AIR POLLUTION** - urban elderly	Asian study	5' *ATG9B*	eQTL - Artery
	rs2373929	G	A	46%	1	**CORONARY ARTERY DISEASE** [153]	Middle East study	Intronic	eQTL - Artery
	rs3763486	T	C	20%	2	**SKIN BASAL CELL CARCINOMA** [154] **STROKE** [155]	American studies	5' *ATG9B*	(eQTL)
	rs3800787	G	C	40%	1	**STROKE** [155]		Intronic	N/A
	rs3918220	C	G	0%	1			Intronic	N/A
	rs6464119	T	C	77%	2			Intronic	eQTL - Artery
	rs11769158	A	G	88%	1			5' *ATG9B*	(eQTL)
	rs11760487	G	A	13%	2	**BONE DENSITY** [156]	American study	Intronic	(eQTL)
	rs12666075	G	T	19%	4			Intronic	Not found
	rs13307588	A	G	94%	2	**MYOCARDIAL INFARCTION** [157]	European study	Intronic	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease Susceptibility	Populations	Funct Annot	eQTL GTEX
WIPI1 **NM_017983 1114 eQTL**	rs2909207	T	C	76%	27	**Age-adjusted medium HDL particles** [158]	American and European studies	Intronic	(eQTL)
	rs77156594	A	G	0%	1	**ANENCEPHALY** [159]	American study	**MISSENSE** L406P	Not found
	rs146357218	C	T	0%	1			**MISSENSE** R328Q	Not found
WIPI2 **NM_015610**	**DEVELOPMENTAL ABNORMALITIES** [160] mental retardation, neurological, psychiatric, skeletal and cardiac abnormalities. homozygous (c.G745A ; pV249M). ↓ Binding of the V231M mutant to ATG16L1 (ATG5-12), ↓ WIPI2 puncta, ↓ LC3 lipidation and ↓ autophagic flux.								
WDR45 **NM_007075.3**	**Neurodegeneration with BRAIN IRON ACCUMULATION** [161] **BETA-PROPELLER PROTEIN-ASSOCIATED NEURODEGENERATION** [162] WDR45 mutations →↓ autophagy degradation of ferritin→↑ **iron in the brain** (basal ganglia) X-linked								
ZFYVE1/DFCP1 **NM_021260 1079 eQTL**	rs7155380	T	C	45%	25	**ALZHEIMER DISEASE** [163] Late-Onset	American study	Intronic	eQTL - Brain/Nerve
	ZFYVE1/DFCP1 (WIPI2 partner) associates with lipid droplets.[164]								

IV LC3-conjugation system LAP AUTOPHAGY

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG3 **NM_022488 98 eQTL**	rs13082005	G	A	40%	4	**NSCLC** [67] Theragnosis (Cisplatin)	Asian study	Intronic	(eQTL)
ATG4A **NM_178270 309 eQTL**	rs807181	G	C	45%	2	**CERVICAL CANCER** [165] **↑ HPV INFECTION** RISK - **↓** autophagy	Asian study	Intronic	(eQTL)
	rs807183	G	A					Intronic	(eQTL)
	rs807185	A	T	64%	1	**LUNG CANCER** [166]	Asian study	Intronic	(eQTL)
	rs5973822	A	G	6%	1	**CERVICAL CANCER** [165] **CROHN DISEASE** [147] Granulomas **OVARIAN CANCER** [167]	Asian study European study Asian study	3'UTR miRNA binding site	(eQTL)
	rs7880351	G	C	45%	1	**ccRCC** [117] Theragnosis (Pazopanib) **↑** OS PFS	European study	Intronic	(eQTL)
ATG4B **NM_013325.5 1758 eQTL**	rs3771570	C	T	13%	21	**PROSTATE CANCER** [168]	World collaboration	5' *ATG4B*	(eQTL)
	rs35320439	T	C	33%	1	**CROHN DISEASE** [169]	European and Asian study	5' *ATG4B*	(eQTL)
ATG4C **NM_032852 2531 eQTL**	rs11208029	A	G	14%	109	**TUBERCULOSIS** [170]	African study	Intronic	(eQTL)
	rs6587988	C	T			**CARDIOVASCULAR DISEASES** [144] total cholesterol, triglycerides	European study	Intronic	eQTL - Artery **↓** exp [171]
	rs11208030	G	A			**KASHIN-BECK DISEASE** [171]	Asian study	Intronic	eQTL – Heart **↓** mRNA / protein exp[171]
	rs4409690	G	A			**KASHIN-BECK DISEASE** [171]	Asian study	Intronic	(eQTL) **↓** exp[171]
	rs12097658	T	C					Intronic	

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG4C **NM_032852 2531 eQTL**	rs6670694	G	A	42%	96	**ccRCC** [117] Theragnosis (Pazopanib) ↑ PFS	European study	Intronic	(eQTL)
	rs6683832	G	A	56%	33	**ATHEROSCLEROSIS** [172] **ccRCC** [117] Theragnosis (Pazopanib) ↑PFS	American study European study	Intronic	eQTL - Artery
ATG4D **NM_032885 274 eQTL**	rs2304165	C	T	15%	16	**CROHN DISEASE** [147] Granulomas	European study	synonymous	(eQTL)
	rs7248026	T	G	25%	31			5' *ATG4D*	(eQTL)
	rs10439163	A	G	40%	23	**CARDIOVASCULAR DISEASES** [144] LDL and cholesterol **CROHN DISEASE** [147] Granulomas	European study European study	5' *ATG4D*	eQTL - Heart, Colon
EGR1 **NM_001964.2 8 eQTL**	rs4902647	C	T	46%	22	**MULTIPLE SCLEROSIS** [173]	American study	3' *EGR1*	(eQTL)
	rs7729723	A	G	36%	9	**CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)** [5,174] **X Smoking**-induced disease [105]	Asian study American study	5' *EGR1*	(eQTL)
	rs11743810	C	T	54%	7	**SCHIZOPHRENIA** [175]	Asian study	Intronic	(eQTL)
GABARAP **NM_007278.1 37 eQTL**	rs222843	T	C	38%	22	**NICOTINE DEPENDENCE** [176] **x Smoking**-induced disease **NICOTINE AND ALCOHOL DEPENDENCE** [177]	American study Asian and American study	**PROMOTER** (MISSENSE CLDN7)	eQTL - Brain/Nerve ↑ exp [177]
	rs17710	A	T	15%	2	**NICOTINE DEPENDENCE** [176,177]	American	**3'-UTR**	(eQTL)
GABARAPL2 **NM_007285 97 eQTL**	rs12599322	G	A	5%	26	**DNA DAMAGE** [73]	Asian study	RP11-77K12.8	eQTL
GABARAPL3 **NM_028287 15 eQTL**	rs6496667	C	A	20%	110	**RHEUMATOID ARTHRITIS** [178]	Asian study	5' *GABARAPL3*	(eQTL)

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
GABARAPL1 **NM_031412** **257 eQTL**	in **AUTISM SPECTRUM** disorder-associated pathways. deletions of GABARAPL1 in autism [179] GABARAPL1 is the **most highly expressed gene** among the family in the **central nervous system**.								
MAP1LC3A **NM_181509** **27368 eQTL**	rs1040747	C	G	36%	43	**CHRONIC Q FEVER** [180] ***x C. burnetii***-induced cytokine production - Protective	European study	3'UTR	eQTL - Blood
	rs2424994	C	T	15%	1	**CORONARY ARTERY DISEASE** [144]	European study	5' *MAP1LC3A*	eQTL - Heart
	rs6088521	A	C	49%	1			5' *MAP1LC3A*	eQTL - Heart
MAP1LC3B **NM_022818** **1437 eQTL**	rs8051218	T	C	6%	4	**ASTHMA** [66]	American study	Intronic	(eQTL)
	rs7204722	C	T	82%	2			Intronic	(eQTL)
	rs933717	T	C	44%	26	**SLE**[181]	Asian study	3' *MAP1LC3B*	eQTL – Blood ↑ exp[181]
MAP1LC3C **NM_001004343** **2 eQTL**	rs1776161	G	A	42%	1	**UTERINE LEIOMYOMAS** [182] Clinical Trial	American study	Exon1	N/A

Several ***cancer-associated mutations in LC3*** have been reported that either attenuate its binding to **ATG7** and subsequent lipidation (*LC3B* **Y113C**) [183] or its interaction and cleavage by **ATG4** (*LC3A* **R70C/H** rs778324131, *LC3B* **T113** rs200708875, and *LC3*C **R76C** rs776473823) [184]. These ***loss-of-function LC3 mutations*** could confer tumor-promoting features as they are reducing but not completely blocking autophagy in cells, and thus still support some level of autophagy for the continuous growth of tumor cells at later stages. Melanoma/hepatocellular carcinoma [185,186].

GABARAPs and LC3s have opposite roles in regulating ULK1 for autophagy induction [187]

It has been reported that mutation of the ULK1 LIR that disrupts the Atg8-family protein-ULK1 interaction drastically reduces the activity of ULK1, autophagic degradation of SQSTM1, and phagophore formation in response to starvation. Similarly, disruption of the ATG13-Atg8-family protein interaction suppresses ULK1 activity and autophagosome formation. By reconstituting Atg8-family protein-depleted cells with individual Atg8-family members, it has been shown that:

- The GABARAP subfamily (GABARAP and GABARAPL1) positively regulates ULK1 activity and autophagosome formation in response to starvation.
- In contrast, the LC3 subfamily (LC3B and LC3C) negatively regulates ULK1 activity and phagophore formation.

V - *ATG12*-conjugation system.

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
	rs490010	A	G	48%	20	**ccRCC** [117] Theragnosis (Pazopanib) ↓PFS	European study	Intronic	(eQTL)
	rs473543	**A**	**G**			**BREAST CANCER** [188] Theragnosis (Anthracycline and/or taxane) ↑PFS	Asian study	5' *ATG5*	(eQTL)
	rs506027	**T**	**C**			**CROHN DISEASE** [189] Theragnosis (anti-TNF) ↑ OS **SEPSIS** [190] ↑ TNF IL1B	European study Asian study	5' *ATG5* promoter	(eQTL) ↓ exp [190] ↑ exp [191–193]
						ASTHMA [190–192] ↑ neutrophil**s**	American and Asian studies		
ATG5 **NM_004849.2** **509 eQTL**	rs510432	T	C	44%	12	**APLASTIC ANEMIA** [194] ↓ RISK	Asian study	5' *ATG5* promoter	(eQTL) ↓ exp [190] ↑ exp[124] ↑ exp[191–193]
						ASTHMA [191–193] ↑ neutrophils	American and Asian studies		
						CROHN DISEASE [189] Theragnosis (anti-TNF) ↑ OS	European study		
						HCC [195] **HBV-related diseases**	Asian study		
						NSCLC EGFR* [196] Theragnosis (gefitinib) ↑ OS PFS	Asian study		
						LUNG FIBROSIS [197] ↓ RISK x **COAL**	Asian study		
						MELANOMA [198] Bad prognosis ↓ tumor-infiltrating lymphocytes	American study		
						SEPSIS [190] ↑ TNF IL1B	Asian study		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG5 **NM_004849.2 509 eQTL**	rs2245214	C	G	36%	11	**BLADDER CANCER** [199] autophagy (macrophages) ↓ BCG vaccine-induced trained immunity	Middle East study	Intronic	(eQTL)
						MELANOMA [198] Bad prognosis ↓ tumor-infiltrating lymphocytes	American study		
						NSCLC [149]	European study		
						PAGET DISEASE [200]	European study		
						Q FEVER [180] **x *C. burnetii* infection** - Protective	European study		
						SLE[201,202]	American studies		
						SYSTEMIC SCLEROSIS [203]	World		
						THYROID CANCER [204]	European study		
	rs633724	C	T			**ASTHMA** [66]	American study	Intronic	(eQTL)
	rs573775	G	A	28%	1	**ASTHMA** [193]	Asian study	Intronic	(eQTL) ↑ exp (PBMC) [205]
						APLASTIC ANEMIA [194]	Asian study		
						BEHÇET DISEASE [205] ↓ RISK	Asian study		
						SLE[202,206,207] ↑ IFNA IL10	American study and European studies		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG5 ***NM_004849.2*** ***509 eQTL***	rs548234	C	T	68%	5	**HCC** [208] Associated with Chronic Hepatitis B virus infection **HEPATITIS B** virus infection [208] **NEUROMYELITIS OPTICA** [209] RISK of demyelination ↑T cell exp **SLE** [203,210] Protective	Asian study Asian study Asian study and World collaboration	3' *ATG5*	N/A
	rs688810	A	G	22%	1	**NSCLC EGFR*** [196] Bad theragnosis (Gefitinib) ↓PFS	Asian study	5' *ATG5*	(eQTL)
	rs803360	G	C	48%	26	**ACQUIRED APLASTIC ANEMIA** [194] Protective	Asian study	Intronic	(eQTL)
	rs3827644	G	C			**SYSTEMIC SCLEROSIS** [203,211]	European study World	Intronic	(eQTL)
	rs9372120	T	G	19%	31	**MULTIPLE MYELOMA** [212] **RHEUMATOID ARTHRITIS** [213] **SYSTEMIC SCLEROSIS** [203]	American study American study World collaboration	Intronic	(eQTL)
	rs9373839	T	C			**CROHN DISEASE** [189] Theragnosis (anti-TNF) **SYSTEMIC SCLEROSIS** [203]	American study World	Intronic	(eQTL)
	rs6568431	A	C	60%	14	**CHRONIC HEPATITIS B VIRUS (HBV) INFECTION** [208] **SLE** [201,202] ↑ anemia and renal involvement (PBMC)	American studies	3' *ATG5*	N/A ↑ exp[208]
	rs6937876	G	A			**AUTOIMMUNE DEMYELINATING DISEASE** [194,209] Protective	Asian studies		N/A
	rs12201458	**C**	**A**	12%	2	**ASTHMA** [191,192]	American studies	Intronic	N/A
	rs12212740	**G**	**A**	13%	4	**ASTHMA** [66,193] Protective	American and Asian studies	Intronic	N/A
	rs17067724	A	G	1%	1	**HCC** [214] Protective	Asian study	Intronic RP1-60O19.1	N/A

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG7 **NM_001144912 5828 eQTL**	rs8154	T	C	31%	1	**LUAD (EGFR*)** [196] **BREAST CANCER** [215] Bad prognostic ↓ PFS and OS	Asian study Asian study	Synonymous methylation meQTL[215]	eQTL – Lung ↑ exp[215]
	rs1375206	C	G	60%	36	**ASTHMA** [193] ↓serum IL8 levels **PARKINSON disease** [216]	Asian study Asian study	Intronic	(eQTL)
	rs1470612	C	T	18%	77	**CEREBRAL PALSY** [217]	Asian study	Intronic	(eQTL)
	rs2594971	G	A	65%	45	**ASTHMA** [193] ↓serum IL8 levels	Asian study	5' *ATG7*	(eQTL)
	rs2594975	T	C	51%	1	**MYOCARDIAL INFARCTION** [218] ↑ binding of transcription factors, transcription	Asian study	5' *ATG7*	Not found
	rs7635838	T	C	59%	35	**CARDIOVASCULAR DISEASE** [144] HDL	European study	Intronic	(eQTL)
	rs2447607	C	G,T	59	14	**Systolic BLOOD PRESSURE** [144]	European study	Intronic	eQTL muscle
	rs36117895	T	C	3%	56	**HUNTINGTON DISEASE** [219]	European study	**MISSENSE** V471A	(eQTL)
ATG10 **NM_001131028 16437 eQTL**	rs1864182	C	A	58%	11	**BREAST CANCER** [220] Protective	Asian study	**MISSENSE** P220H	eQTL - Lung
						NSCLC [221] Poor survival **NSCLC EGFR*** [196] Theragnosis (Gefitinib) ↓ RISK for acquired RESISTANCE. ↑ RISK of primary RESISTANCE	Asian study Asian study		
						LUNG FIBROSIS [197] Protective **x COAL**	Asian study		
						MELANOMA [198] ↑ tumor-infiltrating lymphocytes (TILs)	American study		

