Potential genetic biomarkers of suicide risk in the mexican population: A systematic literature review.

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Abstract

Suicide is defined as the action of harming oneself with the intention of dying. It is estimated that worldwide one suicide occurs every 40 seconds, making it a major health problem. Studies in families have suggested that suicide has a genetic component, around the world studies have been carried out in search of genetic variants associated with suicidal behavior, these variants could be useful as potential biomarkers to identify people at risk of suicide. In this area in Mexico, some studies of variants in genes related to neurotransmission and other important pathways have been carried out and a possible association of variants located in genes has been suggested: SLC6A4, SAT-1, TPH-2, ANKK1, GSHR, SCARA50, RGS10, STK33, COMT, and FKBP5. This systematic review shows the genetic studies on the Mexican population. This article contributes by compiling the existing information on genetic variants and genes associated with suicidal behavior, said variants in the future could be used as potential biomarkers to identify people at risk of suicide.

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Keywords:

Biomarkers; Genetic; Suicidal behavior; Suicide; Mexican; Genomic.

1. Introduction

Suicide is defined as the act of killing oneself in a voluntary way by self-directed injurious behavior with the intent to die (Krug et al., 2002). According to the World Health Organization, approximately 2% of people commit suicide worldwide each year, worldwide, average annual figures show that more than 800,000 people commit suicide, which is equivalent to one death every 40 seconds (Pawlak et al., 2016).

In Mexico, from 1990 to 2018, the suicide mortality rate increased from 2.2 to 5.2 suicides per 100,000 inhabitants. Since 2000, the increase has been accentuated in the younger population. In 2020, a suicide rate of 6.2 per 100,000 inhabitants was reported, which denotes a constant increase in suicides nationwide (INEGI, 2018).

Suicide and suicidal behavior

Suicidal behavior (SB) is a complex phenomenon with a wide spectrum of severity. Studies in family cases have shown the "progression" of the stages of suicidal ideation (SI) and behavior. In addition, biological studies had indicated the overlapping of the suicide attempted (SA) and the suicide completed (SC) (Tulchinsky & Varavikova, 2014; Turecki & Brent, 2016). The most serious consequence of SB is the SC, which is a global character problem imperative to attend (Tulchinsky & Varavikova, 2014). The nomenclature of suicide behavior is further explained in table 1 (Turecki & Brent, 2016).

Table 1 Nomenclature suicidal behavior

Nomeclature suicidal behavior (SB)	Definition
Suicidal ideation (SI)	Passive SI: Thoughts of wanting to be dead with any plan or intention. Activate SI: Thoughts about self-injurious life-threatening measures can be the identification of

	a method, devising a plan or the intention to perform an act.
Suicide attempt (SA)	Self-injurious act with the intention of dying.
Suicide completed (SC)	Fatal act caused himself with the intention of dying.

SI: Suicidal ideation , SA: Suicide attempt , SC: Suicide completed

The genetic component of suicide

Family studies suggest the relationship of the genetic component with SB (Ruderfer et al., 2020). Previous studies have shown greater agreement in cases of SC and SA in monozygotic twins than in their dizygotic counterparts (Roy et al., 1991). More recent studies provide evidence on possible family heritability, supporting that suicidal behavior has a genetic component (Ballard et al., 2019; Campos et al., 2020). For this reason, molecular studies are focused on genes that encode a variety of proteins such as transporters, enzymes, and receptors, to know the influence they could have on SB (Bondy et al., 2006).

Studies focused on the search for biomarkers in the field of psychiatry could have the potential to provide useful information to determine the clinical diagnosis, prognosis, or response to treatment in psychiatric disorders (Andreazza et al., 2019). In the Mexican population, several studies have been carried out that look for an association between different genetic variants and SB, finding variants with potential application as biomarkers of suicide risk. The studies have focused mainly on genes involved in pathways such as serotonergic and dopaminergic neurotransmission.

2. Materials and methods

Literature search strategy

We conducted an electronic search for studies investigating the association between genetic variants and suicidal behavior in the Mexican population. The systematic search was

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carried out in the PubMed, Google scholar, Scopus, and web of science databases. The keywords used were: “polymorphism”, “variant”, “suicide”, “association”, “linkage” “suicidal behavior”, “gene”, “genetic”, “genomic” and “Mexican population”. English-language and peer-reviewed articles from January 2010 to March 2022 were included.

