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Review Article

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Single Nucleotide Polymorphisms and Suicidal Behavior

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Abstract

A major worldwide social health issue is suicide and suicidal behavior. Recently, research has been undertaken in order to support the theory that there is a definitive link between certain genetic factors and the prevalence of suicide. It is estimated be the World Health Organization (WHO), that suicide is responsible for approximately 2% of annual worldwide deaths. Unfortunately, the etiology of this has proven to be exceptionally complex, but the studies carried out have pointed towards genetic factors as a possible leading cause. Suicidal Attempters (SA) and suicidal behavior is considered complex due to the interaction between various environmental as well as genetic factors. These factors being: alcohol and substance abuse, psychiatric disorders, stress, among other features.

Keywords

Psychiatric disorder; Genetic factor; Health; Suicidal behavior

Introduction

In accordance with the studies carried out, evidence points towards cytokines and their respective Single Nucleotide Polymorphisms (SNPs) as enacting a key role in disrupting Specific Neurobiological Pathways [1-3]. What these studies show, is that by Single Nucleotide Polymorphisms (SNPs) in select genes coding for cytokines within the serotonergic and dopaminergic neurobiological pathways lead to increased rates in suicidal tendencies as well as an increased susceptibility to various confounders, that themselves, act as risk factors for suicide attempters [4].

SNPs are defined as single nucleotide substitutions between a single base from the four nucleotide bases A, T, C, and G for another. This means that there are up to four possible genome combinations or versions for each single SNP location, due to the four different bases available. In order for SNP classification, two or more versions of these SNP versions must be present and expressed in at least 1% of the general population. The distinct types of SNPs that exist:

- Linked (indicative) SNPs: SNPs which are neither present in the relevant genes, nor are they affecting protein function in any way? Nonetheless they do play a role in specific drug responses, and disease incidence
- Causative SNPs: SNPs which exist within the relevant genes and affect protein
- Function and in turn affect suicidal tendencies and drug response. The two types of causative SNPs being: SNPs which are neither present in the relevant genes, nor are they affecting protein function in any way. Nonetheless they do play a role in specific drug responses, and disease incidence

Causative SNPs

SNPs which exist within the relevant genes and affect protein function and in turn affect suicidal tendencies and drug response. The two types of causative SNPs being:

Coding SNPs: That reside in the coding region of the relevant gene, and disrupt the amino acid sequence of the gene's respective coded protein.

Non-coding SNPs: That reside within the regulatory sequence of the gene, and therefore disrupting the location, level, and/or timing of the gene expression [5].

The aim of these studies is to, first and foremost, to study the causal link between SNP and Suicide. Secondly to understand how specific SNPs ranging from distal and proximal factors (e.g. genetic loading, family history of suicide) and proximal factors (e.g. existence of psychiatric disorder, events conferring acute stress) affect suicidal tendencies.

In order to successfully evaluate these studies, and to assess the objectives, the results will be analysed by looking at the literature and results from the perspective of SNPs and how they exist within the context of distal factors, and proximal factors.

Literature Review

Distal factors

The distal factors concerning suicidal behavior encompass various criteria, they are known to aggregate via familial relation and inheritance, the risk genetic variants are independent of any pre-existing or underlying psychotic disorders, and these risk genetic variants are critical for the normal function of neurobiological pathways, and are therefore linked to suicidal behavior and any associated endo-phenotypes [6].

For all the investigations carried out, a general procedure was put in place: DNA is obtained from willing adult participants who have been clinically diagnosed as SA or have shown signs of suicidal behavior by licensed psychiatrists. Genotyping of relevant SNPs were undergone. Meta-analysis for all relevant species of genetic variation in SA was carried out through Armitage trend tests and Chi squared analysis. Binary regression models were used for evaluation, and to observe any gene-gene and gene-environment interactions relative to the SNPs [7].

