

Chapter 4

Genetics of Suicidal Behaviour

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Suicidal behaviour is a complex and multifactorial behaviour. About million people commit suicide each year. Suicide is ranked second among cause of death in adolescent. Although, suicidal behaviour has been attributed to various factors including, psychological and economical, there is a great deal of evidence point to interaction of genetics and environment that may significantly contribute to the suicidal behaviour. In this chapter, we will first discuss epidemiology of suicidal behaviour describing family, twin, and adoption studies. We will then examine the major candidate gene studies. Lastly, we will review recent progress in genome-wide association study and next-generation sequence in the suicidal behaviour. We will also address the new ideas and future directions in order to find the susceptible genetic factors associated with suicidal behaviour.

Genetic Epidemiology

Familial clustering of suicidal behaviour and psychopathology has been reported for adolescent suicide attempters. Mittendorfer-Rutz, Rasmussen, and Wasserman (2008) conducted the largest epidemiology studies with 14,440 suicide attempters and 14,440 healthy controls that were born in Sweden between 1968 and 1980. For youth suicide attempt, familial risk factors were siblings (OR 3.4; 2.8–4.1), maternal (OR 2.7; 2.5–3.1), and paternal (OR 1.9; 1.7–2.1). The important risk factors included were familial personality, substance abuse disorders, maternal

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schizophrenia, non-affective psychoses, organic disorders, and parental neurotic stress-related and somatoform disorders (1.9–3.2 fold increase), and paternal (OR 1.9; 1.6–2.3) and maternal (OR 1.8; 1.3–2.4) suicide completion. It was found that familial suicide completion had stronger effect on suicide attempt of earlier onset and in boys. About half of all suicide attempts were attributed to familial psychopathology (13%), family suicide attempt (7%), suicide completion (1%), and own psychopathology. This familial study directly supports the evidence that genetic risk factors contribute to the suicidal behaviour.

Twin studies are a useful way for analysing concordance. Individuals share 100% genes between monozygotic twins and share 50% genes between dizygotic twins. Twin study can separate environmental variance from genetic factor. Roy, Segal, Centerwall, and Robinette (1991) examined 176 twin pairs in which one or both twins had committed suicide. Interestingly, they found concordant difference between monozygotic twin pairs (11.3%) and dizygotic twin pairs (1.8%). The presence of psychiatric disorder in the twins and their families was examined in 11 twin pairs, two of whom were concordant for suicide. Out of 13, 11 twin suicide victims had been treated for psychiatric disorders. In addition, twins in 10 pairs had other first- or second-degree relatives who had been treated for psychiatric disorders. These twin data suggest that genetic factors related to suicide may largely represent a genetic predisposition for the psychiatric disorders associated with suicide. Statham et al. (1998) examined the epidemiology and genetics of suicidality, which included reports of persistent suicidal thoughts or a plan or suicide attempt in a large number of community-based samples of monozygotic and dizygotic twin pairs (5995 twins). They found that lifetime prevalence of suicidal thoughts and attempts was remarkably constant across birth cohorts, and across gender. History of suicide attempts or persistent thoughts in the respondent's co-twin remained a powerful predictor in monozygotic pairs, but was not consistently predictive in dizygotic pairs. Overall, genetic factors accounted for approximately 45% of the variance in suicidal thoughts and behaviour. Voracek and Loibl (2007) conducted a systematic review of twins study and they collected 32 studies, which included 19 case reports, 5 register-based studies, 4 population-based epidemiological studies, and 4 surviving co-twins study. From register-based studies and case reports, concordance for completed suicide was significantly more frequent among monozygotic (24.1%) than dizygotic twin pairs (2.3%). From population-based epidemiological studies, heritability of suicidal behaviour was estimated at 30–55%. This twin study suggests strong genetic contributions to the suicide risk.