Study selection

For the identification and selection of the studies, the PRISMA statements were used according to the following inclusion criteria: 1) Studies that analyze the association between genetic variants and suicidal behavior, suicide attempt or completed suicide in adolescents or adults 2) Studies carried out in a Mexican population. Duplicates and studies that were not conducted in Mexican subjects were excluded. For the selection, a first filter was applied where the titles and abstracts were analyzed, studies that did not meet the criteria were excluded. Subsequently, the full text of the studies that passed the initial filter was exhaustively reviewed, selecting only the studies that met the established inclusion criteria. Case-control genotyping and genome-wide association studies were included. We grouped the studies into the following sections according to the pathways in which the analyzed genes are involved: Involved in serotonergic neurotransmission, dopaminergic neurotransmission, neurotransmitter metabolism and involved in other pathways. The flowchart of the selection strategy according to the PRISMA statements (Page et al., 2021) is shown in Figure 1. More details about each of the included studies are described in Table 2. The findings in the Mexican population are presented below.

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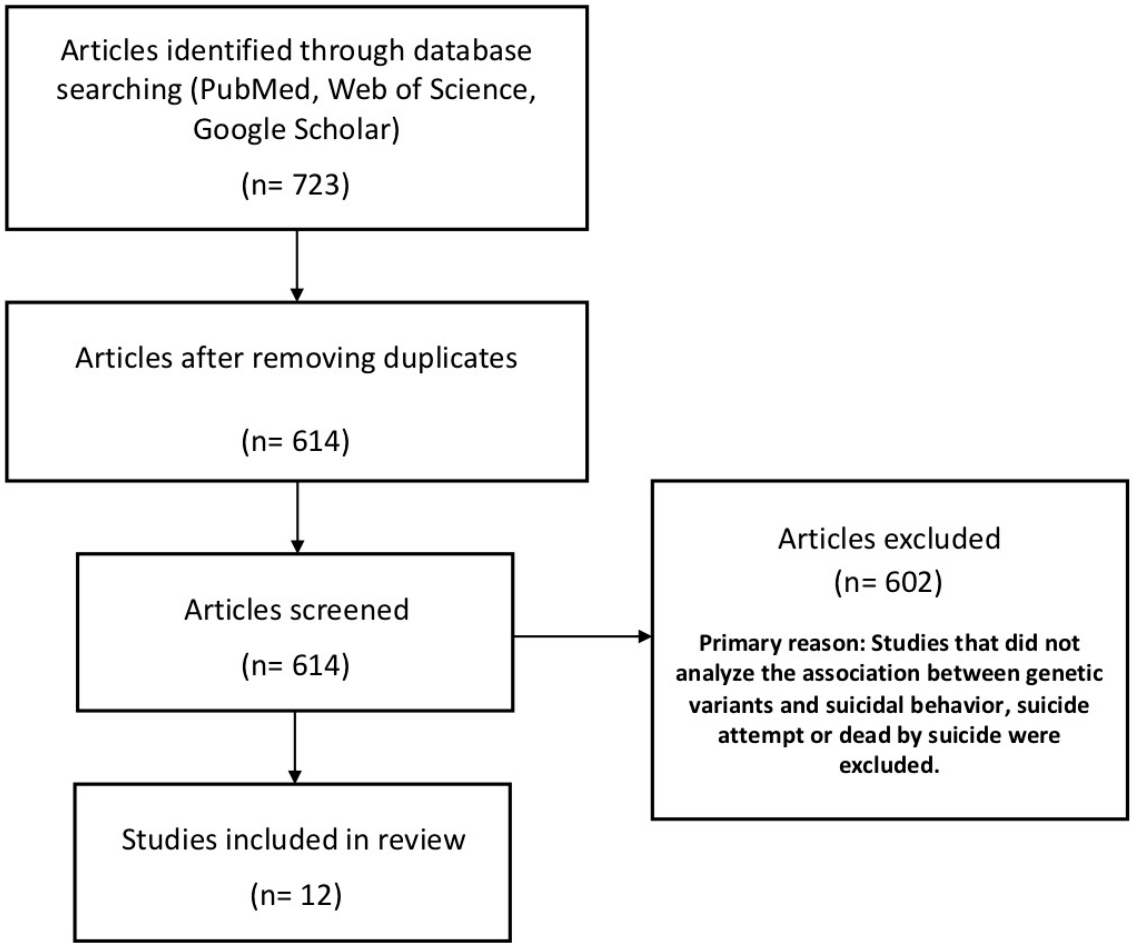

Fig 1. Flow chart of study identification and selection.