The tests performed relevant to distal factors are

5HTR2A rs6313 (T102C) T vs C allele

Through the use of case-control model, and evaluation via meta-analysis studies, the *rs6313* SNP in the *5HTR2A* gene was observed in order to establish a direct association between the genetic variation present and any suicidal behavior. This test involved 161 patients with pre-existing suicidal records, and were then compared to 244 control

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specimens without pre-existing conditions. These were evaluated through meta-analysis of A) C allele vs T allele; B) T allele versus C allele; C) Caucasian populace, D) Asian populace, and E) self-destruction attempters with schizophrenia.

The raw results determined that there was indeed a causal link between suicide attempts and the presence of the *rs6313* SNP, versus the control group which did not show the same tendencies. Despite this however, meta-analyses debunked initial findings, and ascertained that *rs6313* SNP did not have as major a role as initially theorized in the behavior of suicidal patients. The following comparisons were used to draw said conclusions [8].

TGF-β1 codon 10

Through the use of case-control model, and evaluation via meta-analysis studies, the *rs1982073* SNP in the *TGF-b1* codon 10 gene was observed in order to establish a direct association between the genetic variation present and any suicidal behavior. This test involved 145 patients with pre-existing suicidal records, and were then compared to 200 control specimens without pre-existing conditions. These were evaluated through meta-analysis by using an allele specific oligonucleotide Polymerase Chain Reaction (PCR) to compare the T/T allele with the T/C allele.

The raw results determined that there was once again a definitive link between suicide attempts and the presence of the *rs1982073* SNP at the T/T allele with 41.7% of sample demonstrating said results, versus the control group which did not show the same tendencies only 27%. The analysis showed a greater tendency for suicide with the T/T allele than the T/C allele at *TGF-b1* codon 10 polymorphisms [9].

SLC1A2, SLC1A3, 5-HTR1B and *NTRK2*

For this SNP study, 18 candidate genes were observed:(*COMT, 5-HT2A, 5-HT1A, 5-HTR1B, TPH1, MAO-A, TPH2, DBH, CNR1, BDNF, ABCG1, GABRA5, GABRG2, GABRB2, SLC1A2, SLC1A3, NTRK2, CRHR1*)-for 28 suspect polymorphisms, and their already established link to suicide.

The analysis showed four specific, recurring SNPs that demonstrated a greater propensity for developing and expressing suicidal tendencies than the others, these being: *rs4755404, rs2269272, rs6296* and *rs1659400*. Thus, establishing that SNP at the *NTRK2* gene (at various loci) have shown clear risk association for SA [10].

Interpretation

In summation, through both statistical and biological data collection and analysis, it can be clearly stated that there is indeed a definite causal significance between the presence of genetic variations in the form of SNPs at specific coding genes, and a greater risk association factor with developing and exhibiting suicidal behavior in SA when observing SNP prevalence in distal pathways of an individual. Unfortunately, the results presented are not concrete, and are at best inconclusive-in the sense that from a raw data standpoint correlation between SNP and suicide is evident, but when meta-analysis is performed, results are less than indicative of the initial hypothesis.

Proximal Factors

Alcohol

There is an exponential increase in rates of suicide when comparing those with alcohol dependency conditions to the normal populations. An approximate 60 to 120 times increase [11]. Alcohol dependency, similarly to suicidal tendencies is a multifactorial disorder that is reliant on various interacting genetic and environmental factors. Since it is known that the serotonergic and dopaminergic pathways play an integral role in regulating psychopathologies such as suicide [12], any dysfunction (see SNP) in these systems caused by alcohol dependency, could therefore have great significance in suicidal behavior. The genes that play a role here are:

Tryptophan Hydroxylase 2 (TPH 2)

Tryptophan Hydroxylase 2 (TPH2) is a gene that codes for the rate limiting enzyme in serotonin synthesis, hence by observing this it is possible to observe the action of alcohol related suicide [13,14]. Results here showed that depending on the SNPs (genetic variants) tested there was only a very mild association with suicide and alcohol dependency SNPs of neurobiological pathways [15,16].

