ARTICLE

Genetics in relation to psychiatry

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Introduction

The gene is the basic unit of genetic information that lies within each chromosomal deoxyribonucleic acid (DNA) sequence. In 1965, the scientific study of heredity which arguably began with Gregor Mendel's work on peas, gradually developed into five major disciplines - biochemical genetics, developmental genetics, molecular genetics, cytogenetics, and population genetics. The human genome's 35,000 genes are located on 22 pairs of autosomal chromosomes and two sex chromosomes, comprising approximately three billion base pairs of DNA. A fundamental distinction in population genetics, dating back to Wilhelm Johannsen's work in 1909, is between Genotype and Phenotype.

Classical genetic approach

Twin studies and adoption studies (adoptees study, adoptee's family study, and crossfostering study).

Molecular genetic approach

Molecular genetic techniques (restriction enzymes, molecular cloning, southern blotting, DNA sequencing, and polymerase chain reaction), molecular genetic studies (genetic marker and linkage study), and association studies.

Recent literature

Heritabilities were as follows: posttraumatic stress disorder (PTSD) symptoms 41% ($P<0.001$), anxiety symptoms 61% ($P<0.001$), and depressive symptoms 66% ($P<0.001$). The genetic correlation ($\rho g>0$) of PTSD symptoms with anxiety symptoms was 0.75 ($P<0.001$) and with depressive symptoms it was 0.71 ($P<0.001$). The genetic correlation of anxiety with depressive symptoms was 0.54 ($P<0.001$) (Goenjian et al. 2008).

Bergemann et al. (2010) suggests that predisposing genetic factors likely reside on the mtDNA. Thus, the data strengthen the hypothesis that energy metabolism may be involved in the pathogenesis of depression.

Roche et al. (2009) supports for tryptophan hydroxylase-2 as a susceptibility gene for bipolar affective disorder. Zhang et al. (2009) gave the first evidence for the single nucleotide polymorphism rs778293 in G72 as a potential candidate in altering risk for borderline personality disorder (BPD) in the Chinese Han population. McAuley et al. (2009) found that HTR2A is associated with bipolar disorder.

Gressier et al. (2009) study suggests a significant effect of 5-HTTLPR genotype on antidepressant efficacy in depressed women but not in men, with both selective serotonin reuptake inhibitor (SSRI) and non-SSRI drugs. Villafuerte et al. (2009) suggest that an enhanced capacity of HTR1B or HTR1A transcriptional activity may impair desensitization of the autoreceptors during SSRI treatment.

Phosphodiesterase-4A expression is reduced in cerebella of patients with bipolar disorder (Fatemi et al. 2008). Brain-derived neurotrophic factor (BDNF) plays an important role in the survival, differentiation, and outgrowth of selected peripheral and central neurons throughout adulthood. Growing evidence suggests that BDNF is involved in the pathophysiology of mood disorders (Liu et al. 2008). Grigoroiu-Serbanescu et al. (2008) support for the involvement of genetic variation in TPH2 in the aetiology of bipolar I disorder.

Iatropoulos et al. (2009) found association study and mutational screening of SYNGR1 as a candidate susceptibility gene for schizophrenia. Zuo et al. (2009) shows that DTNBP1 is a risk gene for schizophrenia in European-Americans. Variation at DTNBP1 may modify risk for schizophrenia in this population.

Some of the HLA antigens are associated with schizophrenia and significant increase were observed for HLA A*03 antigen along with the significant decrease for HLA A*25, A*31 and HLA B*51. The study provides the evidence for the possible existence of susceptibility locus for schizophrenia within the HLA region. This preliminary observation may help to understand the aetiological basis of this disorder and the study may further strengthen the HLA antigens as the marker for schizophrenia (Singh et al. 2008).

Evidence for association between structural variants in lissencephaly-related genes and executive deficits in schizophrenia or bipolar patients from a Spanish isolate population has been found by Tabarés-Seisdedos et al. (2008). Polymorphisms in the BDNF gene may be associated with variation in frontal lobe

morphology. Associations seem to be stronger in patients with schizophrenia than in healthy controls (Varnäs et al. 2008).

-141C Ins/Del polymorphism of the dopamine D2 receptor gene is associated with schizophrenia in a Spanish population (Lafuente 2008).

Reduced PON1 activity in patients and their relatives might result from the combined effects of more than one polymorphic variant in PON1 or other genes and/or increased oxidative stress, supporting the hypothesis that reactive oxygen species-mediated cellular damage might contribute to the neuropathology of schizophrenia (Kucukali et al. 2008).

Recent evidence has identified the NR4A1 (NUR77, NGFI-B) gene as a strong candidate for involvement in tardive dyskinesia (TD). The NR4A1 single nucleotide polymorphism (SNP) marker rs2603751 showed a nominal association with the risk of TD, as well as with the extent of TD based on the Abnormal Involuntary Movements Scale (AIMS) scores. The haplotype generated by the markers rs2603751 and rs2701124 also showed association with TD and, after adjustment for multiple testing, both the NR4A1 marker rs2603751 and the haplotype continued to show a trend toward association with TD (Novak et al. 2010).