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Table 2 Studies that examined the association between genetic variants and suicidal behavior in the Mexican population.

Study	Samples	Method	Genes	Variants analyzed
Tovilla Zarate *et al.* 2011	105 SA 236 HC	qPCR	*COMT*	rs4680 (Val108/158Met)
Gonzalez Castro *et al*. 2013	152 SA 264 HC	PCR end point	*5HTR1A*	rs6295 rs1423691 rs878567
Sarmiento Hernandez *et al*. 2014	53 adolescents diagnosed with depression (14 SA and 39 WAS).	PCR	*SLC6A4*	5-HTTLPR
Tovilla Zarate *el al*. 2015	169 SA 218 HC	PCR end point	*SAT-1*	rs6526342 (A-1537C)
Lopez Narvaez *et al.* 2015	263 SA 200 HC	PCR end point	*TPH-1* *TPH-2*	*TPH-1*= rs21102 and rs1607395 *TPH-2*= rs4290270, rs7305115, and rs1007023

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Molina Guzman *et al.* 2017	183 SA 208 HC	qPCR	*HTR2C*	rs547536 rs2192372 rs4272555 rs6318 rs2428707
Genis Mendoza *et al.* 2017	166 SA 123 HC	PCR	*DRD2* *ANKK1*	*DRD2*= rs6275 *DRD2*= rs1799978 *ANKK1*= rs1800497
Sarmiento Hernandez *et al.* 2019	200 adolescents with depression and history of SB 235 HC	PCR	*SLC6A4*	5-HTTLPR
Sanabrais Jimenez *et al.* 2019	183 SA 183 patients WSA	qPCR	*CRHR1* *CRHR2*	*CRHR1*= rs110402, rs242924, and rs16940665 *CRHR2*= rs2190242, rs2284217. And rs2014663
Gonzalez Castro *et al.* 2019	37 SA 155 HC	Infinium PsychArray BeadChip	*Multiple genes*	580 000 genetic variants

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Hernandez Diaz et al. 2021	146 SA 277 HC	qPCR	*FKPB5*	rs4713916 rs4713902 rs1360780 rs9296158 rs3800373

GWAS: Genome-Wide Association study HC: Healthy control without a history of suicidal behavior SA: Suicide attempt, SB: Suicidal behavior, WSA: Without suicide attempt

3. Results

3.1 Potential genetic biomarkers of suicide risk in genes involved in serotonergic neurotransmission.

Serotonin 1A and 2C (HTR1A and HTR2C). These genes encode receptors that are found in various regions of the brain, participate in neurotransmission, bind mainly to serotonin, and regulate neuronal activity through the activation of the release of intracellular calcium deposits. (NCBI, 2022g, 2022h)

HTR1A gene. It is located in Chr5:63,957,874-63,962,507 (GRCh38/hg38), the receptor that encodes participates in the regulation of dopamine levels, it is involved in neuronal activity, mood, and behavior (Donaldson et al., 2016; NCBI, 2022g; Philippe et al., 2018; Serretti et al., 2009). In the Mexican population, the variants rs6295, rs1423691, and rs878567 were genotyped in subjects with SA vs. controls, however, no statistically significant differences were found in any of the variants analyzed (González-Castro et al., 2013).