Dopamine Receptor Gene (DRD2) and ANKK1

This study evaluated chosen SNPs in the *DRD2* and *ANKK1* genes in individuals who demonstrated alcohol dependence syndrome. Results here suggested that the *TGA2* haplotype SNP at the select genes demonstrated a much higher frequency of suicide attempts, versus non-alcoholics [17,18].

Substance Abuse (See Drugs)

Using certain narcotic substances leads to a number of disruption in normal neurotransmitters functions in the brain, namely the opioid system. As such these disturbances may play a crucial part in the pathophysiology of suicidal behavior by interfering with normal function.

OPRM1

206 participants that have previously exhibited lifetime Major Depressive Episodes (MDE) and/or are SA, with a history of drug abuse were used for this test. Of these 41 (19.9%) showed independent MDE, suicidal tendencies were reported by 106 (50.9%) with 79 individuals actually attempting suicide. The number of substances on which individuals met criteria for a lifetime substance use disorder (abuse or dependence) ranged from 1-8 [mean=4.33 (SD=1.55)] [19].

Mental Disease (Schizoprenia): γ-aminobutyric acid GABRG2

γ-amino butyric acid GABRG2 is involved in the pathophysiology of schizophrenia; which is a severe neuropsychiatric disorder that has shown exceptionally high tendencies for suicidal; behavior development. The SNPs *rs*183294 and *rs209356* at this gene exhibited high risk association with suicide and schizophrenia development, often times coupled with alcohol and substance abuse [20,21].

Stress

Hypothalamic-Pituitary-Adrenal axis (HPA) (*CRHR1, NR3C1*, and *AVPBR1*). A higher level of stress exposure leads to higher levels of suicide. The biological pathway of stress regulation is governed by HPA and its corresponding associate genes. Therefore, any dysfunction here caused by SNP genetic variation, will lead to disrupted cortisol activity, which in turn disturbs feedback regulation, and ultimately leads to a higher risk association with suicidal tendencies. However, the data here was not able to show any significant involvement of this mechanism with stress coping and suicide attempts.

Interpretation

All in all, the observations here have established that alcohol dependency can and does play a significant role in increasing the risk of developing suicidal tendencies, if and when there is prevalence of SNP in pathways that are involved in serotonergic and dopaminergic neurobiological symptoms. On the other hand, the results seem to be, generally, very modest and are unable to provide concrete evidence of the association of SNPs in the proximal suicide factors.

Ethnic Populations against SNP Prevalence

In Table 1, Key Ö=Present, x=Absent.

SNP prevalence	*5HTR2A rs6313 (T102C)*	*rs1982073 TGF-b1 codon 10*	*SLC1A2, SLC1A3, 5-HTR1B* and *NTRK2 rs4755404, rs2269272, rs6296* and *rs1659400*	*TPH2, DRD2, ANKK1, OPRM1*	*GABGR2, rs183294* and *rs209356*
Poland	Ö	Ö	Ö	Ö	Ö
Malaysia	Ö	Ö	x	x	Ö
Mexico	Ö	Ö	x	Ö	x

Table 1: Details of the prevalence of common suicidal SNPs plotted against presence in studied populations.

Conclusion

The SNPs that have been observed and evaluated throughout the course of this study have demonstrated a clear link between SNP and Suicide. As well as providing a functional understanding of how specific SNPs in the distal and proximal neurobiological pathways affect suicidal tendencies. Though often it has been shown that these results are somewhat vague and even inconclusive towards the hypothesis and as such further studies into the susceptibility of SNPs and how they lend themselves to increased suicide association need to be undertaken, especially proximal factors. By carrying forward this line of research, it is hopeful that we gain a clearer picture of the complex genetic and environmental interactions that govern suicidal behavior, and the involvement of polymorphisms within them. So that it may one day be possible to assess the likelihood of an individual being a SA, and preempt any undesired behavior by supplying therapy for the relevant conditions.

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