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG10 **NM_001131028 16437 eQTL**	[rs1864183](#)	C	T	49%	22	**HCC** [214]	Asian study	**MISSENSE** T212M	eQTL - Lung
						HNSCC RISK to develop laryngeal cancer [150] **NPC**, Bad Theragnosis (Radiotherapy) [222]	European study Asian study		
						NSCLC Poor survival[221] Theragnosis (Platinum)[67]	Asian study Asian study		
						PAGET DISEASE [200] Protective	European study		
						TUBERCULOSIS [223] ↑ IL8	Asian study		
	[rs3734114](#)	T	C	21%	36	**TUBERCULOSIS** [222] ↑ IL8	Asian study	Missense	(eQTL)
	[rs4703533](#)	C	G	39%	4	**HNSCC NPC** [222] Bad Theragnosis (Radiotherapy)	Asian study	Intronic	
	[rs10036653](#)	A	T	20%	1	**NSCLC** [224] ↓ RISK of brain metastasis **NSCLC EGFR*** [196] Theragnosis (Gefitinib) ↓ acquired resistance ↑ PFS ↑ OS	Asian study Asian study	5' *ATG10* ↑ OCT4 binding [196]	eQTL - Lung
	[rs10514231](#)	C	T	66%	1	**BREAST CANCER** [220] Protective **NSCLC** [221] Poor survival **HCC** [214] Protective **HNSCC NPC** [222] Bad Theragnosis (radiotherapy)	Asian study Asian study Asian study Asian study	Intronic	eQTL - Lung, Breast ↑ exp[214]
	[rs9447453](#)	C	A	11%	1	**Delayed age of MENOPAUSE** [225]	American study	5' *ATG10*	N/A

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG10 **NM_001131028 16437 eQTL**	rs1485587	A	G	47%	18	**ALZHEIMER DISEASE** [226]	American study	Intronic	eQTL - Brain
	rs324913	T	C			**ECZEMA HERPETICUM** [227] ↓ IFNγ	American study	Intronic	eQTL -Skin
	rs891159	G	A	22%	43	**ALZHEIMER DISEASE** [226]	American study	Intronic	eQTL - Brain
	rs4703879	A	G						eQTL - Brain
	rs7707921	T	A			**BREAST CANCER** [228]	European study	Intronic	eQTL - Breast
	rs73134739	T	C			**BREAST CANCER** [229]	Asian study	Intronic	eQTL - Breast
ATG12 **NM_004707 268 eQTL**	rs26532	C	A	78%	1	**NSCLC** [224] RISK of brain metastasis	Asian study	Intronic	eQTL - Brain
	rs26537	T	C	40%	5	**HNSCC**[230] **HCC** [214]	Asian study Asian study	Intronic	eQTL ↑ exp [230]
	rs26538	C	T			**NSCLC EGFR*** [196] Bad prognosis ↓ PFS **LUNG FIBROSIS** [197] **x COAL** - Protective	Asian study Asian study	Intronic	eQTL - Lung ↓ exp [196]
	rs1058600	C	T	23%	12	**NSCLC** [231] Theragnosis (Radiotherapy)	American study	3'UTR	eQTL - Lung
ATG16L1 **NM_030803 2507 eQTL**	rs2289476	C	A	6%	25	**CROHN DISEASE** [41,232,233] **x SMOKING**	European and American studies	Intronic	(eQTL)
	rs4663402	A	T	4%	18	**HNSCC** [230] **HCC** [214]	Asian study Asian study	Intronic	eQTL - Esophagus
	rs4663421	G	C			♀ **ANKYLOSING SPONDYLITIS** [234]	Asian study	Intronic	(eQTL)
	rs6758317	C	T	18%	3			Intronic	(eQTL)
	rs6754677	G	A	62%	8	**CROHN DISEASE** [235]	Asian study	Intronic	(eQTL)
	rs78835907	G	A	5%	1	**PROSTATE CANCER** [236] Bad prognostic	Asian study	N/A	N/A

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG16L1 **NM_030803 2507 eQTL**	[rs2241880](#)	A	G	53%	71	**CARDIOVASCULAR DISEASE** [237] RISK in postmenopausal women	Caucasian study	**MISSENSE** T300A	eQTL - Colon Thyroid
						COPD [238] **x SMOKING -** Protective	European study		
						COLORECTAL CANCER ↓ RISK ↓ metastasis ↑ IFN (indep. of autophagy) [239] ↑ RISK[240]	European study		
						CROHN DISEASE [41,232,233,235,241] Complications after CD ileocolectomy **x SMOKING**	European, American and Asian studies		
						GASTRIC CANCER [109,242] **x *H. pylori* infection**	Asians-Oceanian study		
						HCC RISK-based surveillance in cirrhosis [243] Protective: **HEPATITIS B** virus-related HCC [244]	European study Asian study		
						HNSCC [150] Oral carcinoma	European study		
						NSCLC **EGFR***minor allele: ↑ RISK Bad prognosis [196] Protective ↓ RISK of brain metastasis [224,238]	Asian and European studies		
						MELANOMA [198] Younger age	World collaboration		
						PREMATURE DELIVERY [245]	European Study		
						THYROID CANCER [246] Protective	European study		
						UROPATHOGENIC *E. coli* [247] Protective	American study		
	[rs13005285](#)	T	G	66%	8	**PALMOPLANTAR PUSTULOSIS** [248]	European study	Intronic	eQTL - Skin

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
ATG16L2 **NM_033388 222 eQTL**	rs10751215	T	C	47%	33	**Metastatic ccRCC** [117] **NSCLC** [231] Theragnosis (Radiotherapy) ↑ATG16L2 ↓ autophagosome ↑ inflammation	European study American study	Intronic	(eQTL)
	rs10898880	C	A					5' *ATG16L2*	(eQTL) ↑ **exp**[231]
	rs11605818	A	G	2%	1	**SLE** [249]	European study	Intronic	N/A
	rs11235604	C	T	0% As 10%	1	**CROHN DISEASE** [250–252] Protective **SLE** [253–255] with IgA nephropathy or lupus nephritis **NSCLC EGFR*** [196] Bad Theragnosis (Gefitinib)	American and Asian studies American and Asian studies Asian study	**MISSENSE** R220W	N/A ↓ **exp**
	rs11235667	A	G	0% As 11%	1	**SLE** [255] POL2, YY1, and FOXa binding sites	American and Asian Study	3' *ATG16L2*	N/A
CHMP2B **NM_014043 7278 eQTL**	rs1002765	G	A	11%	1	**ATROPHIC GASTRITIS** [256] precancerous **x *H. pylori* infection** **GASTRIC CANCER** [256] **x *H. pylori* infection**	Asian study	Intronic not specific MIR4795	(eQTL)
	rs63751126	A	C	0%	1	**ALS** [257]	European study	**MISSENSE** Q206H	Not found
	rs63751048	C	T	0%	1	**FRONTOTEMPORAL DEMENTIA** [258] protein-truncating mutation	European study	nonsense	Not found
	rs63750652	G	A,C	0%	1			splice acceptor	Not found
	rs63750653	G	T	0%	1			**MISSENSE** N148T	Not found
LAMP1 **NM_005561 74 eQTL**	rs9577229	C	T	0%	1	**TUBERCULOSIS** [223]	Asian and European study	**MISSENSE** A204V	(eQTL)
	rs12871648	A	C	33%	1	**PARKINSON DISEASE** [259]	American study	Intronic	N/A
LAMP2 **NM_015104 820 eQTL**	rs727504953	G	A	0%	1	**DANON DISEASE** [260] cardiomyopathy, skeletal myopathy, and intellectual disability	Asian study	**MISSENSE** G93R	Not found ↓ exp [260]

VI - *AUTOPHAGY RECEPTORS*

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
DRAM1 **NM_018370** **4677 eQTL** **induces the formation of the phagophore by binding p62/SQSTM-1** [261,262]	rs7955890	C	T	11%	40	**NSCLC** [67] Theragnostic (Platinum) ↑ PFS	Asian study	Intronic	eQTL - Lung
	rs17032060	G	A					3'UTR	N/A
	rs77694286	A	G	1%	24	**TYPE 2 DIABETES** [263] higher protein intake	American and European study **GWA 91,114**	Intronic	(eQTL) ↓ exp [263]
SQSTM1 **NM_003900** **339 eQTL**	rs104893941	C	T	1%	1	**ALZHEIMER DISEASE** [264] Early-onset Rare germinal SQSTM1 mutations are associated with neurodegenerative diseases, such as ALS-FTD [265], Parkinson disease, Alzheimer disease [264], and also Paget disease of bone, metabolic diseases, obesity, and insulin resistance [266,267]	European study	**MISSENSE** P308L	N/A
NBR1 **NM_005899** **10,959 eQTL** **Not specific. Commun NBR1, NBR2, BRCA1**	rs17599948	G	C	6%	6	**PROSTATE CANCER** [268] progression to lethal cancer after radiotherapy **BREAST CANCER** [269] Rare BRCA1 3'UTR SNPs	American study American and European study	Intronic	eQTL – Breast, Prostate
CALCOCO2 **NM_005831** **1311 eQTL**	rs8074034	A	G	49%	26	**GLIOBLASTOMA** [270] pediatric	American and European study	Intronic	eQTL- Brain
	rs2303015	T	C	4%	75	**BACTERIAL PERITONITIS** [271] (spontaneous) in patients with alcoholic cirrhosis **CROHN DISEASE** [272]	European study American and European study	**MISSENSE** V272A	eQTL - Colon

Gene	variant	Ref	Alt	EUR freq	LD	Disease	Populations	Funct Annot	eQTL GTEX
WDFY3 **NM_014991 347 eQTL**	rs76117213	G	A	1%	1	**ALZHEIMER DISEASE** [273]	American study	Intronic	N/A
	rs17009220	G	C	6%	1			Intronic	N/A
	Heterozygous, mostly ***de novo*** **variants in WDFY3** result in a mild **NEURODEVELOPMENTAL** delay (intellectual disability, autism/hyperactivity disorder) **and opposing effects on brain size** [274]**: Loss-of-function** variants (truncating and missense) causing **haploinsufficiency** lead to **MACROCEPHALY. In contrast,** variants in the PH-domain of WDFY3 leads to **MICROCEPHALY, via dysregulation of the WNT-pathway**. Proliferating cortical neural progenitors highly express WDFY3, further supporting a role for this molecule in the regulation of prenatal neurogenesis.								
OPTN **NM_021980 473 eQTL**	rs3829923	C	T	34%	3	**GLAUCOMA** [275]	European study	CCDC3	N/A
	rs10796021	TT	T,TC	44%	1			CCDC3	Not found
	rs7921853	T	G	51%	1			Intronic	(eQTL)
	rs765884	T	C	28%	13			Intronic	(eQTL)
	rs11258194	T	A	3%	2	**GLAUCOMA** [276] **DIABETIC RETINOPATHY** [277]	Asian study Middle East study	**MISSENSE** M98K	N/A
	rs2234968	G	A	26%	4	**GLAUCOMA** [276]	American and Asian studies	synonymous	(eQTL)
	rs10906308	G	A	22%	18	**GLAUCOMA** [278]	American study	Intronic	Not found
	rs825411	A	G	54%	4	**PAGET DISEASE** [279]	European and Oceanian study	Intronic	(eQTL)
	rs1561570	T	C	50%	3			Intronic	(eQTL)

Supplementary information references

1. Cheong H, Wu J, Gonzales LK, Guttentag SH, Thompson CB, Lindsten T. Analysis of a lung defect in autophagy-deficient mouse strains. Autophagy [Internet] 2014; 10:45–56. Available from: https://www.tandfonline.com/doi/full/10.4161/auto.26505

2. Maciel M, Hernández-Barrientos D, Herrera I, Selman M, Pardo A, Cabrera S. Impaired autophagic activity and ATG4B deficiency are associated with increased endoplasmic reticulum stress-induced lung injury. Aging (Albany NY) [Internet] 2018; 10:2098–112. Available from: http://www.aging-us.com/article/101532/text

3. Cabrera S, Maciel M, Herrera I, Nava T, Vergara F, Gaxiola M, López-Otín C, Selman M, Pardo A. Essential role for the ATG4B protease and autophagy in bleomycin-induced pulmonary fibrosis. Autophagy [Internet] 2015; 11:670–84. Available from: http://www.tandfonline.com/doi/full/10.1080/15548627.2015.1034409

4. Abdel Fattah E, Bhattacharya A, Herron A, Safdar Z, Eissa NT. Critical Role for IL-18 in Spontaneous Lung Inflammation Caused by Autophagy Deficiency. J Immunol [Internet] 2015; 194:5407–16. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1402277

5. Chen Z-H, Kim HP, Sciurba FC, Lee S-J, Feghali-Bostwick C, Stolz DB, Dhir R, Landreneau RJ, Schuchert MJ, Yousem SA, et al. Egr-1 Regulates Autophagy in Cigarette Smoke-Induced Chronic Obstructive Pulmonary Disease. PLoS One [Internet] 2008; 3:e3316. Available from: https://dx.plos.org/10.1371/journal.pone.0003316

6. Chen Z-H, Lam HC, Jin Y, Kim H-P, Cao J, Lee S-J, Ifedigbo E, Parameswaran H, Ryter SW, Choi AMK. Autophagy protein microtubule-associated protein 1 light chain-3B (LC3B) activates extrinsic apoptosis during cigarette smoke-induced emphysema. Proc Natl Acad Sci [Internet] 2010; 107:18880–5. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1005574107

7. Kesireddy VS, Chillappagari S, Ahuja S, Knudsen L, Henneke I, Graumann J, Meiners S, Ochs M, Ruppert C, Korfei M, et al. Susceptibility of microtubule-associated protein 1 light chain 3β (MAP1LC3B/LC3B) knockout mice to lung injury and fibrosis. FASEB J [Internet] 2019; 33:12392–408. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1096/fj.201900854R

8. Yeganeh B, Lee J, Ermini L, Lok I, Ackerley C, Post M. Autophagy is required for lung development and morphogenesis. J Clin Invest [Internet] 2019; 129:2904–19. Available from: https://www.jci.org/articles/view/127307

9. Wen W, Yu G, Liu W, Gu L, Chu J, Zhou X, Liu Y, Lai G. Silencing FUNDC1 alleviates chronic obstructive pulmonary disease by inhibiting mitochondrial autophagy and bronchial epithelium cell apoptosis under hypoxic environment. J Cell Biochem 2019; 120:17602–15.

