Neuropsychiatric Disorders and Their Genetics

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Introduction

Adult-onset Neuropsychiatric Disorders (e.g., schizophrenia and bipolar disorder) and Neurodegenerative Diseases (e.g., Alzheimer's Disease (AD), Parkinson's Disease (PD), and Fronto Temporal Dementia (FTD)) are common but etiologically complex disorders of the adult brain that cause significant emotional and financial burdens for patients, relatives, caregivers, and the state. Although both genetic and nongenetic variables play a role in susceptibility to these diseases, a slew of family, twin, and adoption studies show that genetic factors play a significant part in the genesis of these disorders. It was believed that identifying these genetic variables would give a way to understand more about the brain or biochemical mechanisms behind these disorders, as well as a reasonable foundation for developing successful treatments. Early genetic studies in Alzheimer's and Parkinson's disease have backed up this theory. Traditional genetic linkage approaches, together with educated predictions about candidate genes in the linked chromosomal intervals, were employed to map and clone multiple genes with causal mutations in these researches. Genetic linkage was one of the first methods for discovering genetic risk loci for mental diseases. Linkage studies are usually done in big families with several members who are sick, and they are based on the assumption that genetic markers within a few million nucleotide bases of a disease allele are more likely to be inherited with it. Within a family, co-segregation of the disease with a certain marker allele implicates the chromosomal region where the marker is placed in the condition. Linkage studies are best suited for Mendelian diseases with one or a few genetic loci exerting a substantial influence on risk, with considerable success in locating the Huntington's disease gene and those producing Alzheimer's disease early onset variants. However, despite decades of effort, linkage studies have failed to reliably identify risk loci for prevalent neuropsychiatric illnesses, showing that the genetic contribution to these disorders is neither simple monogenic nor oligo genic. These causal genes encode proteins that accumulate in the brain in these disorders [Amyloid Precursor Protein (APP) and tau], or proteins involved in the posttranslational processing of these accumulating proteins. Mutations in APP, a neurotoxic proteolytic product of which, the Aβ-peptide-peptide, is a key component of amyloid or senile plaques, have been discovered in Alzheimer's Disease (a pathological deposit in the brain of patients with AD). Schizophrenia (SZ), Bipolar Disorder (BD), Major Depressive Disorder (MDD), and Attention Deficit Hyperactivity Disorder (ADHD) are all prevalent but severely debilitating neuropsychiatric disorders. Despite the fact that they are thought to represent alterations in brain function, they are not accompanied by evident neuropathology, and the molecular mechanisms behind them remain largely understood. However, it is apparent that the majority of neuropsychiatric illnesses are at least partly heritable, and it has long been hoped that the discovery of susceptibility genes will give much-needed insight into their molecular aetiology, potentially leading to more successful therapies. Technological breakthroughs in genome analysis, along with huge sample sizes, have resulted in considerable advances in our understanding of the genetic architecture of major neuropsychiatric illnesses and the genetic loci implicated in these disorders during the last decade. The similar "positional cloning" method was used to find mutations in the presenilin genes (two homologous genes encoding polytopic transmembrane proteins). Following functional research, it was shown that the presenilins are components of new enzyme complexes involved in the physiologic -secretase proteolytic cleavage of Amyloid Precursor Protein (APP), and that mutation in this complex create an excess of a particularly neurotoxic isoform of Aβ (Aβ 42). The clearing of Aβ appears to be aided by a fourth AD gene, APOE, which was discovered using the same positional mapping method. In instances of FTD, a disease characterised by intraneuronal deposits of the tau protein, linkage mapping and candidate gene analysis led to the finding of mutations in the tau gene. Multiple genetic determinants interact in the setting of poorly understood environmental circumstances to produce clinically varied phenotypes in neurodevelopmental and neuropsychiatric diseases, resulting in complex characteristics. In a diversified genetic background, affected people have various risk alleles, making it challenging to find potential disease genes. Despite this challenge, hundreds of potential genes have been identified with DNA copy number variations or Single Nucleotide Polymorphisms (SNPs) from clinically diagnosed patients. Because of the efficacy of contemporary genetic screening tools, candidate genes for Autism Spectrum Disorders (ASDs), X-Linked Intellectual Impairment (XLID), Attention Deficit Hyperactivity Disorder (ADHD), and Schizophrenia have been identified (SZ). Whole-genome sequencing (exome capture) and computational techniques that combine protein interaction data have recently aided in the development of hypotheses about the molecular pathways and processes that are likely to underlying these illnesses. ASDs are a collection of clinically heterogeneous neurodevelopmental disorders with high genetic variation that affect 1–2% of the population. Despite the fact that extensive twin studies have revealed monozygotic concordance rates of up to 90% heritability, the underlying genetic variables remain largely understood. Only three genetic loci (5p14.113, 5p15.214, and 7q31–q35) show statistically significant association with ASDs, implying that common variation accounts for a modest percentage of ASD heritability. Recent copy number variation and SNP data, on the other hand, demonstrate that numerous uncommon variations exist in essential neuronal molecules that operate in synaptic connections.

Genome-Wide Association Studies

The basic purpose of Genome-Wide Association Studies (GWAS) and other genetic association studies are to elucidate the molecular pathways responsible for disease initiation, with the goal of eventually translating these findings into therapeutic practise. While GWAS and other genetic association studies have made significant progress in understanding many diseases, most neuropsychiatric disorders have yet to meet original expectations. This is owing to the difficulty in determining the biological effect of variations that have been found to be strongly linked to the condition. More philosophically, it is being widely recognized that understanding processes in biology requires examining interactions across the entire system, and this may be especially true for brain problems. The GWAS method is used to find statistically significant overrepresentation of certain Single-Nucleotide Polymorphism (SNP) alleles in a group of afflicted people compared to a healthy control group. This is done for a panel of hundreds of thousands of SNPs that have been chosen to "tag" each Linkage Disequilibrium (LD) block at least once across the genome. Because of the genome's LD structure, any detected variation will be surrounded by hundreds to thousands of additional variants that are likewise highly linked with the characteristic. The identification of the causal variation responsible for the statistical correlation of the tagged SNP and the variable under study is thus the first stumbling block in understanding GWAS data.