Adoption studies have also been conducted in the suicide behaviour. Schulsinger, Ketty, Rosenthal, and Wender (1979) examined 57 suicide victims, which were adopted in the Danish family. They compared the suicide rates between biological relatives of suicide victims and non-suicidal adoptee control group, which were found to be 4.46 and 0.74%, respectively. None of the relatives of the adopted families were affected by suicide. Another study reported by Von Borczyskowski, Lindblad, Vinnerljung, Reintjes, and Hjern (2011) was conducted in the Swedish registry with a national cohort of 2,471,496 individuals, including

176,000 adoptees for suicide during 1987–2001. They found that biological parent suicide and severe psychiatric morbidity which were the major risk factors for suicide in adopted and in non-adopted offspring.

Candidate Gene Association Studies of Suicidal Behaviour

Gene studies of most candidates are based on case-control association study design. The basic principle of genetic association studies is the hypothesis of common disease and common variants. The groups of cases and controls are enrolled in the association study and the allele or genotype frequencies are determined and compared statistically. If the polymorphisms are more frequent in one group than the other group, the genetic variants show association with the disease and the candidate gene may be the susceptible genes for suicide or psychiatric diseases. The selections of genetic variants for the study are usually based on the plausible hypothesis, such as serotonin transporter for antidepressants. It is noticeable that the association studies have several limitations. First, spurious positive findings and false-positive findings are unavoidable due to the population stratification. Second, if the sample sizes are small, then the statistical power is very low. Lastly, most of common variants are located within the intron regions and elucidation of function relevance is confronted. Such limitations also include clinical and diagnostic heterogeneity, low statistical power if sample sizes are small, often limited biological evidence of candidate gene selection, and unknown functional relevance of tested single nucleotide polymorphisms (SNPs), as well as population stratification within the sample leading to spurious positive findings or false-negative associations. Despite these limitations, the candidate gene association studies are still an effective solution in finding for susceptible genes in suicide victims. Here we summarize the candidate gene studies in suicidal behaviour examined using association studies.

Serotonergic System

Studies showing the role of serotonin, a monoamine neurotransmitter, in suicidal behaviour date back to the 70s of the last century. Serotonergic functions have been demonstrated to be critical for the regulation of impulsive, aggressive, and suicidal behaviour (Koller, Bondy, Preuss, Bottlender, & Soyka, 2003; Virkkunen et al., 1989). For example, several studies have reported that the expression of genes associated with serotonergic system is altered in the post-mortem brains of suicide victims, especially in the prefrontal cortex. These include 5HT_{2A}, 5HT_{1A}, and 5HT_{2C} (Celada, Puig, Amargós-Bosch, Adell, & Artigas, 2004; Holmes, 2008; Sugden et al., 2009). Clinical studies also found that the concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) is decreased in the

cerebrospinal fluid of the suicidal patients (Asberg, 1997; Placidi et al., 2001). Most of the genetic association studies are conducted using the genes of serotonergic neurotransmission pathway.

Tryptophan Hydroxylase (TPH1)