Koefoed et al. (2010) suggests that the chlecystokinin (CCK) system may play a role in the pathogenesis of panic disorder (PD), with susceptibility alleles both protecting and contributing to the disease. Both common and rare variants seem to be involved. The involvement of the CCK system may also contribute to the increased prevalence of PD in women.

Markunas et al. (2010) suggested that SLC9A9 may be related to hyperactive-impulsive symptoms in attention-deficit/hyperactivity disorder (ADHD) and the disruption of SLC9A9 may be responsible for the behavioural phenotype observed in the inversion family. The association with SLC9A9 is particularly interesting as it was recently implicated in a genome-wide association study for ADHD. Further investigation of the role of SLC9A9 in ADHD and other behavioural disorders is warranted.

Elia et al. (2009) suggests the strongest signal emerged from SNPs in the promoter region (rs3808585) and in an intron (rs17426222, rs4732682, rs573514) of ADRA1A, all located within the same haplotype block. Some of the SNPs in HTR2A and COMT have already been reported by others, whereas other SNPs will need confirmation in independent samples in ADHD.

Raznahan et al. (2009) found serotonin transporter genotype and neuroanatomy in autism spectrum disorders. Mohammad et al. (2009) found that aberrations in folate metabolic pathway and altered susceptibility to autism.

van der Vegt et al. (2009) found that high activity of monoamine oxidase A is associated with externalizing behaviour in maltreated and nonmaltreated adoptees.

Jessen et al. (2010) concluded that they did not replicate the Val66Met effect on hippocampal volume in neither patients with major depression nor in healthy participants whereas recently, an association of the Val66Met polymorphism of the BDNF with hippocampal volume in patients with major depression has been reported.

Prata et al. (2009) supports the hypothesis that NRG1 may play a role in the development of bipolar disorder, especially in psychotic subtypes, albeit with different alleles to previous association reports in schizophrenia and bipolar disorder.

Lind et al. (2009) suggests that DAT1 genetic variation influences drinking behaviour in the Finnish population, where the rs6350 A and rs463379 G alleles provide a protective role against high alcohol consumption and alcohol dependence, respectively. A systematic search for DAT1 variants that affect gene function or expression in the Finnish and other populations is warranted.

Briant et al. (2010) provides evidence for an association of two variants of the OPRL1 gene, rs6090041 and rs6090043, with vulnerability to develop opiate addiction, suggesting a role for nociceptin/orphanin FQ receptor in the development of opiate addiction. Philibert et al. (2010) found that genetic variation at or near the GABRA2 locus significantly affects vulnerability not only to alcohol dependence, but to other forms of substance use including nicotine dependence and cannabis dependence, and that the effects may be sex dependent.

Kinnally et al. (2009) suggested that gene-environment interactions influenced not only disadvantageous outcomes, but also sensitivity to features of the environment that could alleviate these outcomes.

The heritabilities found in a multigenerational family study indicated that the genetic make-up of some individuals rendered them substantially more vulnerable than others to develop symptoms of PTSD, anxiety, and depression. A large proportion of the genetic liability for PTSD, anxiety, and depression were shared. The findings offered promise for identifying susceptibility genes for these phenotypes (Goengen 2008).

Mutations in the gene SLITRK1 (Slit and Trk-like 1) have been reported in patients with Tourette's disorder but, no evidence for SLITRK1 playing a major role in Tourette's disorder (Zimprich et al. 2008). PDE4A expression is altered in patients with bipolar disorder and provide potential new therapeutic avenues for treatment of this disorder (Fatemi et al. 2008).

Dehning et al. (2010) found a nominally significant association between both polymorphisms in the HTR2C and the Gelles de la Tourette syndrome, which was more pronounced in male patients.

The dyslexia susceptibility locus 2 on chromosome 6p21-p22 is one of the best-replicated linkage regions in dyslexia. Ludwig et al. (2008) suggested a complex deletion/compound short tandem repeat (STR) polymorphism in intron 2 of DCDC2 as the causative mutation. Evidence for linkage was found on chromosomes 1, 4, 9, and 18. The highest linkage peak was found on chromosome 9p at marker D9S286 with a logarithm of odds score of 3.548 (empirical P=0.0001). Chromosome 9: linkage for BPD features (Distel et al. 2008).

There is evidence for an association between structural variants in genes for lissencephaly, which are involved in neuronal migration, and prefrontal cognitive deficits in schizophrenia and bipolar patients (Tabarés-Seisdedos et al. 2008).

Conclusion

Genes encode proteins, not psychiatric symptoms or mental illnesses. The subtle molecular abnormalities encoded by genes do not cause mental illness but can bias brain circuits toward inefficient information processing, which may lead to mental illness under certain circumstances. Advances in genetics will make a major impact on clinical psychiatry, and should bring practical benefits for both prevention and treatment.

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