10. Qu X, Yu J, Bhagat G, Furuya N, Hibshoosh H, Troxel A, Rosen J, Eskelinen E-L, Mizushima N, Ohsumi Y, et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest [Internet] 2003; 112:1809–20. Available from: http://www.jci.org/articles/view/20039

11. Yue Z, Jin S, Yang C, Levine AJ, Heintz N. Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. Proc Natl Acad Sci [Internet] 2003; 100:15077–82. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.2436255100

12. Takahashi Y, Coppola D, Matsushita N, Cualing HD, Sun M, Sato Y, Liang C, Jung JU, Cheng JQ, Mul JJ, et al. Bif-1 interacts with Beclin 1 through UVRAG and regulates autophagy and tumorigenesis. Nat Cell Biol [Internet] 2007; 9:1142–51. Available from: http://www.nature.com/articles/ncb1634

13. Kaizuka T, Mizushima N. Atg13 Is Essential for Autophagy and Cardiac Development in Mice. Mol Cell Biol [Internet] 2016; 36:585–95. Available from: http://mcb.asm.org/lookup/doi/10.1128/MCB.01005-15

14. Gan B, Peng X, Nagy T, Alcaraz A, Gu H, Guan J-L. Role of FIP200 in cardiac and liver development and its regulation of TNFα and TSC–mTOR signaling pathways. J Cell Biol [Internet] 2006; 175:121–33. Available from: https://rupress.org/jcb/article/175/1/121/34356/Role-of-FIP200-in-cardiac-and-liver-development

15. Taneike M, Yamaguchi O, Nakai A, Hikoso S, Takeda T, Mizote I, Oka T, Tamai T, Oyabu J, Murakawa T, et al. Inhibition of autophagy in the heart induces age-related cardiomyopathy. Autophagy [Internet] 2010; 6:600–6. Available from: https://www.tandfonline.com/doi/full/10.4161/auto.6.5.11947

16. Song Z, An L, Ye Y, Wu J, Zou Y, He L, Zhu H. Essential role for UVRAG in autophagy and maintenance of cardiac function. Cardiovasc Res [Internet] 2014; 101:48–56. Available from: https://academic.oup.com/cardiovascres/article-lookup/doi/10.1093/cvr/cvt223

17. Zaglia T, Milan G, Ruhs A, Franzoso M, Bertaggia E, Pianca N, Carpi A, Carullo P, Pesce P, Sacerdoti D, et al. Atrogin-1 deficiency promotes cardiomyopathy and premature death via impaired autophagy. J Clin Invest [Internet] 2014; 124:2410–24. Available from: http://www.jci.org/articles/view/66339

18. Kaushal GP, Shah S V. Autophagy in acute kidney injury. Kidney Int [Internet] 2016; 89:779–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26924060

19. Jiang M, Wei Q, Dong G, Komatsu M, Su Y, Dong Z. Autophagy in proximal tubules protects against acute kidney injury. Kidney Int [Internet] 2012; 82:1271–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22854643

20. Lenoir O, Tharaux P-L, Huber TB. Autophagy in kidney disease and aging: lessons from rodent models. Kidney Int [Internet] 2016; 90:950–64. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253816301739

21. Wang C, Mendonsa GR, Symington JW, Zhang Q, Cadwell K, Virgin HW, Mysorekar IU. Atg16L1 deficiency confers protection from uropathogenic Escherichia coli infection in vivo. Proc Natl Acad Sci U S A [Internet] 2012; 109:11008–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22715292

22. Gawriluk TR, Hale AN, Flaws JA, Dillon CP, Green DR, Rucker EB. Autophagy is a cell survival program for female germ cells in the murine ovary. REPRODUCTION [Internet]

2011; 141:759–65. Available from: https://rep.bioscientifica.com/view/journals/rep/141/6/759.xml

23. Chew TS, O'Shea NR, Sewell GW, Oehlers SH, Mulvey CM, Crosier PS, Godovac-Zimmermann J, Bloom SL, Smith AM, Segal AW. Optineurin deficiency in mice contributes to impaired cytokine secretion and neutrophil recruitment in bacteria-driven colitis. Dis Model Mech [Internet] 2015; 8:817–29. Available from: http://dmm.biologists.org/cgi/doi/10.1242/dmm.020362

24. Oestreich AK, Chadchan SB, Popli P, Medvedeva A, Rowen MN, Stephens CS, Xu R, Lydon JP, Demayo FJ, Jungheim ES, et al. The Autophagy Gene Atg16L1 is Necessary for Endometrial Decidualization. Endocrinology [Internet] 2020; 161. Available from: https://academic.oup.com/endo/article/doi/10.1210/endocr/bqz039/5686885

25. Li L, Shen C, Nakamura E, Ando K, Signoretti S, Beroukhim R, Cowley GS, Lizotte P, Liberzon E, Bair S, et al. SQSTM1 is a pathogenic target of 5q copy number gains in kidney cancer. Cancer Cell [Internet] 2013; 24:738–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24332042

26. Santanam U, Banach-Petrosky W, Abate-Shen C, Shen MM, White E, DiPaola RS. Atg7 cooperates with Pten loss to drive prostate cancer tumor growth. Genes Dev [Internet] 2016; 30:399–407. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26883359

27. Liang XH, Jackson S, Seaman M, Brown K, Kempkes B, Hibshoosh H, Levine B. Induction of autophagy and inhibition of tumorigenesis by beclin 1. Nature [Internet] 1999; 402:672–6. Available from: http://www.nature.com/articles/45257

28. Vega-Rubín-de-Celis S, Zou Z, Fernández ÁF, Ci B, Kim M, Xiao G, Xie Y, Levine B. Increased autophagy blocks HER2-mediated breast tumorigenesis. Proc Natl Acad Sci [Internet] 2018; 115:4176–81. Available from: http://www.pnas.org/lookup/doi/10.1073/pnas.1717800115

29. Aita VM, Liang XH, Murty VVVS, Pincus DL, Yu W, Cayanis E, Kalachikov S, Gilliam TC, Levine B. Cloning and Genomic Organization of Beclin 1, a Candidate Tumor Suppressor Gene on Chromosome 17q21. Genomics [Internet] 1999; 59:59–65. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0888754399958512

30. Wei H, Wei S, Gan B, Peng X, Zou W, Guan J-L. Suppression of autophagy by FIP200 deletion inhibits mammary tumorigenesis. Genes Dev [Internet] 2011; 25:1510–27. Available from: http://genesdev.cshlp.org/cgi/doi/10.1101/gad.2051011

31. Xia H, Wang W, Crespo J, Kryczek I, Li W, Wei S, Bian Z, Maj T, He M, Liu RJ, et al. Suppression of FIP200 and autophagy by tumor-derived lactate promotes naïve T cell apoptosis and affects tumor immunity. Sci Immunol [Internet] 2017; 2:eaan4631. Available from: https://immunology.sciencemag.org/lookup/doi/10.1126/sciimmunol.aan4631

32. Wei H, Gan B, Wu X, Guan J-L. Inactivation of FIP200 Leads to Inflammatory Skin Disorder, but Not Tumorigenesis, in Conditional Knock-out Mouse Models. J Biol Chem [Internet] 2009; 284:6004–13. Available from: http://www.jbc.org/lookup/doi/10.1074/jbc.M806375200

33. Delaney JR, Patel CB, Bapat J, Jones CM, Ramos-Zapatero M, Ortell KK, Tanios R, Haghighiabyaneh M, Axelrod J, DeStefano JW, et al. Autophagy gene haploinsufficiency drives chromosome instability, increases migration, and promotes early ovarian tumors. PLOS Genet [Internet] 2020; 16:e1008558. Available from: https://dx.plos.org/10.1371/journal.pgen.1008558

34. Inami Y, Waguri S, Sakamoto A, Kouno T, Nakada K, Hino O, Watanabe S, Ando J, Iwadate M, Yamamoto M, et al. Persistent activation of Nrf2 through p62 in hepatocellular carcinoma cells. J Cell Biol [Internet] 2011; 193:275–84. Available from: https://rupress.org/jcb/article/193/2/275/36414/Persistent-activation-of-Nrf2-through-p62-in

35. Takamura A, Komatsu M, Hara T, Sakamoto A, Kishi C, Waguri S, Eishi Y, Hino O, Tanaka K, Mizushima N. Autophagy-deficient mice develop multiple liver tumors. Genes Dev [Internet] 2011; 25:795–800. Available from: http://genesdev.cshlp.org/cgi/doi/10.1101/gad.2016211

36. Lee YA, Noon LA, Akat KM, Ybanez MD, Lee T-F, Berres M-L, Fujiwara N, Goossens N, Chou H-I, Parvin-Nejad FP, et al. Autophagy is a gatekeeper of hepatic differentiation and carcinogenesis by controlling the degradation of Yap. Nat Commun [Internet] 2018; 9:4962. Available from: http://www.nature.com/articles/s41467-018-07338-z

37. Saitoh T, Fujita N, Jang MH, Uematsu S, Yang B-G, Satoh T, Omori H, Noda T, Yamamoto N, Komatsu M, et al. Loss of the autophagy protein Atg16L1 enhances endotoxin-induced IL-1beta production. Nature [Internet] 2008; 456:264–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18849965

38. Cadwell K, Liu JY, Brown SL, Miyoshi H, Loh J, Lennerz JK, Kishi C, Kc W, Carrero JA, Hunt S, et al. A key role for autophagy and the autophagy gene Atg16l1 in mouse and human intestinal Paneth cells. Nature [Internet] 2008; 456:259–63. Available from: http://www.nature.com/articles/nature07416

39. Cadwell K, Patel KK, Maloney NS, Liu T-C, Ng ACY, Storer CE, Head RD, Xavier R, Stappenbeck TS, Virgin HW. Virus-Plus-Susceptibility Gene Interaction Determines Crohn's Disease Gene Atg16L1 Phenotypes in Intestine. Cell [Internet] 2010; 141:1135–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0092867410005453

40. Bel S, Pendse M, Wang Y, Li Y, Ruhn KA, Hassell B, Leal T, Winter SE, Xavier RJ, Hooper L V. Paneth cells secrete lysozyme via secretory autophagy during bacterial infection of the intestine. Science (80-) [Internet] 2017; 357:1047–52. Available from: https://www.sciencemag.org/lookup/doi/10.1126/science.aal4677

41. Liu T, Kern JT, VanDussen KL, Xiong S, Kaiko GE, Wilen CB, Rajala MW, Caruso R, Holtzman MJ, Gao F, et al. Interaction between smoking and ATG16L1T300A triggers Paneth cell defects in Crohn's disease. J Clin Invest [Internet] 2018; 128:5110–22. Available from: https://www.jci.org/articles/view/120453

42. Liu B, Gulati AS, Cantillana V, Henry SC, Schmidt EA, Daniell X, Grossniklaus E, Schoenborn AA, Sartor RB, Taylor GA. Irgm1-deficient mice exhibit Paneth cell abnormalities and increased susceptibility to acute intestinal inflammation. Am J Physiol Liver Physiol [Internet] 2013; 305:G573–84. Available from:

https://www.physiology.org/doi/10.1152/ajpgi.00071.2013

43. Cabrera S, Fernández ÁF, Mariño G, Aguirre A, Suárez MF, Español Y, Vega JA, Laurà R, Fueyo A, Fernández-García MS, et al. ATG4B/autophagin-1 regulates intestinal homeostasis and protects mice from experimental colitis. Autophagy [Internet] 2013; 9:1188–200. Available from: http://www.tandfonline.com/doi/abs/10.4161/auto.24797

44. He S, Zhao Z, Yang Y, O'Connell D, Zhang X, Oh S, Ma B, Lee J-H, Zhang T, Varghese B, et al. Truncating mutation in the autophagy gene UVRAG confers oncogenic properties and chemosensitivity in colorectal cancers. Nat Commun [Internet] 2015; 6:7839. Available from: http://www.nature.com/articles/ncomms8839

45. Quach C, Song Y, Guo H, Li S, Maazi H, Fung M, Sands N, O'Connell D, Restrepo-Vassalli S, Chai B, et al. A truncating mutation in the autophagy gene UVRAG drives inflammation and tumorigenesis in mice. Nat Commun [Internet] 2019; 10:5681. Available from: http://www.nature.com/articles/s41467-019-13475-w

46. Hara T, Nakamura K, Matsui M, Yamamoto A, Nakahara Y, Suzuki-Migishima R, Yokoyama M, Mishima K, Saito I, Okano H, et al. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature [Internet] 2006; 441:885–9. Available from: http://www.nature.com/articles/nature04724

47. Komatsu M, Waguri S, Chiba T, Murata S, Iwata J, Tanida I, Ueno T, Koike M, Uchiyama Y, Kominami E, et al. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature [Internet] 2006; 441:880–4. Available from: http://www.nature.com/articles/nature04723

48. Houtman J, Freitag K, Gimber N, Schmoranzer J, Heppner FL, Jendrach M. Beclin1-driven autophagy modulates the inflammatory response of microglia via <scp>NLRP</scp> 3. EMBO J [Internet] 2019; 38. Available from: https://onlinelibrary.wiley.com/doi/abs/10.15252/embj.201899430

49. Ramesh Babu J, Lamar Seibenhener M, Peng J, Strom A-L, Kemppainen R, Cox N, Zhu H, Wooten MC, Diaz-Meco MT, Moscat J, et al. Genetic inactivation of p62 leads to accumulation of hyperphosphorylated tau and neurodegeneration. J Neurochem [Internet] 2008; 106:107–20. Available from: http://doi.wiley.com/10.1111/j.1471-4159.2008.05340.x

50. Krasniak CS, Ahmad ST. The role of CHMP2BIntron5 in autophagy and frontotemporal dementia. Brain Res [Internet] 2016; 1649:151–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006899316301275

51. Ghazi-Noori S, Froud KE, Mizielinska S, Powell C, Smidak M, Fernandez de Marco M, O'Malley C, Farmer M, Parkinson N, Fisher EMC, et al. Progressive neuronal inclusion formation and axonal degeneration in CHMP2B mutant transgenic mice. Brain [Internet] 2012; 135:819–32. Available from: https://academic.oup.com/brain/article-lookup/doi/10.1093/brain/aws006

52. Tang G, Gudsnuk K, Kuo S-H, Cotrina ML, Rosoklija G, Sosunov A, Sonders MS, Kanter E, Castagna C, Yamamoto A, et al. Loss of mTOR-Dependent Macroautophagy Causes Autistic-like Synaptic Pruning Deficits. Neuron [Internet] 2014; 83:1131–43. Available

from: https://linkinghub.elsevier.com/retrieve/pii/S0896627314006515

53. Dere E, Dahm L, Lu D, Hammerschmidt K, Ju A, Tantra M, KÃ¤stner A, Chowdhury K, Ehrenreich H. Heterozygous Ambra1 Deficiency in Mice: A Genetic Trait with Autism-Like Behavior Restricted to the Female Gender. Front Behav Neurosci [Internet] 2014; 8. Available from: http://journal.frontiersin.org/article/10.3389/fnbeh.2014.00181/abstract

54. Le Duc D, Giulivi C, Hiatt SM, Napoli E, Panoutsopoulos A, Harlan De Crescenzo A, Kotzaeridou U, Syrbe S, Anagnostou E, Azage M, et al. Pathogenic WDFY3 variants cause neurodevelopmental disorders and opposing effects on brain size. Brain [Internet] 2019; 142:2617–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31327001

55. Noguchi S, Honda S, Saitoh T, Matsumura H, Nishimura E, Akira S, Shimizu S. Beclin 1 regulates recycling endosome and is required for skin development in mice. Commun Biol [Internet] 2019; 2:37. Available from: http://www.nature.com/articles/s42003-018-0279-0

56. Salah FS, Ebbinghaus M, Muley VY, Zhou Z, Al-Saadi KRD, Pacyna-Gengelbach M, O'Sullivan GA, Betz H, König R, Wang Z-Q, et al. Tumor suppression in mice lacking GABARAP, an Atg8/LC3 family member implicated in autophagy, is associated with alterations in cytokine secretion and cell death. Cell Death Dis [Internet] 2016; 7:e2205–e2205. Available from: http://www.nature.com/articles/cddis201693