HTR2C gene. It is located at ChrX:114,584,078-114,910,061(GRCh38/hg38), the encoded receptor participates in anxiety, thermoregulation, and regulation of cerebrospinal fluid volume. It has been described that the messenger RNA of this gene suffers post-transcriptional editions, which can determine the activity of the receptor, compromising the efficiency to interact with G proteins. In addition, variations in the promoter, coding, and

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non-coding regions have been linked to some mental illnesses (Hill et al., 2020; Levchenko et al., 2020; NCBI, 2022h; Serretti et al., 2009). In a study in the Mexican population, five variants (rs547536, rs2192372, rs4272555, rs6318, and rs2428707) were analyzed and it was found that in women, the C allele of the rs4272555 variant was associated with a decreased risk of SA, while the G allele of the rs2428707 variant was associated with an increased risk of SA (Molina-guzman et al., 2017). However, when performing a meta-analysis of both variants, no significant association was found with SA (C. A. Tovilla-Zárate et al., 2014).

Solute carrier family 6 member 4 (SLC6A4). This gene is located at Chr17:30,194,319-30,236,002 (GRCh38/hg38), encodes a transporter that is widely distributed in the brain, and participates in the regulation of serotonergic signaling by reuptake of serotonin from synaptic clefts to presynaptic neurons. It has been described that a variant in the 44 bp insertion-deletion promoter region (5-HTTLPR) gives rise to long (L) and short (S) alleles with higher and lower transcriptional activity, respectively; an association with the behavior and depression, however so far the results have been contradictory. (Arpawong et al., 2016; Bokor et al., 2020; Hollerbach et al., 2021; NCBI, 2022k). In the Mexican population, the 5-HTTLPR variant was genotyped in adolescents, finding that the SS genotype was more frequent in subjects with a higher number of suicide attempts (Sarmiento Hernández et al., 2014). An association has also been found between the SS genotype and the S allele with a history of depression and SA (Sarmiento-Hernández et al., 2019). However, in a more recent study, this same working group did not find an association between the genotypic or allelic frequency of the 5-HTTLPR variant and SA (Marco Antonio Sanabrais-Jiménez et al., 2021).

3.2 Potential genetic biomarkers of suicide risk in genes involved in dopaminergic neurotransmission

Dopamine D2 receptor (DRD2). This gene is in Chr11:113,409,605-113,475,691 (GRCh38/hg38), encoding a G protein-coupled dopamine receptor that is involved in locomotion, reward circuitry, memory, and learning. In the field of psychiatry, some mutations have been associated with psychiatric disorders (He et al., 2019; Loewenstern et al., 2019; NCBI, 2022e). In a Mexican population, a study in which the rs6275 and

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rs1799978 variants were genotyped in adult subjects found no association with SB (Genis-Mendoza et al., 2017). Another genotyping study of the rs6275 variant conducted in adolescent subjects also found no association with SA (Marco Antonio Sanabrais-Jiménez et al., 2021). Therefore, so far this suggests that these variants are not associated with BS in the Mexican population.

Ankyrin repeat and kinase domain containing 1 (ANKK1). This gene is located in Chr11:113,386,014-113,400,416 (GRCh38/hg38) due to its genomic location it is closely related to the DRD2 gene, ANKK1 encodes a protein kinase that participates in signal transduction, has been related to some psychiatric disorders (Myrga et al., 2016; NCBI, 2022a; Savitz et al., 2013). In a study in the Mexican population, the rs1800497 variant was genotyped and it was found that subjects with the T/T genotype had a higher risk of SB, therefore it is suggested that this variant is associated with SB in the Mexican population (Genis-Mendoza et al., 2017).

3.3 Potential genetic biomarkers of suicide risk in genes involved in neurotransmitter metabolism

Catechol-o-methyl-transferase gene (COMT). This gene is in Chr22:19,941,371-19,969,975 (GRCh38/hg38), encoding an enzyme that participates in the transfer of methyl groups from S-adenosylmethionine in the pathway of degradation of brain catecholaminergic neurotransmitters. It has been associated with illnesses such as schizophrenia and panic disorder (Atake et al., 2015; NCBI, 2022b; Nkam et al., 2017). In the Mexican population, the rs4680 variant in COMT was genotyped in a study of adult subjects, however, no association was found in the allelic distribution or genotypic with the SA (C. Tovilla-Zárate et al., 2011). In another study of rs4680 variant in adolescent subjects, differences were found in the genotypic frequency between cases with SA and controls, in turn, a higher frequency of Met158 allele in subjects with SA (Marco Antonio Sanabrais-Jiménez et al., 2021). The findings in the Mexican population suggest that the rs4680 variant could be associated with suicidal risk in adolescence.