TPH1 is located on the chromosome 11p15.3-p14 and the full-length fragment covers 29 kbp. Serotonin is catalyzed from L-Tryptophan by tryptophan hydroxylase (THP), which is a rate-limiting enzyme (Boullard, Darmon, Ravassard, and Mallet, 1995). To identify the susceptible risk single nucleotide polymorphism (SNP)s for suicidal behaviour, several studies focused on common variants associated with *TPH1* gene. Early studies focused on the two SNPs: A779C (rs1799913) and A218C (rs1800532). Both these SNPs are located on intron 7. Nielsen et al. (1994) reported variation on a polymorphism in intron 7 with an A to C substitution at nucleotides 779 (A779C) which was associated with a history of violent suicide attempts. Following this, two studies found C allele as the risk variant (Nielsen et al., 1998; Roy et al., 2001) and one study showed increased frequency of the A allele in suicide attempters (Mann et al., 1997). The first meta-analysis conducted by Lalovic and Turecki (2002) reported no association between A218C with suicide behaviour. Another meta-analysis investigated A218C in Caucasians, which showed that suicidal patients frequently carried A218 allele (Rujescu, Giegling, Sato, Hartmann, & Möller, 2003). A meta-analysis summarizing 9 studies reported an association between A218C polymorphisms and suicidal behaviour (Bellivier, Chaste, and Malafosse, 2004). Li, Duan, and He (2006) performed meta-analysis of 22 studies and confirmed this evidence. Another meta-analysis was conducted by Clayden, Zaruk, Meyre, Thabane, and Samaan (2012) which further supported the involvement of A218C and suicidal behaviour. Recently, González-Castro et al. (2014) collected 37 literatures about genetic association studies of *TPH1* and reviewed 2 polymorphisms (one is A218C, the other is A779C). This meta-analysis study involved a total number of sample 5683 cases and 11,652 controls. Meanwhile, subgroup analyses were performed in the Caucasian and Asian populations. The results demonstrated that both A218C and A779C were susceptible to suicide behaviour. Other studies examining the A allele of the A218C showed frequent association with suicide attempters than non-attempters (Abbar et al., 2001; Galfalvy et al., 2009; Souery et al., 2001; Tsai et al., 1999). On the other hand, the C allele was associated with suicide attempts in two studies (Paik, Toh, Kim, & Lee, 2000; Stefulj, Kubat, Baliija, & Jernej, 2006). Other common variants identified within the promoter region are T7180G, C7065T, A6526G, and G5806T. The A allele of the A6526G was found to be in linkage disequilibrium with A779C and was associated with suicide attempts (Galfalvy et al., 2009; Rotondo et al., 1999). A study by Turecki et al. (2001) showed risk haplotype associated with suicide completion (6526G–5806T–218C). An association between the haplotype TCAAA of T7180G-C7065T-A6526G-A218C-A779C SNPs and suicide attempts have also been reported (Liu et al., 2006).

Several studies support the evidence that *TPHI* is involved in the personality trait, especially anger and aggression. Rujescu et al. (2002) reported that individuals with “A” allele had higher scores on the trait Anger Scale of the State-Trait Anger Expression Inventory, STAX in the healthy control and suicide attempters. Baud et al. (2009) also reported that suicide attempters with “AA” genotype had lower score on the anger than with CC genotype. Cicchetti, Rogosch, and Thibodeau (2012) examined common variants in the *TPHI* in child maltreatment and non-maltreatment low-income children. Interestingly, they found that *TPHI* polymorphisms moderated the effects of maltreatment subtype on adult reports of antisocial. Andre et al. (2013) analysed the interaction between the *TPHI* genotype, treatment response, and the different temperament dimensions in 97 subjects with major depression who was treated serotonin reuptake inhibitors. They found *TPHI* genotype and treatment response had interactive effects on both HA1 and HA2 scores. Interaction between CC genotype and remission or treatment status differentiates between different temperament profiles. Karanović et al. (2016) assessed *TPHI* variant rs1800532 and its possible interaction with recent stressful life events as risk factors for suicide attempt in Serbian psychiatric patients, including 165 suicide attempters and 188 suicide non-attempters. They found that rs1800532 and recent stressful life events were independently associated with suicide attempt, while rs1800532 did not moderate the effect of recent stressful life events on suicide attempt vulnerability.

Tryptophan Hydroxylase (TPH2)

Walther et al. (2003) first reported a second TPH isoform in mice and termed it TPH2. Breidenthal, White, and Glatt (2004) screened the whole genomic region and identified several common variants in this gene, which served for several association studies. Zill et al. (2004) investigated the SNPs and haplotype in 263 suicide victims and 266 healthy controls with 10 SNPs in the *TPH2* gene. One SNP was detected to be significantly associated with suicide ($p = 0.004$). Haplotype analysis also supported for this association ($p = 0.001$). Several case-control studies reported association between *TPH2* gene and suicide. Some studies showed positive results, but others showed negative results. Lately, González-Castro, Juárez-Rojop, López-Narváez, and Tovilla-Zárate (2014) conducted a meta-analysis focusing three SNPs (G603T, A473T, and G19918A) in 4196 cases and 5990 controls. The meta-analysis did not find any significant association with patients showing suicidal behaviour. Choong, Tee, and Tang (2014) selected 9 SNPs and conducted a meta-analysis with a total of 2536 cases and 3101 controls in 11 case-control studies. No significant results were detected, suggesting that *TPH2* may not play a significant role in suicidal behaviour. Interestingly, polymorphisms in the *TPH2* gene were found in relation to personality traits like aggression or impulsivity, emotional regulation, and neuroticism (Perez-Rodriguez et al. 2010; Hong et al. 2011).