57. Poillet-Perez L, Xie X, Zhan L, Yang Y, Sharp DW, Hu ZS, Su X, Maganti A, Jiang C, Lu W, et al. Autophagy maintains tumour growth through circulating arginine. Nature [Internet] 2018; 563:569–73. Available from: http://www.nature.com/articles/s41586-018-0697-7

58. Allot A, Peng Y, Wei C-H, Lee K, Phan L, Lu Z. LitVar: a semantic search engine for linking genomic variant data in PubMed and PMC. Nucleic Acids Res [Internet] 2018; 46:W530–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29762787

59. Ward LD, Kellis M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res [Internet] 2012; 40:D930–4. Available from: https://academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkr917

60. Ward LD, Kellis M. HaploReg v4: systematic mining of putative causal variants, cell types, regulators and target genes for human complex traits and disease. Nucleic Acids Res [Internet] 2016; 44:D877-81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26657631

61. Carithers LJ, Ardlie K, Barcus M, Branton PA, Britton A, Buia SA, Compton CC, DeLuca DS, Peter-Demchok J, Gelfand ET, et al. A Novel Approach to High-Quality Postmortem Tissue Procurement: The GTEx Project. Biopreserv Biobank [Internet] 2015; 13:311–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26484571

62. Zhang R-R, Liang L, Chen W-W, Wen C, Wan B-S, Luo L-L, Zhao Y-L, Chen J, Yue J. ULK1 polymorphisms confer susceptibility to pulmonary tuberculosis in a Chinese population. Int J Tuberc Lung Dis [Internet] 2019; 23:265–71. Available from:

https://www.ingentaconnect.com/content/10.5588/ijtld.18.0174

63. Morgan AR, Lam W-J, Han D-Y, Fraser AG, Ferguson LR. Association Analysis of ULK1 with Crohn's Disease in a New Zealand Population. Gastroenterol Res Pract [Internet] 2012; 2012:1–6. Available from: http://www.hindawi.com/journals/grp/2012/715309/

64. Zhang X, Han R, Wang M, Li X, Yang X, Xia Q, Liu R, Yuan Y, Hu X, Chen M, et al. Association between the autophagy-related gene ULK1 and ankylosing spondylitis susceptibility in the Chinese Han population: a case–control study. Postgrad Med J [Internet] 2017; 93:752–7. Available from: http://pmj.bmj.com/content/93/1106/752.abstract

65. Horne DJ, Graustein AD, Shah JA, Peterson G, Savlov M, Steele S, Narita M, Hawn TR. Human ULK1 Variation and Susceptibility to Mycobacterium tuberculosis Infection. J Infect Dis [Internet] 2016; 214:1260–7. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1093/infdis/jiw347

66. Poon AH, Chouiali F, Tse SM, Litonjua AA, Hussain SNA, Baglole CJ, Eidelman DH, Olivenstein R, Martin JG, Weiss ST, et al. Genetic and histologic evidence for autophagy in asthma pathogenesis. J Allergy Clin Immunol [Internet] 2012; 129:569–71. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674911015582

67. Wang S, Song X, Zhao X, Chen H, Wang J, Wu J, Gao Z, Qian J, Bai C, Li Q, et al. Association between polymorphisms of autophagy pathway and responses in non-small cell lung cancer patients treated with platinum-based chemotherapy. Yi chuan = Hered [Internet] 2017; 39:250–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28420621

68. Henckaerts L, Cleynen I, Brinar M, John JM, Van Steen K, Rutgeerts P, Vermeire S. Genetic variation in the autophagy gene ULK1 and risk of Crohn's disease. Inflamm Bowel Dis [Internet] 2011; 17:1392–7. Available from: https://academic.oup.com/ibdjournal/article/17/6/1392-1397/4631112

69. Al Eissa MM, Fiorentino A, Sharp SI, O'Brien NL, Wolfe K, Giaroli G, Curtis D, Bass NJ, McQuillin A. Exome sequence analysis and follow up genotyping implicates rare ULK1 variants to be involved in susceptibility to schizophrenia. Ann Hum Genet [Internet] 2018; 82:88–92. Available from: http://doi.wiley.com/10.1111/ahg.12226

70. Fung H-C, Scholz S, Matarin M, Simón-Sánchez J, Hernandez D, Britton A, Gibbs JR, Langefeld C, Stiegert ML, Schymick J, et al. Genome-wide genotyping in Parkinson's disease and neurologically normal controls: first stage analysis and public release of data. Lancet Neurol [Internet] 2006; 5:911–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442206705786

71. Wolthers BO, Frandsen TL, Baruchel A, Attarbaschi A, Barzilai S, Colombini A, Escherich G, Grell K, Inaba H, Kovacs G, et al. Asparaginase-associated pancreatitis in childhood acute lymphoblastic leukaemia: an observational Ponte di Legno Toxicity Working Group study. Lancet Oncol [Internet] 2017; 18:1238–48. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204517304242

72. Yao L, Zhong W, Zhang Z, Maenner MJ, Engelman CD. Classification tree for detection

of single-nucleotide polymorphism (SNP)-by-SNP interactions related to heart disease: Framingham Heart Study. BMC Proc [Internet] 2009; 3:S83. Available from: http://bmcproc.biomedcentral.com/articles/10.1186/1753-6561-3-S7-S83

73. Li Z, Xin J, Chen W, Liu J, Zhu M, Zhao C, Yuan J, Jin G, Ma H, Du J, et al. Genetic variants in autophagy associated genes are associated with DNA damage levels in Chinese population. Gene [Internet] 2017; 626:414–9. Available from: http://dx.doi.org/10.1016/j.gene.2017.05.017

74. Huyghe JR, Jackson AU, Fogarty MP, Buchkovich ML, Stančáková A, Stringham HM, Sim X, Yang L, Fuchsberger C, Cederberg H, et al. Exome array analysis identifies new loci and low-frequency variants influencing insulin processing and secretion. Nat Genet [Internet] 2013; 45:197–201. Available from: http://www.nature.com/articles/ng.2507

75. Berger MD, Yamauchi S, Cao S, Hanna DL, Sunakawa Y, Schirripa M, Matsusaka S, Yang D, Groshen S, Zhang W, et al. Autophagy-related polymorphisms predict hypertension in patients with metastatic colorectal cancer treated with FOLFIRI and bevacizumab: Results from TRIBE and FIRE-3 trials. Eur J Cancer [Internet] 2017; 77:13–20. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0959804917307864

76. Broberg K, Huynh E, Engström KS, Björk J, Albin M, Ingvar C, Olsson H, Höglund M. Association between polymorphisms in RMI1, TOP3A, and BLM and risk of cancer, a case-control study. BMC Cancer [Internet] 2009; 9:140. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-9-140

77. Peter B, Wijsman EM, Nato AQ, Matsushita MM, Chapman KL, Stanaway IB, Wolff J, Oda K, Gabo VB, Raskind WH. Genetic Candidate Variants in Two Multigenerational Families with Childhood Apraxia of Speech. PLoS One [Internet] 2016; 11:e0153864. Available from: https://dx.plos.org/10.1371/journal.pone.0153864

78. Etheredge AJ, Finnell RH, Carmichael SL, Lammer EJ, Zhu H, Mitchell LE, Shaw GM. Maternal and infant gene-folate interactions and the risk of neural tube defects. Am J Med Genet Part A [Internet] 2012; 158A:2439–46. Available from: http://doi.wiley.com/10.1002/ajmg.a.35552

79. Kelemen LE, Sellers TA, Schildkraut JM, Cunningham JM, Vierkant RA, Pankratz VS, Fredericksen ZS, Gadre MK, Rider DN, Liebow M, et al. Genetic Variation in the One-Carbon Transfer Pathway and Ovarian Cancer Risk. Cancer Res [Internet] 2008; 68:2498–506. Available from: http://cancerres.aacrjournals.org/cgi/doi/10.1158/0008-5472.CAN-07-5165

80. Li Y-J, Guggenheim JA, Bulusu A, Metlapally R, Abbott D, Malecaze F, Calvas P, Rosenberg T, Paget S, Creer RC, et al. An International Collaborative Family-Based Whole-Genome Linkage Scan for High-Grade Myopia. Investig Opthalmology Vis Sci [Internet] 2009; 50:3116. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.08-2781

81. Stein JL, Hibar DP, Madsen SK, Khamis M, McMahon KL, de Zubicaray GI, Hansell NK, Montgomery GW, Martin NG, Wright MJ, et al. Discovery and replication of dopamine-related gene effects on caudate volume in young and elderly populations (N=1198) using genome-wide search. Mol Psychiatry [Internet] 2011; 16:927–37.

Available from: http://www.nature.com/articles/mp201132

82. Koopmann TT, Adriaens ME, Moerland PD, Marsman RF, Westerveld ML, Lal S, Zhang T, Simmons CQ, Baczko I, dos Remedios C, et al. Genome-Wide Identification of Expression Quantitative Trait Loci (eQTLs) in Human Heart. PLoS One [Internet] 2014; 9:e97380. Available from: https://dx.plos.org/10.1371/journal.pone.0097380

83. Van Laer L, Huyghe JR, Hannula S, Van Eyken E, Stephan DA, Mäki-Torkko E, Aikio P, Fransen E, Lysholm-Bernacchi A, Sorri M, et al. A genome-wide association study for age-related hearing impairment in the Saami. Eur J Hum Genet [Internet] 2010; 18:685–93. Available from: http://www.nature.com/articles/ejhg2009234

84. Laaksovirta H, Peuralinna T, Schymick JC, Scholz SW, Lai S-L, Myllykangas L, Sulkava R, Jansson L, Hernandez DG, Gibbs JR, et al. Chromosome 9p21 in amyotrophic lateral sclerosis in Finland: a genome-wide association study. Lancet Neurol [Internet] 2010; 9:978–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1474442210701848

85. Liu X, He J, Gao F-B, Gitler AD, Fan D. The epidemiology and genetics of Amyotrophic lateral sclerosis in China. Brain Res [Internet] 2018; 1693:121–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006899318301057

86. Ferrari R, Mok K, Moreno JH, Cosentino S, Goldman J, Pietrini P, Mayeux R, Tierney MC, Kapogiannis D, Jicha GA, et al. Screening for C9ORF72 repeat expansion in FTLD. Neurobiol Aging [Internet] 2012; 33:1850.e1-1850.e11. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0197458012001625

87. Williams KA, Lee M, Hu Y, Andreas J, Patel SJ, Zhang S, Chines P, Elkahloun A, Chandrasekharappa S, Gutkind JS, et al. A Systems Genetics Approach Identifies CXCL14, ITGAX, and LPCAT2 as Novel Aggressive Prostate Cancer Susceptibility Genes. PLoS Genet [Internet] 2014; 10:e1004809. Available from: https://dx.plos.org/10.1371/journal.pgen.1004809

88. Harley ITW, Niewold TB, Stormont RM, Kaufman KM, Glenn SB, Franek BS, Kelly JA, Kilpatrick JR, Hutchings D, Divers J, et al. The Role of Genetic Variation Near Interferon-Kappa in Systemic Lupus Erythematosus. J Biomed Biotechnol [Internet] 2010; 2010:1–11. Available from: https://www.hindawi.com/journals/bmri/2010/706825/

89. Karch CM, Wen N, Fan CC, Yokoyama JS, Kouri N, Ross OA, Höglinger G, Müller U, Ferrari R, Hardy J, et al. Selective Genetic Overlap Between Amyotrophic Lateral Sclerosis and Diseases of the Frontotemporal Dementia Spectrum. JAMA Neurol [Internet] 2018; 75:860. Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/jamaneurol.2018.0372

90. Fogh I, Ratti A, Gellera C, Lin K, Tiloca C, Moskvina V, Corrado L, Soraru G, Cereda C, Corti S, et al. A genome-wide association meta-analysis identifies a novel locus at 17q11.2 associated with sporadic amyotrophic lateral sclerosis. Hum Mol Genet [Internet] 2014; 23:2220–31. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddt587

91. Jones AR, Woollacott I, Shatunov A, Cooper-Knock J, Buchman V, Sproviero W, Smith

B, Scott KM, Balendra R, Abel O, et al. Residual association at C9orf72 suggests an alternative amyotrophic lateral sclerosis-causing hexanucleotide repeat. Neurobiol Aging [Internet] 2013; 34:2234.e1-2234.e7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0197458013001036

92. Luty AA, Kwok JBJ, Thompson EM, Blumbergs P, Brooks WS, Loy CT, Dobson-Stone C, Panegyres PK, Hecker J, Nicholson GA, et al. Pedigree with frontotemporal lobar degeneration – motor neuron disease and Tar DNA binding protein-43 positive neuropathology: genetic linkage to chromosome 9. BMC Neurol [Internet] 2008; 8:32. Available from: http://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-8-32

93. Harms MB, Cady J, Zaidman C, Cooper P, Bali T, Allred P, Cruchaga C, Baughn M, Libby RT, Pestronk A, et al. Lack of C9ORF72 coding mutations supports a gain of function for repeat expansions in amyotrophic lateral sclerosis. Neurobiol Aging [Internet] 2013; 34:2234.e13-2234.e19. Available from: http://dx.doi.org/10.1016/j.neurobiolaging.2013.03.006

94. Wason JMS, Dudbridge F. Comparison of multimarker logistic regression models, with application to a genomewide scan of schizophrenia. BMC Genet [Internet] 2010; 11:80. Available from: https://bmcgenet.biomedcentral.com/articles/10.1186/1471-2156-11-80

95. Bahari G, Hashemi M, Taheri M, Naderi M, Eskandari-Nasab E, Atabaki M. Association of IRGM Polymorphisms and Susceptibility to Pulmonary Tuberculosis in Zahedan, Southeast Iran. Sci World J [Internet] 2012; 2012:1–5. Available from: http://www.hindawi.com/journals/tswj/2012/950801/

96. McCarroll SA, Huett A, Kuballa P, Chilewski SD, Landry A, Goyette P, Zody MC, Hall JL, Brant SR, Cho JH, et al. Deletion polymorphism upstream of IRGM associated with altered IRGM expression and Crohn's disease. Nat Genet [Internet] 2008; 40:1107–12. Available from: http://www.nature.com/articles/ng.215

97. Prescott NJ, Dominy KM, Kubo M, Lewis CM, Fisher SA, Redon R, Huang N, Stranger BE, Blaszczyk K, Hudspith B, et al. Independent and population-specific association of risk variants at the IRGM locus with Crohn's disease. Hum Mol Genet [Internet] 2010; 19:1828–39. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddq041

98. Parkes M, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, Fisher SA, Roberts RG, Nimmo ER, Cummings FR, Soars D, et al. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn's disease susceptibility. Nat Genet [Internet] 2007; 39:830–2. Available from: http://www.nature.com/articles/ng2061

99. Brest P, Corcelle EA, Cesaro A, Chargui A, Belaïd A, Klionsky DJ, Vouret-Craviari V, Hebuterne X, Hofman P, Mograbi B. Autophagy and Crohn's disease: at the crossroads of infection, inflammation, immunity, and cancer. Curr Mol Med [Internet] 2010; 10:486–502. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20540703

100. Ajayi TA, Innes CL, Grimm SA, Rai P, Finethy R, Coers J, Wang X, Bell DA, McGrath JA, Schurman SH, et al. Crohn's disease IRGM risk alleles are associated with altered gene

expression in human tissues. Am J Physiol Liver Physiol [Internet] 2019; 316:G95–105. Available from: https://www.physiology.org/doi/10.1152/ajpgi.00196.2018