Spermidine/spermine N1-acetyltransferase 1 (SAT-1). Located in ChrX:23,783,173-23,786,210 (GRCh38/hg38), this gene encodes an enzyme with acetyltransferase activity

 doi:10.20944/preprints202301.0197.v1

involved in the metabolism of polyamines, participating in the transport and regulation of intracellular levels. Its association with psychiatric disorders has been reported. (Monson et al., 2016; NCBI, 2022j; Pantazatos et al., 2015). In a study in a Mexican population, the rs6526342 variant was genotyped, however, no association was found between allelic or genotypic distribution with SB. The analysis by gender revealed that in males a significant difference was found in allelic frequency between the cases and the control group. (Tovilla-Zarate, 2015).

Tryptophan hydroxylase 1 and 2 (TPH-1 and TPH-2). These genes are located at Chr11:18,017,555-18,046,269 and Chr12:71,938,845-72,186,618 respectively, both are paralogous and encode enzymes with hydroxylase activity that are involved in the serotonin synthesis pathway. Mutations in the TPH-1 gene have been associated with schizophrenia, anxiety, bipolar disorder, and suicidal behavior. On the other hand, mutations in the TPH-2 gene have been associated with bipolar disorder and major depression (Choi et al., 2010; Lai et al., 2005; NCBI, 2022l, 2022m; Wigner et al., 2018). In the Mexican population rs21102 and 1607395 TPH-1 gene variants, and rs4290270, rs7305115 of TPH-2 gene variants were genotyped and a significant difference was found between the distribution of the A/A genotype and the A allele of the rs7305115 variant in the group of SA cases. Also, haplotype analysis revealed an association between the GA haplotype of the *TPH-2* gene variants (rs4290270 and rs7305115) with a higher risk of SA. However, no differences were observed in the allelic or genotypic distributions of the rs21102, 1607395, and rs4290270 variants (López-Narváez et al., 2015).

Monoamine Oxidase A (MAOA). This gene encodes a mitochondrial enzyme responsible for oxidative deamination in the central nervous system and peripheral tissues, it participates in the metabolism of neuroactive amines (dopamine, norepinephrine, and serotonin) and vasoactive amines. It has been associated with affective, mood, and behavioral disorders. (Kolla et al., 2017; Kolla & Bortolato, 2020; NCBI, 2022i; Sampaio et al., 2015). This gene in the upstream regulatory region has a 30 base pair variable number tandem repeat region (uVNTR), the number of repeats in this region determines the transcriptional efficiency (Hollerbach et al., 2021). In our population, in a study of

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adolescent subjects, no association was found between SA and the genotypic or allelic frequencies of uVNTR (Marco Antonio Sanabrais-Jiménez et al., 2021).

3.4 Potential genetic biomarkers of suicide risk in genes involved in other pathways

Corticotropin-releasing hormone receptor 1 and Corticotropin-releasing hormone receptor 2 (CRHR1 and CRHR2). These genes are in Chr17:45,784,280-45,835,828 and chr7:30,649,406-30,700,129 (GRCh38/hg38) respectively, both are paralogous and encode G protein-coupled receptors that have affinity to corticotropin-releasing hormone and related peptides, therefore these participate in the regulation of the hypothalamic-pituitary-adrenal axis. These genes are of interest in the psychiatric field because they are involved in endocrine and behavioral responses to stress, which have been implicated in psychiatric disorders. (Ching-López et al., 2015; NCBI, 2022c, 2022d; Smoller, 2016; Xiao et al., 2011). In the Mexican population, three variants in the *CRHR1* gene (rs110402, rs242924, and rs16940665) and three in the *CRHR2* gene (rs2190242, rs2284217, and rs2014663) were analyzed, however, no association was observed between SA and allelic, genotypic or haplotypes distribution (M A Sanabrais-Jiménez et al., 2019).