Serotonin Transporter

The function of serotonin transporter (5-HTT) is to reuptake the released serotonin from the synaptic cleft. A function insertion/deletion variant in the promoter region contain two or three alleles called short(s) and long (IA and IG). Polymorphisms in HTTLPR have been associated with numerous neuropsychiatric disorders, including schizophrenia, depression, and aggression. These disorders in turn increase the susceptibility of suicidal behaviour. Anguelova, Benkelfat, and Turecki (2003) conducted a meta-analysis pooling 12 studies investigating the 5-HTT promoter polymorphism. A total of 1,168 cases (suicide completers and suicide attempters) and 1,371 controls (comprised of 10 Caucasian populations, 1 US population and 1 Chinese population) were studied. A significant association of the s allele was demonstrated with suicidal behaviour. Lin and Tsai (2004) also performed a meta-analysis but reported no association between 5-HTTLPR polymorphism and suicidal behaviour ($p = 0.379$). When they compared subjects with the same psychiatric diagnosis, the genotypes carrying the s allele were significantly more frequent in suicide attempters than in non-attempters ($p = 0.004$). In addition, the s allele was associated with violent suicide ($p = 0.0001$) but not with non-violent suicide ($p = 1.00$). Li and He (2007) provided a comprehensive meta-analysis pooling 39 studies and found that long alleles to be associated with decreased risk of suicide attempts (OR 0.88; 95% CI 0.80–0.97). Clayden et al. (2012) analysed the association between the serotonin transporter s allele and suicidal behaviour in 31 primary case-control studies (6324 cases and 10,285 controls). The results revealed no significance association, however, subgroups of suicide attempters demonstrated significance association with serotonin transporter (*SLC6A4*) 5-HTTLPR [OR 1.13 (95% CI 1.05–1.21), $p = 0.001$], suggesting that the 5-HTTLPR and rs1800532 polymorphisms are significantly associated with suicide attempts, but not with completed suicides. A recent meta-analysis by Schild, Pietschnig, Tran, and Voracek (2013) included 2536 cases and 3984 controls and further supported the involvement of the 5-HTTLPR in suicidal behaviour. Anguelova, Benkelfat, and Turecki (2003) combined 12 studies investigating 5-HTT promoter 44 bp insertion/deletion polymorphism in a total of 1,599 and 2,539 subjects. The combined evidence was significant association with the 5-HTT locus (OR 1.1795%, CI 1.04–1.32, $p = 0.009$), suggesting that 5-HTT may play a role in the predisposition to suicide. Several other studies found an association between the SS genotype/S allele and increased lethality (Saiz et al., 2011; Wasserman et al., 2007) and violent attempts (Neves et al., 2008, 2010). In a large cohort of 5608 controls and subjects suffering from various psychiatric disorders, Perroud et al. (2010) studied the frequency of haplotypes and corresponding genotypes combining the 5-HTTLPR and the other serotonin transporter promoter functional variant (rs25531). They found that a very rare G-14/G-16 genotype was carried by only three subjects who were women with a history of suicide attempt. Taken together, these studies provide evidence that 5-HTTLPR may play crucial role in the suicidal behaviour.

Serotonin Receptors

Serotonin receptors, a G protein-coupled receptor super family, consist of receptors named 5-HT1 to 5-HT7 (Cowen, 1991). Here, we focus on the genetics of serotonin receptors in the context of suicidal behaviour.