101. Brest P, Lapaquette P, Souidi M, Lebrigand K, Cesaro A, Vouret-Craviari V, Mari B, Barbry P, Mosnier J-F, Hébuterne X, et al. A synonymous variant in IRGM alters a binding site for miR-196 and causes deregulation of IRGM-dependent xenophagy in Crohn's disease. Nat Genet [Internet] 2011; 43:242–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21278745

102. Kimura T, Watanabe E, Sakamoto T, Takasu O, Ikeda T, Ikeda K, Kotani J, Kitamura N, Sadahiro T, Tateishi Y, et al. Autophagy-Related IRGM Polymorphism Is Associated with Mortality of Patients with Severe Sepsis. PLoS One [Internet] 2014; 9:e91522. Available from: https://dx.plos.org/10.1371/journal.pone.0091522

103. King KY, Lew JD, Ha NP, Lin JS, Ma X, Graviss EA, Goodell MA. Polymorphic Allele of Human IRGM1 Is Associated with Susceptibility to Tuberculosis in African Americans. PLoS One [Internet] 2011; 6:e16317. Available from: http://dx.plos.org/10.1371/journal.pone.0016317

104. Yao Q, Zhu Y, Wang W, Song Z, Shao X, Li L, Song R, An X, Qin Q, Li Q, et al. Polymorphisms in Autophagy-Related Gene IRGM Are Associated with Susceptibility to Autoimmune Thyroid Diseases. Biomed Res Int [Internet] 2018; 2018:1–7. Available from: https://www.hindawi.com/journals/bmri/2018/7959707/

105. Lu Y, Li Q, Peng J, Zhu Y, Wang F, Wang C, Wang X. Association of autophagy-related IRGM polymorphisms with latent versus active tuberculosis infection in a Chinese population. Tuberculosis [Internet] 2016; 97:47–51. Available from: http://dx.doi.org/10.1016/j.tube.2016.01.001

106. Xie H, Li C, Zhang M, Zhong N, Chen L. Association between IRGM polymorphisms and tuberculosis risk. Medicine (Baltimore) [Internet] 2017; 96:e8189. Available from: http://journals.lww.com/00005792-201710270-00013

107. Folwaczny M, Tsekeri E, Glas J. A haplotypic variant at the IRGM locus and rs11747270 are related to the susceptibility for chronic periodontitis. Inflamm Res [Internet] 2018; 67:129–38. Available from: http://dx.doi.org/10.1007/s00011-017-1101-z

108. Rufini S, Ciccacci C, Di Fusco D, Ruffa A, Pallone F, Novelli G, Biancone L, Borgiani P. Autophagy and inflammatory bowel disease: Association between variants of the autophagy-related IRGM gene and susceptibility to Crohn's disease. Dig Liver Dis [Internet] 2015; 47:744–50. Available from: http://dx.doi.org/10.1016/j.dld.2015.05.012

109. Castaño-Rodríguez N, Kaakoush NO, Goh K-L, Fock KM, Mitchell HM. Autophagy in Helicobacter pylori Infection and Related Gastric Cancer. Helicobacter [Internet] 2015; 20:353–69. Available from: http://doi.wiley.com/10.1111/hel.12211

110. Ge J, Li L, Jin Q, Liu YC, Zhao L, Song H-H. Functional IRGM polymorphism is associated with language impairment in glioma and upregulates cytokine expressions. Tumor Biol [Internet] 2014; 35:8343–8. Available from: http://link.springer.com/10.1007/s13277-014-2091-x

111. Yang D, Chen J, Shi C, Jing Z, Song N. Autophagy Gene Polymorphism is Associated

with Susceptibility to Leprosy by Affecting Inflammatory Cytokines. Inflammation [Internet] 2014; 37:593–8. Available from: http://link.springer.com/10.1007/s10753-013-9773-1

112. Lin YC, Chang PF, Lin HF, Liu K, Chang MH, Ni YH. Variants in the autophagy-related gene IRGM confer susceptibility to non-alcoholic fatty liver disease by modulating lipophagy. J Hepatol [Internet] 2016; 65:1209–16. Available from: http://dx.doi.org/10.1016/j.jhep.2016.06.029

113. Simon TG, Deng X, Liu C, Chung RT, Long MT. The immunity-related GTPase M rs13361189 variant does not increase the risk for prevalent or incident steatosis; results from the Framingham Heart Study. Liver Int [Internet] 2019; 39:1022–6. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/liv.14039

114. Yuan L, Ke Z, Ma J, Guo Y, Li Y. IRGM gene polymorphisms and haplotypes associate with susceptibility of pulmonary tuberculosis in Chinese Hubei Han population. Tuberculosis [Internet] 2016; 96:58–64. Available from: http://dx.doi.org/10.1016/j.tube.2015.10.014

115. BURADA F, PLANTINGA TS, IOANA M, ROSENTUL D, ANGELESCU C, JOOSTEN LA, NETEA MG, SAFTOIU A. IRGM gene polymorphisms and risk of gastric cancer. J Dig Dis [Internet] 2012; 13:360–5. Available from: http://doi.wiley.com/10.1111/j.1751-2980.2012.00602.x

116. Intemann CD, Thye T, Niemann S, Browne ENL, Amanua Chinbuah M, Enimil A, Gyapong J, Osei I, Owusu-Dabo E, Helm S, et al. Autophagy Gene Variant IRGM −261T Contributes to Protection from Tuberculosis Caused by Mycobacterium tuberculosis but Not by M. africanum Strains. PLoS Pathog [Internet] 2009; 5:e1000577. Available from: https://dx.plos.org/10.1371/journal.ppat.1000577

117. SANTONI M, PIVA F, DE GIORGI U, MOSCA A, BASSO U, SANTINI D, BUTI S, LOLLI C, TERRONE C, MARUZZO M, et al. Autophagic Gene Polymorphisms in Liquid Biopsies and Outcome of Patients with Metastatic Clear Cell Renal Cell Carcinoma. Anticancer Res [Internet] 2018; 38:5773–82. Available from: http://ar.iiarjournals.org/lookup/doi/10.21873/anticanres.12916

118. Ng D, Hu N, Hu Y, Wang C, Giffen C, Tang Z-Z, Han X-Y, Yang HH, Lee MP, Goldstein AM, et al. Replication of a genome-wide case-control study of esophageal squamous cell carcinoma. Int J Cancer [Internet] 2008; 123:1610–5. Available from: http://doi.wiley.com/10.1002/ijc.23682

119. Shulman JM, Chipendo P, Chibnik LB, Aubin C, Tran D, Keenan BT, Kramer PL, Schneider JA, Bennett DA, Feany MB, et al. Functional Screening of Alzheimer Pathology Genome-wide Association Signals in Drosophila. Am J Hum Genet [Internet] 2011; 88:232–8. Available from: http://dx.doi.org/10.1016/j.ajhg.2011.01.006

120. Mangino M, Richards JB, Soranzo N, Zhai G, Aviv A, Valdes AM, Samani NJ, Deloukas P, Spector TD. A genome-wide association study identifies a novel locus on chromosome 18q12.2 influencing white cell telomere length. J Med Genet [Internet] 2009; 46:451–4. Available from: http://jmg.bmj.com/cgi/doi/10.1136/jmg.2008.064956

121. Zhang N, Zheng Y, Liu J, Lei T, Xu Y, Yang M. Genetic variations associated with

telomere length confer risk of gastric cardia adenocarcinoma. Gastric Cancer [Internet] 2019; 22:1089–99. Available from: http://link.springer.com/10.1007/s10120-019-00954-8

122. Abulí A, Fernández-Rozadilla C, Giráldez MD, Muñoz J, Gonzalo V, Bessa X, Bujanda L, Reñé JM, Lanas A, García AM, et al. A two-phase case–control study for colorectal cancer genetic susceptibility: candidate genes from chromosomal regions 9q22 and 3q22. Br J Cancer [Internet] 2011; 105:870–5. Available from: http://www.nature.com/articles/bjc2011296

123. SanGiovanni JP, Lee PH. AMD-Associated Genes Encoding Stress-Activated MAPK Pathway Constituents Are Identified by Interval-Based Enrichment Analysis. PLoS One [Internet] 2013; 8:e71239. Available from: https://dx.plos.org/10.1371/journal.pone.0071239

124. Hamet P, Haloui M, Harvey F, Marois-Blanchet F-C, Sylvestre M-P, Tahir M-R, Simon PHG, Kanzki BS, Raelson J, Long C, et al. PROX1 gene CC genotype as a major determinant of early onset of type 2 diabetes in slavic study participants from Action in Diabetes and Vascular Disease. J Hypertens [Internet] 2017; 35:S24–32. Available from: http://journals.lww.com/00004872-201705001-00005

125. Schuetz JM, Daley D, Graham J, Berry BR, Gallagher RP, Connors JM, Gascoyne RD, Spinelli JJ, Brooks-Wilson AR. Genetic Variation in Cell Death Genes and Risk of Non-Hodgkin Lymphoma. PLoS One [Internet] 2012; 7:e31560. Available from: https://dx.plos.org/10.1371/journal.pone.0031560

126. Sabarinathan R, Wenzel A, Novotny P, Tang X, Kalari KR, Gorodkin J. Transcriptome-Wide Analysis of UTRs in Non-Small Cell Lung Cancer Reveals Cancer-Related Genes with SNV-Induced Changes on RNA Secondary Structure and miRNA Target Sites. PLoS One [Internet] 2014; 9:e82699. Available from: http://dx.plos.org/10.1371/journal.pone.0082699

127. Kazachkova N, Raposo M, Ramos A, Montiel R, Lima M. Promoter Variant Alters Expression of the Autophagic BECN1 Gene: Implications for Clinical Manifestations of Machado-Joseph Disease. The Cerebellum [Internet] 2017; 16:957–63. Available from: http://link.springer.com/10.1007/s12311-017-0875-4

128. Darabi H, McCue K, Beesley J, Michailidou K, Nord S, Kar S, Humphreys K, Thompson D, Ghoussaini M, Bolla MK, et al. Polymorphisms in a Putative Enhancer at the 10q21.2 Breast Cancer Risk Locus Regulate NRBF2 Expression. Am J Hum Genet 2015; 97:22–34.

129. Ross CJ, Towfic F, Shankar J, Laifenfeld D, Thoma M, Davis M, Weiner B, Kusko R, Zeskind B, Knappertz V, et al. A pharmacogenetic signature of high response to Copaxone in late-phase clinical-trial cohorts of multiple sclerosis. Genome Med [Internet] 2017; 9:50. Available from: http://genomemedicine.biomedcentral.com/articles/10.1186/s13073-017-0436-y

130. Jeong T-J, Shin M-K, Uhm Y-K, Kim H-J, Chung J-H, Lee M-H. Association of UVRAG polymorphisms with susceptibility to non-segmental vitiligo in a Korean sample. Exp Dermatol [Internet] 2010; 19:e323–5. Available from: http://doi.wiley.com/10.1111/j.1600-0625.2009.01039.x

131. Bleibel WK, Duan S, Huang RS, Kistner EO, Shukla SJ, Wu X, Badner JA, Dolan ME. Identification of genomic regions contributing to etoposide-induced cytotoxicity. Hum Genet [Internet] 2009; 125:173–80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3624763/pdf/nihms412728.pdf

132. Kathiresan S, Manning AK, Demissie S, D'Agostino RB, Surti A, Guiducci C, Gianniny L, Burtt NP, Melander O, Orho-Melander M, et al. A genome-wide association study for blood lipid phenotypes in the Framingham Heart Study. BMC Med Genet 2007; 8:1–10.

133. Gómez-Ramos A, Podlesniy P, Soriano E, Avila J. Distinct X-chromosome SNVs from some sporadic AD samples. Sci Rep [Internet] 2016; 5:18012. Available from: http://www.nature.com/articles/srep18012

134. Cronin S, Tomik B, Bradley DG, Slowik A, Hardiman O. Screening for replication of genome-wide SNP associations in sporadic ALS. Eur J Hum Genet [Internet] 2009; 17:213–8. Available from: http://www.nature.com/articles/ejhg2008194

135. Brožová K, Krásničanová H, Rusina R. Megalencephalic leukoencephalopathy with subcortical cysts without macrocephaly: A case study of comorbid Turner's syndrome. Clin Neurol Neurosurg [Internet] 2019; 184:105400. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0303846719301969

136. Zhou Z, Sturgis EM, Liu Z, Wang L-E, Wei Q, Li G. Genetic variants of NOXA and MCL1 modify the risk of HPV16-associated squamous cell carcinoma of the head and neck. BMC Cancer [Internet] 2012; 12:159. Available from: http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-12-159

137. Shin H-D, Cheong H-S, Park B-L, Kim L-H, Han C-S, Lee I-H, Park S-K. Common MCL1 polymorphisms associated with risk of tuberculosis. BMB Rep [Internet] 2008; 41:334–7. Available from: http://koreascience.or.kr/journal/view.jsp?kj=E1MBB7&py=2008&vnc=v41n4&sp=334

138. Jiang Y, Wang W, Wang J, Lu Y, Chen Y, Jin L, Lin D, He F, Wang H. Functional regulatory variants of MCL1 contribute to enhanced promoter activity and reduced risk of lung cancer in nonsmokers: Implications for context-dependent phenotype of an antiapoptotic and antiproliferative gene in solid tumor. Cancer [Internet] 2012; 118:2085–95. Available from: http://doi.wiley.com/10.1002/cncr.26502

139. Wang S, Jiang Y, Liu J, Zhao Y, Xiang C, Ma R, Gao H, Jin L, He F, Wang H. Revisiting the role of MCL1 in tumorigenesis of solid cancer: gene expression correlates with antiproliferative phenotype in breast cancer cells and its functional regulatory variants are associated with reduced cancer susceptibility. Tumor Biol [Internet] 2014; 35:8289–99. Available from: http://link.springer.com/10.1007/s13277-014-2108-5

140. Chen W, Zhang Y, Zhu Y, Yang Y, Gong YJ, Miao XP, Zhong R. Association between genetic variants in p53 binding sites and risks of breast cancer in Chinese population. Zhonghua Liu Xing Bing Xue Za Zhi [Internet] 2016; 37:1063–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27539333

141. Zhang J, Kai L, Zhang W, Yin Y, Wang W. Association between genetic variants in p53

binding sites and risks of osteosarcoma in a Chinese population: a two-stage case-control study. Cancer Biol Ther [Internet] 2018; 19:994–7. Available from: https://www.tandfonline.com/doi/full/10.1080/15384047.2018.1456607

142. FitzGerald LM, Kwon EM, Conomos MP, Kolb S, Holt SK, Levine D, Feng Z, Ostrander EA, Stanford JL. Genome-wide Association Study Identifies a Genetic Variant Associated with Risk for More Aggressive Prostate Cancer. Cancer Epidemiol Biomarkers Prev [Internet] 2011; 20:1196–203. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022202X15370834

143. Manduchi E, Williams SM, Chesi A, Johnson ME, Wells AD, Grant SFA, Moore JH. Leveraging epigenomics and contactomics data to investigate SNP pairs in GWAS. Hum Genet [Internet] 2018; 137:413–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29797095

144. Portilla-Fernandez E, Ghanbari M, van Meurs JBJ, Danser AHJ, Franco OH, Muka T, Roks A, Dehghan A. Dissecting the association of autophagy-related genes with cardiovascular diseases and intermediate vascular traits: A population-based approach. PLoS One [Internet] 2019; 14:e0214137. Available from: http://dx.plos.org/10.1371/journal.pone.0214137

145. Mitjans M, Begemann M, Ju A, Dere E, Wüstefeld L, Hofer S, Hassouna I, Balkenhol J, Oliveira B, van der Auwera S, et al. Sexual dimorphism of AMBRA1-related autistic features in human and mouse. Transl Psychiatry 2017; 7:e1247.