FK506 binding protein 5 (FKBP5). This gene is in Chr6:35,573,585-35,728,583 (GRCh38/hg38), encodes a protein with cis-trans prolyl isomerase activity and belongs to the family of immunophilins involved in immunoregulation processes and has been associated with the stress response through the regulation of the glucocorticoid receptor sensitivity. This gene has been associated with major depressive disorder (Hernández-Díaz et al., 2021; Keijser et al., 2021; Li et al., 2019; NCBI, 2022f) In the Mexican population, five variants of the FKBP5 gene (rs4713916, rs4713902, rs1360780, rs9296158, and rs3800373) were analyzed, finding an association of the T allele of the rs1360780 variant and suicidal risk in both genders being higher in males. Interestingly, the C allele of the rs3800373 variant was associated as a protective allele in both genders, suggesting greater protection in females (Hernández-Díaz et al., 2021).

Genome-wide association study. On the other hand, a gene-level association study found 118 variants associated with SB, of which the following four are located in the genes:

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GSHR (rs565105), *SCARA50* (rs2685393), *RGS10* (rs561361616), and *STK33* (rs11041981) turned out to be the most significant (González-Castro et al., 2019).

4. Discussion

The genetic studies investigating the association between genetic variants and SB carried out to date in the Mexican population have focused mainly on genes involved in serotonergic neurotransmission, dopaminergic neurotransmission, neurotransmitter metabolism, and other pathways such as the hypothalamic-pituitary-adrenal axis. The variants that have shown association are in the genes *SLC6A4*, *SAT-1*, *TPH-2*, *ANNK1*, *GSHR*, *SCARA50*, *RGS10*, *STK33*, *COMT,* and *FKBP5*, it is suggested that these variants in the future could be used as biomarkers of suicidal risk (Table 3).

Table 3 Potential genetic biomarkers of suicide risk in the Mexican population.

Study	Genes /Variant	Findings
Sarmiento Hernandez et al. 2014	*SLC6A4* /5-HTTLPR	More often the SS genotype was found in subjects with greater number of suicide attempts and hopelessness.
Tovilla Zarate el al. 2015	*SAT-1*/ rs6526342	Possible association of the allele of rs6526342 with SB in men.
Lopez Narvaez *et al.* 2015	*TPH-2* / rs4290270 and rs7305115	Association between genotype A/A and the A allele of the rs7305115 variant with SA. Association between the GA haplotype of the *TPH-2* gene variants (rs4290270 and rs7305115) with a higher risk of SA.
Molina Guzman *et al.* 2017	*ANKK1*/rs1800497	Association of the T/T genotype of the rs1800497 variant with SB.

 doi:10.20944/preprints202301.0197.v1

Sarmiento Hernández *et al.* 2019	*SLC6A4*/5-HTTLPR	Association of the genotype SS and the allele S with the history of depression and SA in adolescents.
Gonzalez Castro *et al.* 2019	*GSHR*/ rs565105 *SCARA50*/ rs2685393 *RGS10*/rs561361616 *STK33*/rs11041981	Genes and variants associated with SB are reported. Of the 118 associated variants, 4 of them were the most significant.
Hernandez Diaz et al. 2021	*FKBP5*/ rs1360780 and rs3800373	Association of the C allele of the rs380037 variant with suicide protection. Association of the T allele of the rs1360780 variant with suicide risk

SB: Suicidal behavior

Regarding the 5-HTTLPR variant, contradictory results were found in the Mexican population, the association between the 5-HTTLPR SS genotype of the *SLC6A4* gene and a higher number of suicide attempts was found in Mexican adolescents, in addition, in a greater number of patients, an association of the SS genotype with SA and the S allele with a history of depression and SA was found, however, in a more recent study no association of genotypic or allelic frequency was found (Marco Antonio Sanabrais-Jiménez et al., 2021; Sarmiento-Hernández et al., 2019; Sarmiento Hernández et al., 2014). Compared to the results found in our population, two meta-analyses found an association of the S allele with SB (Clayden et al., 2012; Lin & Tsai, 2004) . Other studies did not find an association between the 5-HTTLPR variant and SB, but they did find an association with violent behavior (Zalsman et al., 2001, 2006).