5-HT1A Receptor

Lemonde et al. (2003) conducted common variant of C1109G on the promoter region in a sample of suicide victims and control subjects. They found that G allele was significantly over-represented in the suicide group. In a total of 191 suicide and 218 healthy control subjects, Samadi et al. (2012) studied association between polymorphisms C1019G, C47T (Pro16Leu), and G815A (Gly272Asp) and suicidal behaviour taking into account age, gender, and the presence of stressful life, and loss events in 1 year prior to suicide. They found that the distribution of C1019G genotypes was significantly different in suicide victims and healthy controls ($p = 0.002$), and the GG genotype was associated with a significantly higher number of more stressful life and loss events in the suicide victims ($p = 0.017$, $p = 0.037$, respectively). Two missense polymorphisms, Pro16Leu and Gly 272 Asp, have also been investigated in the Japanese subjects and the results revealed no significant differences in genotype distribution or allele frequencies between suicide victims and controls. Ohtani, Shindo, and Yoshioka (2004) conducted a meta-analysis for the A652G polymorphisms and reported no association and three further meta-analyses for the C1019G variants were also negative (Rivera, Bermúdez Ocaña, Camarena Medellín, & Tovilla-Zárate, 2012, Schild et al., 2013)

5-HT1B Receptor

The *5-HT1B* gene is located at 6q13 which includes 1.17 kb of axons regions. The *5-HT1B* has received attention due to its association with aggressive and impulsive behaviour. Kia-Keating, Glatt, and Tsuang (2007) performed a meta-analysis of 6 studies with various study designs and did not find significant results for the G861C allele with suicidal behaviour. Another meta-analysis also did not find significant results in a sample of 2,948 cases and 4,066 controls (Clayden et al., 2012). Jensen et al. (2009) reported that a mirSNP, regulated by mir-96, was significantly associated with aggressive behaviour. Conner et al. (2010) genotyped 5 polymorphisms in the *HTR1B* gene (rs11568817, rs130058, rs6296, rs6297, rs13212041) in 361 University students. They found rs13212041 polymorphism, which modulates miRNA-mediated regulation of *HTR1B* expression, can predict self-reported anger and hostility among young men. Recently, Hakulinen et al. (2013) examined a connection between polymorphism of *HTR1B* in 967 participants from a large

population-based sample with 27-year follow-up. They found rs6296 was associated with childhood aggressive behaviour but not with adulthood anger or hostility.

5-HT_{2A} Receptor

Earlier, the density of brain and platelet 5HT_{2A} receptors has been shown to be increased in suicidal patients (Du, Bakish, Lapierre, Ravindran, & Hrdina, 2000). Thus, 5-HT_{2A} receptor has been considered to be a major candidate gene in suicidal behaviour (Bachus et al., 1997). A first meta-analysis with 9 studies, which included 596 suicidal completers or attempters and 1003 healthy controls, showed no association with T102C located in an axon (Anguelova et al., 2003). Later, Li et al. (2006) carried out a meta-analysis of 25 studies on suicidal behaviour and they also did not find significant association with suicide attempter (OR 0.98; 95% CI 0.83–1.16). On the other hand, another SNP in the promoter region A1438G in seven studies showed that A-allele has protective risk of suicide (OR 0.67, 95% CI 0.59–0.89). Fanous et al. (2009) investigated the tagSNPs, spanning *HTR2A* genome regions, in the 270 families with suicidal ideation. They did not find significant association with the any tagSNPs or haplotype and suicidal ideation. Interestingly, Giegling, Hartmann, Möller, & Rujescu, (2006) found that the *HTR2A* variants rs594242-rs6311: G-C and rs6311 C were associated with increased non-violent and impulsive suicidal behaviour, respectively. On the other hand, the CC genotype of the T102C SNP was more frequent among suicide attempters (Vaquero-Lorenzo et al., 2008; Wrzosek et al., 2011). In 227 suicide attempters, 686 non-suicidal psychiatric patients, and 420 healthy controls from a homogeneous Spanish Caucasian population, Saiz et al. (2011) found no differences in genotype frequencies between the three groups.