146. Rietschel M, Mattheisen M, Degenhardt F, Mühleisen TW, Kirsch P, Esslinger C, Herms S, Demontis D, Steffens M, Strohmaier J, et al. Association between genetic variation in a region on chromosome 11 and schizophrenia in large samples from Europe. Mol Psychiatry 2012; 17:906–17.

147. Brinar M, Vermeire S, Cleynen I, Lemmens B, Sagaert X, Henckaerts L, Van Assche G, Geboes K, Rutgeerts P, De Hertogh G. Genetic variants in autophagy-related genes and granuloma formation in a cohort of surgically treated Crohn's disease patients. J Crohn's Colitis [Internet] 2012; 6:43–50. Available from: http://dx.doi.org/10.1016/j.crohns.2011.06.008

148. Yamada Y, Sakuma J, Takeuchi I, Yasukochi Y, Kato K, Oguri M, Fujimaki T, Horibe H, Muramatsu M, Sawabe M, et al. Identification of *C21orf59* and *ATG2A* as novel determinants of renal function-related traits in Japanese by exome-wide association studies. Oncotarget [Internet] 2017; 8:45259–73. Available from: http://www.oncotarget.com/fulltext/16696

149. Buffen K, Oosting M, Quintin J, Ng A, Kleinnijenhuis J, Kumar V, van de Vosse E, Wijmenga C, van Crevel R, Oosterwijk E, et al. Autophagy Controls BCG-Induced Trained Immunity and the Response to Intravesical BCG Therapy for Bladder Cancer. PLoS Pathog [Internet] 2014; 10:e1004485. Available from: https://dx.plos.org/10.1371/journal.ppat.1004485

150. Fernández-Mateos J, Seijas-Tamayo R, Klain JCA, Borgoñón MP, Pérez-Ruiz E, Mesía R, del Barco E, Coloma CS, Dominguez AR, Daroqui JC, et al. Analysis of autophagy gene polymorphisms in Spanish patients with head and neck squamous cell carcinoma. Sci Rep [Internet] 2017; 7:6887. Available from: http://www.nature.com/articles/s41598-

017-07270-0

151. Meddens CA, Harakalova M, van den Dungen NAM, Foroughi Asl H, Hijma HJ, Cuppen EPJG, Björkegren JLM, Asselbergs FW, Nieuwenhuis EES, Mokry M. Systematic analysis of chromatin interactions at disease associated loci links novel candidate genes to inflammatory bowel disease. Genome Biol [Internet] 2016; 17:247. Available from: http://dx.doi.org/10.1186/s13059-016-1100-3

152. Kim K-N, Kim JH, Jung K, Hong Y-C. Associations of air pollution exposure with blood pressure and heart rate variability are modified by oxidative stress genes: A repeated-measures panel among elderly urban residents. Environ Heal [Internet] 2016; 15:47. Available from: http://dx.doi.org/10.1186/s12940-016-0130-3

153. Mehrabi Pour M, Nasiri M, Kamfiroozie H, Zibaeenezhad MJ. Association of the ATG9B gene polymorphisms with coronary artery disease susceptibility: A case-control study. J Cardiovasc Thorac Res [Internet] 2019; 11:109–15. Available from: https://doi.org/10.15171/jcvtr.2019.19

154. Zhang M, Liang L, Xu M, Qureshi AA, Han J. Pathway Analysis for Genome-Wide Association Study of Basal Cell Carcinoma of the Skin. PLoS One [Internet] 2011; 6:e22760. Available from: https://dx.plos.org/10.1371/journal.pone.0022760

155. MacClellan LR, Howard TD, Cole JW, Stine OC, Giles WH, O'Connell JR, Wozniak MA, Stern BJ, Mitchell BD, Kittner SJ. Relation of Candidate Genes that Encode for Endothelial Function to Migraine and Stroke. Stroke [Internet] 2009; 40:1–7. Available from: https://www.ahajournals.org/doi/10.1161/STROKEAHA.109.557462

156. Cho K, Demissie S, Dupuis J, Cupples LA, Kathiresan S, Beck TJ, Karasik D, Kiel DP. Polymorphisms in the endothelial nitric oxide synthase gene and bone density/ultrasound and geometry in humans. Bone [Internet] 2008; 42:53–60. Available from: https://linkinghub.elsevier.com/retrieve/pii/S8756328207007429

157. Carreras-Torres R, Kundu S, Zanetti D, Esteban E, Via M, Moral P. Genetic Risk Score of NOS Gene Variants Associated with Myocardial Infarction Correlates with Coronary Incidence across Europe. PLoS One [Internet] 2014; 9:e96504. Available from: https://dx.plos.org/10.1371/journal.pone.0096504

158. Chasman DI, Paré G, Mora S, Hopewell JC, Peloso G, Clarke R, Cupples LA, Hamsten A, Kathiresan S, Mälarstig A, et al. Forty-Three Loci Associated with Plasma Lipoprotein Size, Concentration, and Cholesterol Content in Genome-Wide Analysis. PLoS Genet [Internet] 2009; 5:e1000730. Available from: https://dx.plos.org/10.1371/journal.pgen.1000730

159. Wang L, Ren A, Tian T, Li N, Cao X, Zhang P, Jin L, Li Z, Shen Y, Zhang B, et al. Whole-Exome Sequencing Identifies Damaging de novo Variants in Anencephalic Cases. Front Neurosci [Internet] 2019; 13:1–12. Available from: https://www.frontiersin.org/article/10.3389/fnins.2019.01285/full

160. Jelani M, Dooley HC, Gubas A, Mohamoud HSA, Khan MTM, Ali Z, Kang C, Rahim F, Jan A, Vadgama N, et al. A mutation in the major autophagy gene, WIPI2, associated with global developmental abnormalities. Brain [Internet] 2019; 142:1242–54. Available from: https://academic.oup.com/brain/article/142/5/1242/5433409

161. Kruer MC, Boddaert N. Neurodegeneration with brain iron accumulation: a diagnostic algorithm. Semin Pediatr Neurol [Internet] 2012; 19:67–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22704259

162. Gregory A, Kurian MA, Haack T, Hayflick SJ, Hogarth P. Beta-Propeller Protein-Associated Neurodegeneration [Internet]. 1993. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28211668

163. Lee JH, Cheng R, Graff-Radford N, Foroud T, Mayeux R, National Institute on Aging Late-Onset Alzheimer's Disease Family Study Group. Analyses of the National Institute on Aging Late-Onset Alzheimer's Disease Family Study: implication of additional loci. Arch Neurol [Internet] 2008; 65:1518–26. Available from: http://archneur.jamanetwork.com/article.aspx?doi=10.1001/archneur.65.11.1518

164. Gao G, Sheng Y, Yang H, Chua BT, Xu L. DFCP1 associates with lipid droplets. Cell Biol Int [Internet] 2019; Available from: http://www.ncbi.nlm.nih.gov/pubmed/31293035

165. Mao J, Wu L, Wang W, Ye Y, Yang J, Chen H, Yang Q, Zhang X, Wang B, Chen W. Nucleotide variation in ATG4A and susceptibility to cervical cancer in Southwestern Chinese women. Oncol Lett [Internet] 2017; 15:2992–3000. Available from: http://www.spandidos-publications.com/10.3892/ol.2017.7663

166. He Q, Lu Y, Hu S, Huang Q, Li S, Huang Y, Hu Q, Wu L, Chen W. An intron SNP rs807185 in ATG4A decreases the risk of lung cancer in a southwest Chinese population. Eur J Cancer Prev [Internet] 2016; 25:255–8. Available from: http://journals.lww.com/00008469-201607000-00001

167. Song F-J, Chen K-X. Single-nucleotide polymorphisms among microRNA: big effects on cancer. Chin J Cancer [Internet] 2011; 30:381–91. Available from: http://www.cjcsysu.cn/abstract.asp?idno=17791

168. Eeles RA, Olama AA Al, Benlloch S, Saunders EJ, Leongamornlert DA, Tymrakiewicz M, Ghoussaini M, Luccarini C, Dennis J, Jugurnauth-Little S, et al. Identification of 23 new prostate cancer susceptibility loci using the iCOGS custom genotyping array. Nat Genet [Internet] 2013; 45:385–91. Available from: http://www.nature.com/articles/ng.2560

169. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. Nat Genet [Internet] 2015; 47:979–86. Available from: http://www.nature.com/articles/ng.3359

170. Daya M, van der Merwe L, van Helden PD, Möller M, Hoal EG. Investigating the Role of Gene-Gene Interactions in TB Susceptibility. PLoS One [Internet] 2015; 10:e0123970. Available from: http://dx.plos.org/10.1371/journal.pone.0123970

171. Wu C, Wen Y, Guo X, Yang T, Shen H, Chen X, Tian Q, Tan L, Deng H-W, Zhang F. Genetic association, mRNA and protein expression analysis identify ATG4C as a susceptibility gene for Kashin–Beck disease. Osteoarthr Cartil [Internet] 2017; 25:281–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S106345841630303X

172. Yang Q, Kathiresan S, Lin J-P, Tofler GH, O'Donnell CJ. Genome-wide association and

linkage analyses of hemostatic factors and hematological phenotypes in the Framingham Heart Study. BMC Med Genet [Internet] 2007; 8:S12. Available from: http://bmcmedgenet.biomedcentral.com/articles/10.1186/1471-2350-8-S1-S12

173. Shepard CJ, Cline SG, Hinds D, Jahanbakhsh S, Prokop JW. Breakdown of multiple sclerosis genetics to identify an integrated disease network and potential variant mechanisms. Physiol Genomics 2019; 51:562–77.

174. Chen C-Z, Ou C-Y, Wang R-H, Lee C-H, Lin C-C, Chang H-Y, Hsiue T-R. Association of Egr-1 and autophagy-related gene polymorphism in men with chronic obstructive pulmonary disease. J Formos Med Assoc [Internet] 2015; 114:750–5. Available from: http://dx.doi.org/10.1016/j.jfma.2013.07.015

175. Hu T-M, Chen S-J, Hsu S-H, Cheng M-C. Functional analyses and effect of DNA methylation on the EGR1 gene in patients with schizophrenia. Psychiatry Res [Internet] 2019; 275:276–82. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0165178118316093

176. Lou X-Y, Ma JZ, Sun D, Payne TJ, Li MD. Fine mapping of a linkage region on chromosome 17p13 reveals that GABARAP and DLG4 are associated with vulnerability to nicotine dependence in European-Americans. Hum Mol Genet [Internet] 2007; 16:142–53. Available from: http://academic.oup.com/hmg/article/16/2/142/2355978/Fine-mapping-of-a-linkage-region-on-chromosome

177. Cui WY, Seneviratne C, Gu J, Li MD. Genetics of GABAergic signaling in nicotine and alcohol dependence. Hum Genet 2012; 131:843–55.

178. Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, Kawaguchi T, Stahl EA, Kurreeman FAS, Nishida N, et al. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. Nat Genet [Internet] 2012; 44:511–6. Available from: http://www.nature.com/articles/ng.2231

179. Griswold AJ, Ma D, Cukier HN, Nations LD, Schmidt MA, Chung R, Jaworski JM, Salyakina D, Konidari I, Whitehead PL, et al. Evaluation of copy number variations reveals novel candidate genes in autism spectrum disorder-associated pathways. 2012; 21:3513–23.

180. Jansen AFM, Schoffelen T, Bleeker-Rovers CP, Wever PC, Jaeger M, Oosting M, Adriaans A, Joosten LAB, Netea MG, van Deuren M, et al. Genetic variations in innate immunity genes affect response to Coxiella burnetii and are associated with susceptibility to chronic Q fever. Clin Microbiol Infect [Internet] 2019; 25:631.e11-631.e15. Available from: http://dx.doi.org/10.1016/j.cmi.2018.08.011

181. Qi Y, Zhou X, Nath SK, Sun C, Wang Y, Hou P, Mu R, Li C, Guo J, Li Z, et al. A Rare Variant (rs933717) at FBXO31-MAP1LC3B in Chinese Is Associated With Systemic Lupus Erythematosus. Arthritis Rheumatol [Internet] 2018; 70:287–97. Available from: http://doi.wiley.com/10.1002/art.40353

182. Aissani B, Wiener H, Zhang K. Multiple Hits for the Association of Uterine Fibroids on Human Chromosome 1q43. PLoS One 2013; 8.

183. Nuta GC, Gilad Y, Gershoni M, Sznajderman A, Schlesinger T, Bialik S, Eisenstein M,

Pietrokovski S, Kimchi A. A cancer associated somatic mutation in LC3B attenuates its binding to E1-like ATG7 protein and subsequent lipidation. Autophagy [Internet] 2019; 15:438–52. Available from: https://doi.org/10.1080/15548627.2018.1525476

184. Costa JR, Prak K, Aldous S, Gewinner CA, Ketteler R. Autophagy gene expression profiling identifies a defective microtubule-associated protein light chain 3A mutant in cancer. Oncotarget [Internet] 2016; 7:41203–16. Available from: http://www.oncotarget.com/fulltext/9754

185. Sanborn JZ, Chung J, Purdom E, Wang NJ, Kakavand H, Wilmott JS, Butler T, Thompson JF, Mann GJ, Haydu LE, et al. Phylogenetic analyses of melanoma reveal complex patterns of metastatic dissemination. Proc Natl Acad Sci U S A 2015; 112:10995–1000.

186. Awan FM, Obaid A, Ikram A, Janjua HA. Mutation-structure-function relationship based integrated strategy reveals the potential impact of deleterious missense mutations in autophagy related proteins on hepatocellular carcinoma (HCC): A comprehensive informatics approach. Int J Mol Sci 2017; 18.