The variants in the *SAT1*, *ANKK1*, and *TPH-2* genes also have already been associated with SB in other populations. Concerning to the rs6526342 variant in the *SAT1* gene, suicide risk has already been reported, in a cohort of French-Canadian individuals, they found a higher frequency of the C allele in the group of cases of males with SC (Fiori & Turecki, 2010).

 doi:10.20944/preprints202301.0197.v1

However, in another study in which they explored the association of the expression of the *SAT 1* gene and genetic variants with suicide risk, the association of the rs6526342 variant was not found (Guipponi et al., 2009). The T allele of the rs1800497 variant of the *ANKK1* gene has previously been associated with the risk of suicide in the Japanese and Caucasian populations; in the first case the allele individually while in the Caucasian population it was associated with a haplotype (Jasiewicz et al., 2014; Suda et al., 2009). The rs7305115 variant of the *TPH-2* gene has also been associated with suicidal behavior in the Chinese population, in which a higher frequency of the G allele was found in the group of cases with a history of suicidal behavior (Zhang et al., 2010).

The gene-level study evidenced the association of 4 most significant variants in *GSHR* (rs565105) *SCARA5* (rs2685393) *RGS10* (rs561361616) and *STK33* (rs11041981) genes. These variants had not previously been associated with SB; the authors argue that due to the biological functions in which these genes participate, a possible relationship with suicide could be explained. Concerning to the *GSHR* gene (Growth Hormone Secretagogue Receptor Type 1), it is a gene that encodes a member of the family of G-protein-coupled receptors, which participates in energy homeostasis and mood regulation (Huang et al., 2017; Martínez Damonte et al., 2018). The *SCARA5* gene (Scavenger Receptor Class A Member 5) is a member of the SR family and participates in microglia inflammatory response (Isgren et al., 2017; Tang et al., 2018). The *RGS10* gene (Regulator of G Protein Signaling 10) is a member of the G protein family of regulators, these regulators participate in signal transduction pathways by activating GTPase causing the inactivation of G protein subunits (Martínez Damonte et al., 2018). *STK33* gene (Serine/Threonine Kinase 33) the functions of this gene have not been fully elucidated, it is localized in various brain regions and it is suggested that it may have a structural implication in the brain, in the dynamics of the cytoskeleton, and neuronal regulation (Brauksiepe et al., 2014; Reuss et al., 2017). Despite not having been previously associated with SB, it is suggested that they could be related to psychiatric disorders or indirectly involved with SB, for example, one of the most outstanding functions of the *GSHR* is the ability to form heterodimers with serotonin receptors and dopamine receptors, of which genetic variants have already been associated with SB (Cabral et al., 2017). The *SCARA5* has been associated with psychiatric disorders (Rincón-Cortés et al., 2015; Xu et al., 2013). In turn, the Val38Met polymorphism in the

 doi:10.20944/preprints202301.0197.v1

RGS gene has been studied, however, no association with schizophrenia was found. Also, a postmortem study of *RGS10* proteins in the brains of subjects with depression, schizophrenia, and undiagnosed suicidality did not reveal a significant association (Hishimoto et al., 2004; Rivero et al., 2013). There are no previous reports of the *STK33* gene association but is suggested that the association could be due to the participation in the integration of the neuronal and humoral regulation of the endocrine system (González-Castro et al., 2019). In turn, various genome-wide association analyzes have been carried out in other populations, which have found an association between genes and variants, however, no similar results have been found between the studies (Perlis et al., 2010; Schosser et al., 2011).

An association between a higher frequency of Met158 allele of COMT rs4680 gene variant in adolescents was also reported in our population (Marco Antonio Sanabrais-Jiménez et al., 2021). The results are consistent with a meta-analysis that revealed that the rs4680 variant is associated with suicide risk in women (Sadeghiyeh et al., 2017). In this sense, another meta-analysis found an association between this variant and SB in the Asian population (González-Castro et al., 2018). A study also evaluated a set of genetic variants located in the COMT gene and found an association of the GATA haplotype with SB in the Caucasian population (rs737865, rs6269, rs4633, rs4680) (Bernegger et al., 2018). In addition, it has also been reported that patients with post-traumatic stress disorder in the Asian population with the Val/Val genotype have a greater susceptibility to suicidal ideation (Kwon et al., 2020). However, a study conducted on adults in a Mexican population did not find an association between the rs4680 variant and SA (C. Tovilla-Zárate et al., 2011). The findings in our population suggest that the rs4680 variant could confer suicide risk in adolescence.