Dopaminergic System and Catecholamine's

Soderstrom, Blennow, Manhem, and Forsmen (2001) reported that high cerebrospinal fluid (CSF) levels of the dopamine metabolite HVA correlates with human aggression, whereas Pitchot, Hansenne, and Ansseau (2001) found the involvement of D2-dopaminergic functions in the biology of suicide by demonstrating a smaller growth hormone response to apomorphine, a dopaminergic agonist. These investigators also found that reduced dopamine function in depressed patients was related to suicidal behaviour but not its lethality (Pitchot et al., 2001b). Catechol-O-Methyltransferase (COMT), a major enzyme which can inactivate the activity of dopamine and noradrenalin has received much attention in psychiatric illnesses because of the functional polymorphisms associated with val158met (Chen et al., 2004). Kia-Keating et al. (2007) performed a meta-analysis of a total 519 cases and 933 healthy controls and included 6 studies. They found

Val158Met was significantly associated with suicidal behaviour. Additionally, Calati et al. (2011) summarized 10 studies with 1324 patients but found no association between val158met and suicidal behaviour. Tovilla-Zárate et al. (2011) further confirmed no difference in this functional polymorphism between suicidal patients and healthy control.

Brain-Derived Neurotrophic Factors

BDNF is a member of the neurotrophin family of growth factors (Laske & Eschweiler, 2006). Several studies have revealed that the expression of BDNF is lower in postmortem brain of suicide victims (Dwivedi et al., 2003) as well as in patients with suicidal behaviour (Dwivedi et al., 2003; Lee, Kim, Park, & Kim, 2007). Because of these findings, several studies attempted to study polymorphism in BDNF gene in suicide. The most studied polymorphism in BDNF gene is Val66Met. This polymorphism is a missense mutation at position 66 resulting in a valine to methionine substitution. Previous studies demonstrated that the BDNF val66met polymorphism was associated with impaired cognitive functioning and worse memory functioning in humans (Egan et al., 2003). Hong et al. (2003) found that V66M polymorphism in the BDNF was not associated with suicide attempts in bipolar disorder or major depressed patients. No association between V66M and suicide victims was also reported by Zarrilli et al. (2009). However, Vincze et al. (2008) found the frequency of Met allele in violent bipolar disorder patients was higher than the healthy controls. Kim et al. (2008) studied the allelic and genotypic distributions of BDNF Val/Met in a population of 169 bipolar patients and 251 normal controls and found that the rate of suicide attempts among the Val/Val (11.3%), Val/Met (28.8%), and Met/Met (38.9%) genotype groups were significantly different. Relative to patients with the Val/Val genotype had a 4.9-fold higher risk of suicide attempts than those with the Met/Met genotype. A recent study with combining 11 published studies reported that Met allele was associated with suicide victims ($p = 0.032$, $OR_{met} = 1.16$) (Zai et al., 2012). Iga et al. (2007) studied BDNF Val66Met polymorphism in depressed patients in a Japanese population. They found similar genotypic distributions and allele frequencies among the patients and control subjects. However, when the relationships of the polymorphism with several clinical variables were examined, Met allele had significant effects on psychotic feature and suicidal behaviour and family history. These results suggest that the BDNF Val66Met polymorphism is not related to the development of MDD but related to clinical features of MDD. Another meta-analysis with 8 published studies showed that the met carrier have a higher trend for suicide. The Met allele and genotype show significance with suicide attempt (Zai et al., 2012). Gonzalez-Castro et al. (2015) studied the association of Val66Met BDNF polymorphism in bipolar disorder in a Mexican population. Although their results from the meta-analysis (9,349 cases and 7,437 controls) did not show a significant association in any of the models, however, when they analysed the association between rs6265 and lifetime

history of suicidal behaviour, they found an association between genotype Val–Val and suicide attempt. Recently, Bresin, Sima Finy, and Verona (2013) explored the interaction between retrospective reports of childhood emotional environment and the BDNF Val66Met polymorphism in relation to a history of two main types of self-injurious behaviours: suicide attempt and non-suicidal self-injury, in a sample of individuals with a history of involvement in the criminal justice system. For individuals with two Val alleles, these investigators found a significant direct relationship between emotional maltreatment and self-injurious behaviours. However, the relationship was not significant for Met carriers.