187. Grunwald DS, Otto NM, Park J-M, Song D, Kim D-H. GABARAPs and LC3s have opposite roles in regulating ULK1 for autophagy induction. Autophagy [Internet] 2019; :1–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31208283

188. Li M, Ma F, Wang J, Li Q, Zhang P, Yuan P, Luo Y, Cai R, Fan Y, Chen S, et al. Genetic polymorphisms of autophagy-related gene 5 (ATG5) rs473543 predict different disease-free survivals of triple-negative breast cancer patients receiving anthracycline- and/or taxane-based adjuvant chemotherapy. Chin J Cancer [Internet] 2018; 37:4. Available from: https://doi.org/10.1186/s40880-018-0268-1

189. Deželak M, Repnik K, Koder S, Ferkolj I, Potočnik U. A Prospective Pharmacogenomic Study of Crohn's Disease Patients during Routine Therapy with Anti-TNF-α Drug Adalimumab: Contribution of ATG5 , NFKB1, and CRP Genes to Pharmacodynamic Variability. Omi A J Integr Biol [Internet] 2016; 20:296–309. Available from: http://www.liebertpub.com/doi/10.1089/omi.2016.0005

190. Shao Y, Chen F, Chen Y, Zhang W, Lin Y, Cai Y, Yin Z, Tao S, Liao Q, Zhao J, et al. Association between genetic polymorphisms in the autophagy-related 5 gene promoter and the risk of sepsis. Sci Rep [Internet] 2017; 7:9399. Available from: http://dx.doi.org/10.1038/s41598-017-09978-5

191. Martin LJ, Gupta J, Jyothula SSSK, Butsch Kovacic M, Biagini Myers JM, Patterson TL, Ericksen MB, He H, Gibson AM, Baye TM, et al. Functional Variant in the Autophagy-Related 5 Gene Promotor is Associated with Childhood Asthma. PLoS One [Internet] 2012; 7:e33454. Available from: https://dx.plos.org/10.1371/journal.pone.0033454

192. Zeki AA, Yeganeh B, Kenyon NJ, Post M, Ghavami S. Autophagy in airway diseases: a new frontier in human asthma? Allergy [Internet] 2016; 71:5–14. Available from: http://doi.wiley.com/10.1111/all.12761

193. Pham D Le, Kim S-H, Losol P, Yang E-M, Shin YS, Ye Y-M, Park H-S. Association of autophagy related gene polymorphisms with neutrophilic airway inflammation in adult asthma. Korean J Intern Med [Internet] 2016; 31:375–85. Available from: http://kjim.org/journal/view.php?doi=10.3904/kjim.2014.390

194. You Y, Huo J, Huang J, Wang M, Shao Y, Ge M, Li X, Huang Z, Zhang J, Nie N, et al. Contribution of autophagy-related gene 5 variants to acquired aplastic anemia in Han-Chinese population. J Cell Biochem [Internet] 2019; 120:11409–17. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcb.28418

195. Li N, Fan X, Wang X, Deng H, Zhang K, Zhang X, Han Q, Lv Y, Liu Z. Autophagy-Related 5 Gene rs510432 Polymorphism Is Associated with Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection. Immunol Invest 2019; 48:378–91.

196. Yuan J, Zhang N, Yin L, Zhu H, Zhang L, Zhou L, Yang M. Clinical Implications of the Autophagy Core Gene Variations in Advanced Lung Adenocarcinoma Treated with Gefitinib. Sci Rep [Internet] 2017; 7:17814. Available from: http://dx.doi.org/10.1038/s41598-017-18165-5

197. Yuan J, Han R, Esther A, Wu Q, Yang J, Yan W, Ji X, Liu Y, Li Y, Yao W, et al. Polymorphisms in autophagy related genes and the coal workers' pneumoconiosis in a Chinese population. Gene [Internet] 2017; 632:36–42. Available from: http://dx.doi.org/10.1016/j.gene.2017.08.017

198. White KAM, Luo L, Thompson TA, Torres S, Hu C-AA, Thomas NE, Lilyquist J, Anton-Culver H, Gruber SB, From L, et al. Variants in autophagy-related genes and clinical characteristics in melanoma: a population-based study. Cancer Med [Internet] 2016; 5:3336–45. Available from: http://doi.wiley.com/10.1002/cam4.929

199. Nikseresht M, Shahverdi M, Dehghani M, Abidi H, Mahmoudi R, Ghalamfarsa G, Manzouri L, Ghavami S. Association of single nucleotide autophagy-related protein 5 gene polymorphism rs2245214 with susceptibility to non–small cell lung cancer. J Cell Biochem [Internet] 2019; 120:1924–31. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jcb.27467

200. Usategui-Martín R, García-Aparicio J, Corral-Gudino L, Calero-Paniagua I, Del Pino-Montes J, González Sarmiento R. Polymorphisms in Autophagy Genes Are Associated with Paget Disease of Bone. PLoS One [Internet] 2015; 10:e0128984. Available from: http://dx.plos.org/10.1371/journal.pone.0128984

201. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, Ortmann W, Kosoy R, Ferreira RC, Nordmark G, et al. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet [Internet] 2009; 41:1228–33. Available from: http://www.nature.com/articles/ng.468

202. Ciccacci C, Perricone C, Alessandri C, Latini A, Politi C, Delunardo F, Pierdominici M, Conti F, Novelli G, Ortona E, et al. Evaluation of ATG5 polymorphisms in Italian patients with systemic lupus erythematosus: contribution to disease susceptibility and clinical phenotypes. Lupus [Internet] 2018; 27:1464–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29759048

203. Mayes MD, Bossini-Castillo L, Gorlova O, Martin JE, Zhou X, Chen W V., Assassi S, Ying J, Tan FK, Arnett FC, et al. Immunochip Analysis Identifies Multiple Susceptibility Loci for Systemic Sclerosis. Am J Hum Genet [Internet] 2014; 94:47–61. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002929713005715

204. Plantinga TS, van de Vosse E, Huijbers A, Netea MG, Joosten LAB, Smit JWA, Netea-Maier RT. Role of Genetic Variants of Autophagy Genes in Susceptibility for Non-Medullary Thyroid Cancer and Patients Outcome. PLoS One [Internet] 2014; 9:e94086. Available from: http://dx.plos.org/10.1371/journal.pone.0094086

205. Zheng M, Yu H, Zhang L, Li H, Liu Y, Kijlstra A, Yang P. Association of ATG5 Gene Polymorphisms With Behçet's Disease and ATG10 Gene Polymorphisms With VKH Syndrome in a Chinese Han Population. Investig Opthalmology Vis Sci [Internet] 2015; 56:8280. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.15-18035

206. Alonso-Perez E, Suarez-Gestal M, Calaza M, Blanco FJ, Suarez A, Santos M, Papasteriades C, Carreira P, Pullmann R, Ordi-Ros J, et al. Lack of replication of higher genetic risk load in men than in women with systemic lupus erythematosus. Arthritis Res Ther [Internet] 2014; 16:R128. Available from: http://arthritis-research.biomedcentral.com/articles/10.1186/ar4585

207. López P, Alonso-Pérez E, Rodríguez-Carrio J, Suárez A. Influence of Atg5 Mutation in SLE Depends on Functional IL-10 Genotype. PLoS One [Internet] 2013; 8:e78756. Available from: https://dx.plos.org/10.1371/journal.pone.0078756

208. Li N, Fan X, Wang X, Zhang X, Zhang K, Han Q, Lv Y, Liu Z. Genetic association of polymorphisms at the intergenic region between PRDM1 and ATG5 with hepatitis B virus infection in Han Chinese patients. J Med Virol [Internet] 2019; :jmv.25629. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.25629

209. Cai P-P, Wang H-X, Zhuang J-C, Liu Q-B, Zhao G-X, Li Z-X, Wu Z-Y. Variants of autophagy-related gene 5 are associated with neuromyelitis optica in the Southern Han Chinese population. Autoimmunity [Internet] 2014; 47:563–6. Available from: https://www.tandfonline.com/doi/full/10.3109/08916934.2014.929668

210. Dang J, Li J, Xin Q, Shan S, Bian X, Yuan Q, Liu N, Ma X, Li Y, Liu Q. Gene-gene interaction of ATG5, ATG7, BLK and BANK1 in systemic lupus erythematosus. Int J Rheum Dis [Internet] 2016; 19:1284–93. Available from: http://doi.wiley.com/10.1111/1756-185X.12768

211. Martin J-E, Assassi S, Diaz-Gallo L-M, Broen JC, Simeon CP, Castellvi I, Vicente-Rabaneda E, Fonollosa V, Ortego-Centeno N, González-Gay MA, et al. A systemic sclerosis and systemic lupus erythematosus pan-meta-GWAS reveals new shared susceptibility loci. Hum Mol Genet [Internet] 2013; 22:4021–9. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddt248

212. Mitchell JS, Li N, Weinhold N, Försti A, Ali M, van Duin M, Thorleifsson G, Johnson DC, Chen B, Halvarsson B-M, et al. Genome-wide association study identifies multiple susceptibility loci for multiple myeloma. Nat Commun [Internet] 2016; 7:12050. Available from: http://www.nature.com/articles/ncomms12050

213. Terao C, Raychaudhuri S, Gregersen PK. Recent Advances in Defining the Genetic Basis of Rheumatoid Arthritis. Annu Rev Genomics Hum Genet [Internet] 2016; 17:273–301. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27216775

214. Shen M, Lin L. Functional variants of autophagy-related genes are associated with the

development of hepatocellular carcinoma. Life Sci [Internet] 2019; 235:116675. Available from: https://doi.org/10.1016/j.lfs.2019.116675

215. Zhou J, Hang D, Jiang Y, Chen J, Han J, Zhou W, Jin G, Ma H, Dai J. Evaluation of genetic variants in autophagy pathway genes as prognostic biomarkers for breast cancer. Gene [Internet] 2017; 627:549–55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378111917305036

216. Zhao X, Chen Y, Wang L, Li X, Chen X, Zhang H. Associations of ATG7 rs1375206 polymorphism and elevated plasma ATG7 levels with late-onset sporadic Parkinson's disease in a cohort of Han Chinese from southern China. Int J Neurosci [Internet] 2020; 0:1–9. Available from: https://doi.org/10.1080/00207454.2020.1731507

217. Xia L, Xu J, Song J, Xu Y, Zhang B, Gao C, Zhu D, Zhou C, Bi D, Wang Y, et al. Autophagy-Related Gene 7 Polymorphisms and Cerebral Palsy in Chinese Infants. Front Cell Neurosci [Internet] 2019; 13:1–10. Available from: https://www.frontiersin.org/article/10.3389/fncel.2019.00494/full

218. Zhang P, Zhang J, Zhang Y, Wang S, Pang S, Yan B. Functional variants of the ATG7 gene promoter in acute myocardial infarction. Mol Genet Genomic Med [Internet] 2018; 6:1209–19. Available from: http://doi.wiley.com/10.1002/mgg3.508

219. Metzger S, Saukko M, Van Che H, Tong L, Puder Y, Riess O, Nguyen HP. Age at onset in Huntington's disease is modified by the autophagy pathway: implication of the V471A polymorphism in Atg7. Hum Genet [Internet] 2010; 128:453–9. Available from: http://link.springer.com/10.1007/s00439-010-0873-9

220. Qin Z, Xue J, He Y, Ma H, Jin G, Chen J, Hu Z, Liu X, Shen H. Potentially functional polymorphisms in ATG10 are associated with risk of breast cancer in a Chinese population. Gene [Internet] 2013; 527:491–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378111913008354

221. Xie K, Liang C, Li Q, Yan C, Wang C, Gu Y, Zhu M, Du F, Wang H, Dai J, et al. Role of ATG 10 expression quantitative trait loci in non-small cell lung cancer survival. Int J Cancer [Internet] 2016; 139:1564–73. Available from: http://doi.wiley.com/10.1002/ijc.30205

222. Yang Z, Liu Z. Potentially functional variants of autophagy-related genes are associated with the efficacy and toxicity of radiotherapy in patients with nasopharyngeal carcinoma. Mol Genet Genomic Med [Internet] 2019; 7:1–8. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/mgg3.1030

223. Songane M, Kleinnijenhuis J, Alisjahbana B, Sahiratmadja E, Parwati I, Oosting M, Plantinga TS, Joosten LAB, Netea MG, Ottenhoff THM, et al. Polymorphisms in Autophagy Genes and Susceptibility to Tuberculosis. PLoS One [Internet] 2012; 7:e41618. Available from: http://dx.plos.org/10.1371/journal.pone.0041618

224. Li Q, Zhou X, Huang T, Tang Y, Liu B, Peng P, Sun L, Wang Y, Yuan X. The Thr300Ala variant of ATG16L1 is associated with decreased risk of brain metastasis in patients with non-small cell lung cancer. Autophagy [Internet] 2017; 13:1053–63. Available from: https://www.tandfonline.com/doi/full/10.1080/15548627.2017.1308997

225. Bae H, Lunetta KL, Murabito JM, Andersen SL, Schupf N, Perls T, Sebastiani P. Genetic associations with age of menopause in familial longevity. Menopause [Internet] 2019;

26:1204–12. Available from: http://insights.ovid.com/crossref?an=00042192-201910000-00019

226. Briones N, Dinu V. Data mining of high density genomic variant data for prediction of Alzheimer's disease risk. BMC Med Genet [Internet] 2012; 13:7. Available from: http://www.biomedcentral.com/1471-2350/13/7

227. Howell MD, Gao P, Kim BE, Lesley LJ, Streib JE, Taylor PA, Zaccaro DJ, Boguniewicz M, Beck LA, Hanifin JM, et al. The signal transducer and activator of transcription 6 gene (STAT6) increases the propensity of patients with atopic dermatitis toward disseminated viral skin infections. J Allergy Clin Immunol [Internet] 2011; 128:1006–14. Available from: https://linkinghub.elsevier.com/retrieve/pii/S009167491100916X

228. Dorling L, Kar S, Michailidou K, Hiller L, Vallier A-L, Ingle S, Hardy R, Bowden SJ, Dunn JA, Twelves C, et al. The Relationship between Common Genetic Markers of Breast Cancer Risk and Chemotherapy-Induced Toxicity: A Case-Control Study. PLoS One [Internet] 2016; 11:e0158984. Available from: https://dx.plos.org/10.1371/journal.pone.0158984

229. Guo X, Lin W, Bao J, Cai Q, Pan X, Bai M, Yuan Y, Shi J, Sun Y, Han M-R, et al. A Comprehensive cis-eQTL Analysis Revealed Target Genes in Breast Cancer Susceptibility Loci Identified in Genome-wide Association Studies. Am J Hum Genet [Internet] 2018; 102:890–903. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0002929718301058

230. Song X, Yuan Z, Yuan H, Wang L, Ji P, Jin G, Dai J, Ma H. ATG12 expression quantitative trait loci associated with head and neck squamous cell carcinoma risk in a Chinese Han population. Mol Carcinog [Internet] 2018; 57:1030–7. Available from: http://doi.wiley.com/10.1002/mc.22823

231. Wen J, Liu H, Wang L, Wang X, Gu N, Liu Z, Xu T, Gomez DR, Komaki R, Liao Z, et al. Potentially Functional Variants of ATG16L2 Predict Radiation Pneumonitis and Outcomes in Patients with Non–Small Cell Lung Cancer after Definitive Radiotherapy. J Thorac Oncol [Internet] 2018; 13:660–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1556086418301035

232. Kang J, Kugathasan S, Georges M, Zhao H, Cho JH. Improved risk prediction for Crohn's disease with a multi-locus approach. Hum Mol Genet [Internet] 2011; 20:2435–42. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddr116

233. Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet [Internet] 2007; 39:596–604. Available from: http://www.nature.com/articles/ng2032

234. Li X, Chen M, Zhang X, Wang M, Yang X, Xia Q, Han R, Liu R, Xu S, Xu J, et al. Single nucleotide polymorphisms of autophagy-related 16-like 1 gene are associated with ankylosing spondylitis in females: a case-control study. Int J Rheum Dis [Internet] 2018; 21:322–9. Available from: http://doi.wiley.com/10.1111/1756-185X.13183

235. Kee BP, Ng JG, Ng CC, Hilmi I, Goh KL, Chua KH. Genetic polymorphisms of ATG16L1 and IRGM genes in Malaysian patients with Crohn's disease. J Dig Dis 2020; 21:29–37.