Finally, the most recent study in the Mexican population found the association among rs1360780 and rs3800373 variants of the *FKBP5* gene, with SB. It has previously reported an association of the T/T (rs1360780) and G/G (rs3800373) genotypes with suicidal events in the European population (Brent et al., 2010). Also, the association of haplotypes of the *FKBP5* gene with suicide attempts has been reported in European and Japanese populations (Supriyanto et al., 2011; Szczepankiewicz et al., 2014). The C allele of the rs3800373

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variant and a haplotype of both variants have also been associated with completed suicide (Fudalej et al., 2015).

Study limitations: The main limitation mentioned in some articles is the small number of samples. Collaboration and design of studies involving several research teams belonging to public and private universities, as well as the link with national centers and institutes of investigation is suggested.

Future directions: With the advent of new technologies such as microarrays and SNG, we propose as future directions the large-scale search for genetic variants associated with SB in the Mexican population, to identify and validate new variants useful in the future for the implementation of genomic biomarkers for the early detection of suicide risk. Also, we recommend including population genetic markers, especially in mixed populations like the Mexican population.

5. Conclusion

In this systematic review, we describe an association between SB and genetic variants located in the SLC6A4, SAT-1, TPH-2, ANKK1, GSHR, SCARA50, RGS10, STK33, COMT, and FKBP5 genes in the Mexican population. The evidence suggests that localized genetic variants in these genes might influence susceptibility to suicide, therefore in the future, they could be useful as biomarkers of suicide risk in the Mexican population (Fig 2). However, to date, there are few studies with a genomic approach to suicidal behavior in the Mexican population, so it is important to carry out more studies to expand the information.

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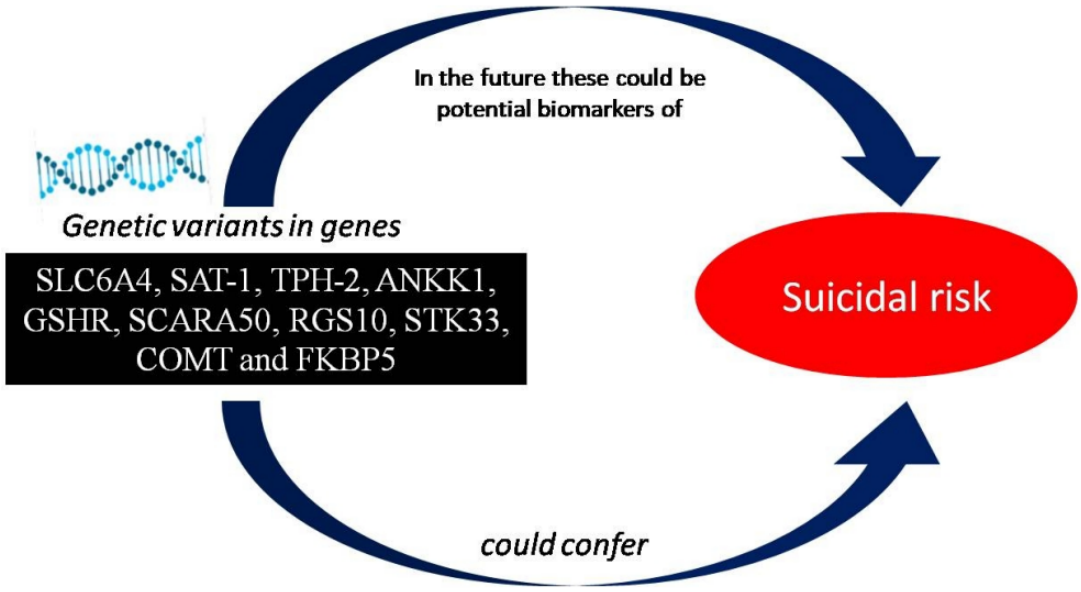

Fig 2. Potential genetic biomarkers of suicidal risk in the Mexican population. Genotyping studies carried out to date suggest that genetic variants in the *SLC6A4*, *SAT-1*, *TPH-2*, *ANKK1*, *GSHR*, *SCARA50*, *RGS10*, *STK33*, *COMT* and *FKBP5* genes could be associated with susceptibility to suicide in the Mexican population.

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Declaration of interest

The authors of this manuscript declare that they have no conflict of interest.

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