Genome-Wide Association Studies of Suicide Behaviour

With the rapid development of technological advances in genomics, Genome-wide association study (GWAS) can scan more than 1 million SNPs across the genome in parallel and provide an in-depth knowledge of the genetic information. Several GWAS studies have emerged in the suicidal behaviour.

Treatment-Emergent Suicidal Ideation

Laje et al. (2009) collected 90 white participants who were treatment-emergent suicidal ideators and matched healthy controls. Based on these subjects, the authors performed a GWAS and 109365 SNPs were genotyped on the Illumina Human-1 Bead chip. One SNP in the gene *PALPLN* reached genome-wide significant and another SNP in the gene *IL28RA* showed a trend. *PAPLN* encodes papil in, a protoglycan-like sulfated glycoprotein. *IL28RA* encodes an interleukin receptor. Perroud et al. (2012) examined to identify genetic variants involved in increasing suicidal ideation during escitalopram and nortriptyline treatment. They studied a total number of 706 major depressed patients treated with escitalopram or nortriptyline and genotyped those using platform based on the Illumina 610-Quad Beadchips. The genetic marker most significantly associated with increasing suicidality was a SNP (rs11143230) located 30 kb down stream of a gene encoding guanine deaminase on chromosome 9q21.13. Two suggestive drug-specific associations within *KCNIP4* (Kv channel-interacting protein 4; chromosome 4p15.31) and near *ELP3* (elongation protein 3 homolog; chromosome 8p21.1) were found in subjects treated with escitalopram. The most significant association with in a set of 33 candidate genes was in the neurotrophic tyrosine kinase receptor type 2 genes. They also found a trend for an association within genes such as *GRIP1*, *NXP1* and *ANK3*, previously associated with psychiatric phenotypes indirectly linked to suicidal behaviour. The results suggest novel pathways involved in increasing suicidal ideation during antidepressant treatment and can help to target treatment to reduce the risk of this dramatic adverse event. A third GWAS on treatment-emergent

suicidal ideators was provided by Menke et al. (2012) in depressed patients ($n = 397$) with suicidal thoughts. They did not find any genome-wide significant variant. The best associated SNP was rs1630535 (p value = 1.3×10^{-7}). Fourteen variants showed nominal significant association with the same risk allele in the replication sample. The study suggests that a combination of genetic markers maybe used to identify patients at risk for treatment-emergent suicidal ideation.

Suicide Attempts

Perlis et al. (2010) reported the first GWAS on suicide attempts. Data on lifetime suicide attempts were extracted from GWAS of bipolar I and II disorder as well as MDD. For suicide attempt in bipolar disorder, rs1466864 was identified to be the most significant. Five loci also showed suggestive association. For suicide attempt in major depressive disorder, rs2576377 in *ABI3BP* gene showed the strongest association where as six loci showed nominal association. Schosser et al. (2011) performed a genome-wide association scan in 251 depressed patients with serious suicidal attempts. No SNP reached the cutoff of genome-wide significance level. For the quantitative trait, GFRA1 was detected to be associated with suicide attempts ($p = 2 \times 10^{-6}$). For the discrete trait of suicide attempt, SNPs in *KIAA1244* and *RGS18* showed suggestive associations. A polymorphism in *NTRK2*, previously associated with suicidality (Kohli et al., 2010; Perroud et al., 2009; Ropret, Zupanc, Komel, & Videtic Paska, 2015), was also validated. Willour et al. (2012) conducted GWAS and compared the SNP genotypes between 1201 bipolar subjects with a history of suicide attempts and 1,497 bipolar subjects without a history of suicide attempts. In all, 2,507 SNPs were identified with an evidence for association at $p < 0.001$. These associated SNPs were subsequently tested for association in a large and independent bipolar sample set. None of these SNPs showed significantly associated in the replication sample after correcting for multiple testing, but the combined analysis of the two sample sets produced an association signal on 2p25 (rs300774) at the threshold of genome-wide significance ($p = 5.07 \times 10^{-8}$). The associated SNPs on 2p25 fall in a large linkage disequilibrium block containing the *ACPI* (acid phosphatase 1) gene, whose expression is significantly elevated in bipolar subjects who completed suicide. Furthermore, the *ACPI* protein is a tyrosine phosphatase that influences Wnt signalling, a pathway regulated by lithium, making *ACPI* a functional candidate for involvement in the phenotype. Mullins et al. (2014) conducted a genome-wide association and meta-analysis. They reported no significant evidence for association at any SNP in the GWAS or meta-analysis. Meanwhile, polygenic score analyses were performed to suicide attempts in the mood disorder cohorts or ideation status in the GENDEP study. Polygenic scores for suicidal behaviour showed no predictive ability for suicidal ideation.