236. Huang C-Y, Huang S-P, Lin VC, Yu C-C, Chang T-Y, Lu T-L, Chiang H-C, Bao B-Y. Genetic variants of the autophagy pathway as prognostic indicators for prostate cancer. Sci Rep [Internet] 2015; 5:14045. Available from: http://dx.doi.org/10.1038/srep14045

237. Orsatti CL, Sobreira ML, Sandrim VC, Nahas-Neto J, Orsatti FL, Nahas EAP. Autophagy-related 16-like 1gene polymorphism, risk factors for cardiovascular disease and associated carotid intima-media thickness in postmenopausal women. Clin Biochem [Internet] 2018; 61:12–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0009912017310640

238. Al-Ali R, Fernández-Mateos J, González-Sarmiento R. Association of autophagy gene polymorphisms with lung cancer. Gene Reports [Internet] 2017; 7:74–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2452014417300109

239. Grimm WA, Messer JS, Murphy SF, Nero T, Lodolce JP, Weber CR, Logsdon MF, Bartulis S, Sylvester BE, Springer A, et al. The Thr300Ala variant in ATG16L1 is associated with improved survival in human colorectal cancer and enhanced production of type I interferon. Gut 2016; 65:456–64.

240. Nicoli ER, Dumitrescu T, Uscatu CD, Popescu FD, Streaţă I, Serban Şoşoi S, Ivanov P, Dumitrescu A, Bărbălan A, Lungulescu D, et al. Determination of autophagy gene ATG16L1 polymorphism in human colorectal cancer. Rom J Morphol Embryol [Internet] 2014; 55:57–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24715166

241. Tsianos VE, Kostoulas C, Gazouli M, Frillingos S, Georgiou I, Christodoulou DK, Katsanos KH, Tsianos E V. ATG16L1 T300A polymorphism is associated with Crohn's disease in a Northwest Greek cohort, but ECM1 T130M and G290s polymorphisms are not associated with ulcerative colitis. Ann Gastroenterol 2020; 33:38–44.

242. Burada F, Ciurea ME, Nicoli R, Streata I, Vilcea ID, Rogoveanu I, Ioana M. ATG16L1 T300A Polymorphism is Correlated with Gastric Cancer Susceptibility. Pathol Oncol Res [Internet] 2016; 22:317–22. Available from: http://link.springer.com/10.1007/s12253-015-0006-9

243. Reuken PA, Lutz P, Casper M, Al-Herwi E, Stengel S, Spengler U, Stallmach A, Lammert F, Nischalke HD, Bruns T. The ATG16L1 gene variant rs2241880 (p.T300A) is associated with susceptibility to HCC in patients with cirrhosis. Liver Int 2019; :2360–7.

244. Wisetsathorn S, Tantithavorn V, Hirankarn N, Tangkijvanich P, Saethang T, Kimkong I. Gene polymorphisms of autophagy machinery and the risk of hepatitis B virus-related hepatocellular carcinoma in a Thai population. ScienceAsia [Internet] 2017; 43:362. Available from: http://www.scienceasia.org/content/viewabstract.php?ms=8751

245. Liassides C, Papadopoulos A, Siristatidis C, Damoraki G, Liassidou A, Chrelias C, Kassanos D, Giamarellos-Bourboulis EJ. Single nucleotide polymorphisms of Toll-like receptor-4 and of autophagy-related gene 16 like-1 gene for predisposition of premature delivery. Medicine (Baltimore) [Internet] 2019; 98:e17313. Available from: http://journals.lww.com/10.1097/MD.0000000000017313

246. Huijbers A, Plantinga TS, Joosten LAB, Aben KKH, Gudmundsson J, den Heijer M, Kiemeney LALM, Netea MG, Hermus ARMM, Netea-Maier RT. The effect of the ATG16L1 Thr300Ala polymorphism on susceptibility and outcome of patients with epithelial cell-derived thyroid carcinoma. Endocr Relat Cancer [Internet] 2012; 19:L15–8. Available from: https://erc.bioscientifica.com/view/journals/erc/19/3/L15.xml

247. Wang C, Bauckman KA, Ross ASB, Symington JW, Ligon MM, Scholtes G, Kumar A, Chang H-W, Twentyman J, Fashemi BE, et al. A non-canonical autophagy-dependent role of the ATG16L1 T300A variant in urothelial vesicular trafficking and uropathogenic Escherichia coli persistence. Autophagy [Internet] 2019; 15:527–42. Available from: https://doi.org/10.1080/15548627.2018.1535290

248. Douroudis K, Kingo K, Traks T, Rätsep R, Silm H, Vasar E, Kõks S. ATG16L1 gene polymorphisms are associated with palmoplantar pustulosis. Hum Immunol 2011; 72:613–5.

249. Ramos PS, Williams AH, Ziegler JT, Comeau ME, Guy RT, Lessard CJ, Li H, Edberg JC, Zidovetzki R, Criswell LA, et al. Genetic analyses of interferon pathway-related genes reveal multiple new loci associated with systemic lupus erythematosus. Arthritis Rheum [Internet] 2011; 63:2049–57. Available from: http://doi.wiley.com/10.1002/art.30356

250. Yang SK, Hong M, Zhao W, Jung Y, Baek J, Tayebi N, Kim KM, Ye BD, Kim KJ, Park SH, et al. Genome-wide association study of Crohn's disease in Koreans revealed three new susceptibility loci and common attributes of genetic susceptibility across ethnic populations. Gut 2014; 63:80–7.

251. Oh SH, Baek J, Kim KM, Lee E-J, Jung Y, Lee YJ, Jin H-S, Ye BD, Yang S-K, Lee J-K, et al. Is Whole Exome Sequencing Clinically Practical in the Management of Pediatric Crohn's Disease? Gut Liver [Internet] 2015; 9:767. Available from: http://www.gutnliver.org/journal/view.html?doi=10.5009/gnl15176

252. Ma T, Wu S, Yan W, Xie R, Zhou C. A functional variant of ATG16L2 is associated with Crohn's disease in the Chinese population. Color Dis [Internet] 2016; 18:O420–6. Available from: http://doi.wiley.com/10.1111/codi.13507

253. Sun C, Molineros JE, Looger LL, Zhou X, Kim K, Okada Y, Ma J, Qi Y, Kim-Howard X, Motghare P, et al. High-density genotyping of immune-related loci identifies new SLE risk variants in individuals with Asian ancestry. Nat Genet [Internet] 2016; 48:323–30. Available from: http://www.nature.com/articles/ng.3496

254. Molineros JE, Yang W, Zhou X, Sun C, Okada Y, Zhang H, Chua KH, Lau Y-L, Kochi Y, Suzuki A, et al. Confirmation of five novel susceptibility loci for Systemic Lupus Erythematosus (SLE) and integrated network analysis of 82 SLE susceptibility loci. Hum Mol Genet [Internet] 2017; 26:ddx026. Available from: https://academic.oup.com/hmg/article-lookup/doi/10.1093/hmg/ddx026

255. Lessard CJ, Sajuthi S, Zhao J, Kim K, Ice JA, Li H, Ainsworth H, Rasmussen A, Kelly JA, Marion M, et al. Identification of a systemic lupus erythematosus risk locus spanning ATG16L2, FCHSD2, and P2RY2 in Koreans. Arthritis Rheumatol [Internet] 2015; 68:n/a-n/a. Available from: http://doi.wiley.com/10.1002/art.39548

256. Xu Q, Wu Y, Li Y, He C, Sun L, Liu J, Yuan Y. SNP-SNP interactions of three new pri-miRNAs with the target gene PGC and multidimensional analysis of H. pylori in the gastric cancer/atrophic gastritis risk in a Chinese population. Oncotarget [Internet] 2016; 7:23700–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26988755

257. Parkinson N, Ince PG, Smith MO, Highley R, Skibinski G, Andersen PM, Morrison KE, Pall HS, Hardiman O, Collinge J, et al. ALS phenotypes with mutations in CHMP2B (charged multivesicular body protein 2B). Neurology [Internet] 2006; 67:1074–7. Available from: http://www.neurology.org/cgi/doi/10.1212/01.wnl.0000231510.89311.8b

258. Skibinski G, Parkinson NJ, Brown JM, Chakrabarti L, Lloyd SL, Hummerich H, Nielsen JE, Hodges JR, Spillantini MG, Thusgaard T, et al. Mutations in the endosomal ESCRTIII-complex subunit CHMP2B in frontotemporal dementia. Nat Genet [Internet] 2005; 37:806–8. Available from: http://www.nature.com/articles/ng1609

259. Pankratz N, Wilk JB, Latourelle JC, DeStefano AL, Halter C, Pugh EW, Doheny KF, Gusella JF, Nichols WC, Foroud T, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. Hum Genet [Internet] 2009; 124:593–605. Available from: http://link.springer.com/10.1007/s00439-008-0582-9

260. Xu J, Wang L, Liu X, Dai Q. A novel LAMP2 p.G93R mutation associated with mild Danon disease presenting with familial hypertrophic cardiomyopathy. Mol Genet Genomic Med [Internet] 2019; 7:1–9. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/mgg3.941

261. Zhang X-D, Qi L, Wu J-C, Qin Z-H. DRAM1 regulates autophagy flux through lysosomes. PLoS One [Internet] 2013; 8:e63245. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23696801

262. Galavotti S, Bartesaghi S, Faccenda D, Shaked-Rabi M, Sanzone S, McEvoy A, Dinsdale D, Condorelli F, Brandner S, Campanella M, et al. The autophagy-associated factors DRAM1 and p62 regulate cell migration and invasion in glioblastoma stem cells. Oncogene [Internet] 2013; 32:699–712. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22525272

263. Merino J, Dashti HS, Li SX, Sarnowski C, Justice AE, Graff M, Papoutsakis C, Smith CE, Dedoussis G V., Lemaitre RN, et al. Genome-wide meta-analysis of macronutrient intake of 91,114 European ancestry participants from the cohorts for heart and aging research in genomic epidemiology consortium. Mol Psychiatry [Internet] 2019; 24:1920–32. Available from: http://www.nature.com/articles/s41380-018-0079-4

264. Cuyvers E, van der Zee J, Bettens K, Engelborghs S, Vandenbulcke M, Robberecht C, Dillen L, Merlin C, Geerts N, Graff C, et al. Genetic variability in SQSTM1 and risk of early-onset Alzheimer dementia: a European early-onset dementia consortium study. Neurobiol Aging [Internet] 2015; 36:2005.e15-2005.e22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0197458015001141

265. Morgan S, Shatunov A, Sproviero W, Jones AR, Shoai M, Hughes D, Al Khleifat A, Malaspina A, Morrison KE, Shaw PJ, et al. A comprehensive analysis of rare genetic variation in amyotrophic lateral sclerosis in the UK. Brain 2017; 140:1611–8.

266. Bolland MJ, Tong PC, Naot D, Callon KE, Wattie DJ, Gamble GD, Cundy T. Delayed development of Paget's disease in offspring inheriting SQSTM1 mutations. J Bone Miner Res [Internet] 2007; 22:411–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17181397

267. Collet C, Michou L, Audran M, Chasseigneaux S, Hilliquin P, Bardin T, Lemaire I, Cornélis F, Launay J-M, Orcel P, et al. Paget's disease of bone in the French population: novel SQSTM1 mutations, functional analysis, and genotype-phenotype correlations. J Bone Miner Res [Internet] 2007; 22:310–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17129171

268. Sanchez A, Schoenfeld JD, Nguyen PL, Fiorentino M, Chowdhury D, Stampfer MJ, Sesso HD, Giovannucci E, Mucci LA, Shui IM. Common variation in BRCA1 may have a role in progression to lethal prostate cancer after radiation treatment. Prostate Cancer Prostatic Dis [Internet] 2016; 19:197–201. Available from: http://www.nature.com/articles/pcan20164

269. Pelletier C, Speed WC, Paranjape T, Keane K, Blitzblau R, Hollestelle A, Safavi K, van den Ouweland A, Zelterman D, Slack FJ, et al. Rare BRCA1 haplotypes including 3'UTR SNPs associated with breast cancer risk. Cell Cycle [Internet] 2011; 10:90–9. Available from: http://www.tandfonline.com/doi/abs/10.4161/cc.10.1.14359

270. Qu H-Q, Jacob K, Fatet S, Ge B, Barnett D, Delattre O, Faury D, Montpetit A, Solomon L, Hauser P, et al. Genome-wide profiling using single-nucleotide polymorphism arrays identifies novel chromosomal imbalances in pediatric glioblastomas. Neuro Oncol [Internet] 2010; 12:153–63. Available from: https://academic.oup.com/neuro-oncology/article-lookup/doi/10.1093/neuonc/nop001

271. Lutz P, Krämer B, Kaczmarek DJ, Hübner MP, Langhans B, Appenrodt B, Lammert F, Nattermann J, Hoerauf A, Strassburg CP, et al. A variant in the nuclear dot protein 52kDa gene increases the risk for spontaneous bacterial peritonitis in patients with alcoholic liver cirrhosis. Dig Liver Dis [Internet] 2016; 48:62–8. Available from: http://dx.doi.org/10.1016/j.dld.2015.09.011

272. Ellinghaus D, Zhang H, Zeissig S, Lipinski S, Till A, Jiang T, Stade B, Bromberg Y, Ellinghaus E, Keller A, et al. Association Between Variants of PRDM1 and NDP52 and Crohn's Disease, Based on Exome Sequencing and Functional Studies. Gastroenterology [Internet] 2013; 145:339–47. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0016508513006203

273. Li QS, Parrado AR, Samtani MN, Narayan VA. Variations in the FRA10AC1 Fragile Site and 15q21 Are Associated with Cerebrospinal Fluid Aβ1-42 Level. PLoS One [Internet] 2015; 10:e0134000. Available from: https://dx.plos.org/10.1371/journal.pone.0134000

274. Le Duc D, Giulivi C, Hiatt SM, Napoli E, Panoutsopoulos A, Harlan De Crescenzo A, Kotzaeridou U, Syrbe S, Anagnostou E, Azage M, et al. Pathogenic WDFY3 variants cause neurodevelopmental disorders and opposing effects on brain size. Brain 2019; 142:2617–30.

275. Wolf C, Gramer E, Müller-Myhsok B, Pasutto F, Reinthal E, Wissinger B, Weisschuh N. Evaluation of nine candidate genes in patients with normal tension glaucoma: a case

control study. BMC Med Genet [Internet] 2009; 10:91. Available from: http://bmcmedgenet.biomedcentral.com/articles/10.1186/1471-2350-10-91

276. Park J, Kim M, Park CK, Chae H, Lee S, Kim Y, Jang W, Chi HY, Park H-YL, Park SH. Molecular analysis of myocilin and optineurin genes in Korean primary glaucoma patients. Mol Med Rep [Internet] 2016; 14:2439–48. Available from: https://www.spandidos-publications.com/10.3892/mmr.2016.5557

277. Saleem S, Azam A, Maqsood SI, Muslim I, Bashir S, Fazal N, Riaz M, Ali SHB, Niazi MK, Ishaq M, et al. Role of ACE and PAI-1 Polymorphisms in the Development and Progression of Diabetic Retinopathy. PLoS One [Internet] 2015; 10:e0144557. Available from: https://dx.plos.org/10.1371/journal.pone.0144557

278. Carbone MA, Chen Y, Hughes GA, Weinreb RN, Zabriskie NA, Zhang K, Anholt RRH. Genes of the Unfolded Protein Response Pathway Harbor Risk Alleles for Primary Open Angle Glaucoma. PLoS One [Internet] 2011; 6:e20649. Available from: https://dx.plos.org/10.1371/journal.pone.0020649

279. Albagha OME, Visconti MR, Alonso N, Langston AL, Cundy T, Dargie R, Dunlop MG, Fraser WD, Hooper MJ, Isaia G, et al. Genome-wide association study identifies variants at CSF1, OPTN and TNFRSF11A as genetic risk factors for Paget's disease of bone. Nat Genet [Internet] 2010; 42:520–4. Available from: http://www.nature.com/articles/ng.562