

Genetic Approaches-Investigating Psychiatry

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Abstract

Rational and logical answers have been the basis of all the sciences. Many questions in the understanding of psychiatric psychopathology and symptoms are rationally understood and a lot more are revealing due to the development of modern investigative techniques. Genetic factors are under active and extensive research for better understanding of psychiatric illnesses. And these approaches have undergone a paradigm shift in the recent times. From basic molecular genetics to the pharmacogenetics, a lot many tools are in the kitty of the investigators. The study of these genetic factors, development of genetic techniques, vis-a-vis the interaction with other factors is an active area of interest.

Keywords: Psychiatry; Genetics; Molecular; Investigation

Introduction

Although the study of phenomenology forms the basis of understanding the psychopathology, the advent of genetic techniques has been complimentary to this newly growing branch of science. With the field of psychiatric genetics experiencing a paradigm shift, the established genetic basis ranges from 70% to 85% in the major psychiatric disorders [1-3]. Research has consistently shown that genetic factors are important in the aetiology of psychiatric disorders and variation in “continuously distributed” psychological traits (such as personality and IQ) but the pattern is not simple [4] this implies that psychiatric disorders are probably caused by the interaction of genetic and environmental factors. Linkage analyses continue to be largely disappointing-even though some loci can be confirmed; positional cloning is considered an unlikely route to identify genes involved in most psychiatric disorders. Co-morbidity and diagnostic uncertainties continue to plague the field. The realization that many susceptibility alleles will be common variants rather than rare mutations makes necessary new approaches to the design, analysis and interpretation of psychiatric genetic studies [5]. The human genome is diploid and consists of 50,000-100,000 genes arranged on 23 pairs of chromosomes carrying the whole blueprint information for sustainability and extinction. To study the genetic influences the most common approaches have been the studies of families, of twins, and of people who have been adopted. These methods are sometimes grouped together under the heading kinship research. The second area is molecular-genetic research, which attempts to pin down the actual genes that researchers believe underlie various traits and disorders [4]. There have been different ways of understanding the influences of genetic and environmental factors on psychiatric disorders. A few of these are described herein.

Molecular Genetics/Biology

The advent of recombinant DNA technology allows scientists to study DNA directly. DNA markers are abundant and present throughout the human genome. In recent years, there has been a rapid increase in the number of molecular genetic investigations of major psychiatric disorders. Molecular genetics is concerned with the search for the mutations, which are responsible for a disorder or which influence its development or outcome [6]. The ultimate aim is to pinpoint the specific mutation within the defective gene, which is responsible for or has an influence on the disease.

The Candidate Gene Approach

A candidate gene is a gene for which there is a prior reason to suggest its involvement in the pathophysiology of the disorder. One current strategy is to identify plausible candidate genes for study. Once a gene has been identified as a candidate gene, it is systematically assessed to determine if, and to what extent, the candidate gene contributes to disease liability. In the case of major psychoses, there are many genes that fall into this category [7]. One of the examples is serotonin transporter gene. Since its discovery in 1996, a serotonin transporter promoter polymorphism (5-HTTLPR) has been cited in more than 100 publications searching for association with traits ranging from compulsive buying through depression to alcoholism and PTSD. Low levels of serotonin degradation products in the cerebrospinal fluid of aggressive and/or suicidal men or monkeys is among the most replicated physiological findings in psychiatry which was latter replicated at human level [8]. Many recent investigations have suggested that the 5HTTLPR polymorphism has a role to play in human depression [9]. Novel techniques such as single nucleotide polymorphisms (SNPs) scored on DNA chips are likely to revolutionize association studies by allowing for simultaneous testing of possibly thousands of candidate genes.

Linkage Analysis

Linkage is said to occur when two genetic traits are co-inherited rather than independently inherited as predicted by Mendel's second law. If the two genetic traits are caused by genes that exist close together on the same chromosome, then recombination between them will occur very rarely during meiosis [6]. The two genetic traits will be

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passed on to subsequent offspring en masse. Linkage analysis and the role of linkage genes have been researched widely in disorders ranging from mood disorders to psychosis to childhood psychiatric disorders [10-13].

Association Study

An alternative method to linkage analysis is association study. This method looks for an association between one allele of a genetic polymorphism and the disease. If a mutation contributes to a disease then, clearly, it will occur more frequently in patients than in controls. Genetic polymorphisms very close to the mutation that contributes to disease are unlikely to be separated because the chance of a recombination event occurring between them is very low. Thus certain alleles at that polymorphism will also occur more frequently in patients than in controls. This phenomenon is often detected between DNA markers from the same location, and is known as linkage disequilibrium. This method has been used successfully in HLA associated diseases [6].

Epistatic Interaction of Genes and Multigenic Inheritance

In addition to heterogeneity, it is anticipated that to increase risk for many complex disorders, multiple deleterious genetic variants are required in combination. This is called multiplicative, epistatic, oligo- or multigenic inheritance [14-16]. Such inheritance is indicated when the risk to very close relatives of those affected is high, but decreases rapidly in more distant relatives, as is observed in both schizophrenia and bipolar disorder [15,17]. To date, autism provides the best evidence for this type of multigenic inheritance [18].

Endophenotypes or Trait Markers

The basic idea of endophenotypes, or trait markers, is to find a trait that is more common in affected individuals than in the general population, but also displayed often by unaffected relatives, marking these individuals as carriers of one of the predisposing alleles. Such a trait should be heritable, frequent in 'high-risk' subjects (parents, siblings or offspring), stable over one's lifetime, and unaffected by medication use [19]. Several potential traits have recently been identified. A low response to alcohol is common in offspring of alcoholics and is predictive of future alcoholism [20].

Psychopharmacogenetics

Psychopharmacogenetics may improve patient care by helping the clinician to individualize a patient's treatment plan based on the individual's genotype at some informative genetic marker [21]. For example, individuals suffering from major depression, obsessive-compulsive disorder, PTSD or several other psychiatric disorders respond favorably to selective serotonin re-uptake inhibitors (SSRIs). However, ~30% of patients do not improve on SSRIs which were homozygous for the low-activity form of 5-HTTLPR [22].

Conclusion

From the above discussion the face of molecular genetics in the field of psychiatry looks promising. However the limited applicability and coverage of individual investigating technique warrants for individualisation of these techniques. The study of genetic endophenotypes and candidate genes look to be at the horizon of new change in genetic research. The use of basic logical techniques like family studies, twin studies and adoption studies still remain at the epitome of standard ground making in psychiatric genetics and are

irreplaceable. The advent of biological and genetic markers will try to give the one to one association in this field but will not and should not surpass the need of emotional and human touch by the professionals in the field of psychiatry. The advent of newer techniques and the role of environment in genetic modulation will further help in marking the genetics of psychiatric illness.

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none

Competing Interests

The authors declare that they have no competing interest.

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