A recent SNP GWAS on severity of suicidal behaviour was published by Zai et al. (2015). This GWAS was conducted in three independent bipolar patients. No genome-wide significant association of any tested markers was found in any of the

bipolar samples, although a number of common variants located on the chromosomes 8 and 10 showed suggestive association. A more recent GWAS on suicidal behaviour was performed by Galfalvy et al. (2015). A consortium of US, Canadian, and German teams assembled 2 groups of cases: suicide attempters and suicides ($n = 577$) and non-attempter psychiatric and healthy controls ($n = 1233$). The test was repeated separating suicide attempter and completed suicide as outcomes. No SNP reached genome-wide significance but several SNPs within *STK3*, *ADAMTS14*, *PSME12*, and *TBX20* genes reached $p < 1 \times 10^{-5}$ level.

In summary, although the results of these GWAS in suicide were all essentially negative, they do suggest interesting candidate genes that may be worthwhile to follow up in future studies. It is becoming increasingly clear that individual's genetic susceptibility factors for suicide are likely to have only minor effects, and very large pooled analyses of cases and controls will be necessary to identify them.

Conclusions and Future Directions

Suicide is a multifactorial and complex disorder. Apart from biological and psychosocial factors, environmental factors are also critical in predisposition of suicidal behaviour. As discussed above, a large number of genetic studies have been conducted in psychiatric disorder patients dissecting suicidal behaviour. Majority of the studies are focused on serotonergic pathways which is logical given that this neurotransmitter is the most implicated in suicide. Several studies link *TPH1* gene with suicide. More recently, *TPH2* gene shows promising results only when haplotypic analysis is done. *5-HTTLPR* (S (L) allele) is another candidate gene which has shown an association with violent suicide attempts. The results of serotonin receptor subtypes are mixed. Several factors may contribute to conflicting results. As pointed out earlier, some studies are positive in Caucasians but negative in Asian population or vice versa. There are several technical and statistical limitations to the candidate gene approach. This has led to GWAS, which has provided some interesting results, although majority of them are negative. There are several issues with GWAS as discussed elegantly by Ward and Kellis (2012). They have discussed the influence of cumulative predictive power, noncoding variants, detection of rare variants, and reproducibility on GWAS studies. At present, most of the susceptible variants are demonstrated to be located on the intron regions on the chromosome. Thus, it is difficult to explain the function of these identified susceptible variants. Whole exome and whole genome sequencing can detect rare variants and functional mutations. Objectively, whole exome and whole genome sequencing have been applied into the many complex diseases, such as cancer, schizophrenia, autism, etc., however, there is yet to find any report in suicide behaviour. Environmental and/or socioeconomic factors need to be considered carefully that can affect phenotype and assessing noncoding mutation is a challenging task. Even with these limitations, the field is moving forward and effort needs to be made to form a consortium where a large number of patients and healthy controls can be recruited and examined in a single study.

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