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A Brief Note on Genetic Epidemiology and Gene Discovery

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Abstract

A significant number of genes that have a significant impact on epilepsy have been identified in recent genetic research; however, the genes that have been identified so far only affect risk in a very small number of patients, primarily those whose families follow Mendelian modes of inheritance. For the upcoming ten years, it will be a major challenge to identify genes in genetically complex epilepsies that affect the vast majority of patients. The types of genetic mechanisms that could be involved, the study designs used to identify them and the findings of recent family and genetic studies of complex epilepsies are all discussed in this chapter. Understanding the relationship between genotype and phenotype is an extremely important goal for gene identification research because of the epilepsy's clinical and etiologic heterogeneity. In order to clarify the "phenotype definition" in the epilepsies, we examine two research designs: studies of family concordance and familial aggregation. These analyses may shed light on the extent to which the various clinically defined epilepsy syndromes differ in terms of their genetic contributions, assisting in the best way to identify epilepsy subgroups with susceptibility genes in common.

Keywords: Etiologic heterogeneity; Diabetes

Introduction

Over the course of the past two decades, more than 20 genes have been identified that have a significant impact on the risk of human epilepsy. These genes have helped some patients figure out what causes their condition and provided important clues to pathogenic mechanisms. However, the genes that have been identified up to this point only have an impact on the risk in a very small number of patients, most of who come from families that are consistent with Mendelian modes of inheritance. The majority of epilepsies do not have a significant family history, so identifying and defining the genetic mechanisms in these "complex epilepsies" will be a major challenge over the next ten years. In this article, we discuss the definition of "complex inheritance" as it relates to epilepsy, the results of the most recent research, and strategies that are most likely to be helpful for identifying genes in these types of epilepsy.

Identification of genetic variation associated with a disease risk may help provide insight into the mechanism of disease pathogenesis and reveal novel targets for preventive and therapeutic interventions in light of the growing body of evidence demonstrating the significance of genetic factors and gene-environment interactions in the etiology of common eye-related disorders. Genomic regions associated with highly penetrant genes related to uncommon familial forms of eye diseases have been identified through family-based research. However, complex phenotypes with late onset, such as age-related macular degeneration (AMD), appear to be polygenic, involving a number of genes at varying degrees of influence [1-4].

Discussion

Single nucleotide polymorphisms (SNPs), or variations in a single base of DNA, account for roughly 90% of human sequence variants. dbSNP, according to (available from: More than 14 million distinct mapped SNPs have been identified and compiled into a genome-wide database (http://www.ncbi.nlm.nih.gov/projects/SNP). The HapMap effort, which can be found at: http://hapmap.org) made it possible to reduce the number of SNPs needed to examine the entire genome to roughly a million representative SNPs, also known as tagging SNPs. This made genome scan methods more effective and less expensive for finding regions with genes that affect diseases.

Genome-wide association studies, also known as GWAS, have been developed over the course of the past few years with the goals of identifying novel disease-associated pathways and evaluating the relationship that exists between traits and a large number of DNA sequence variants that are spread out across the genome in an objective, hypothesis-free manner. In accordance with the common variant-common disease hypothesis of disease pathogenesis, GWAS are designed to identify common SNPs with an allele frequency greater than 5% that may only modestly increase disease risk. 561 GWAS have been reported and categorized at http://www.genome.gov/gwastudies as of this writing. Only in the last two years have more than 250 genetic loci been identified where common variants were consistently associated with a number of polygenic traits. However, despite the significant accomplishments of GWAS, their inconsistent nature is generally acknowledged as a drawback [5,6].

The extreme clinical and etiologic heterogeneity of the disorder is one of the most difficult issues for genetic research on epilepsy. A wide range of distinct syndromes are thought to have distinct pathogenic mechanisms, and the epilepsies, which are broadly defined as recurrent unprovoked seizures, are included in this category. However, it is unclear to what extent the various clinical entities also differ in terms of their genetic contributions; consequently, it is unclear which characteristics ought to be used to divide the epilepsies into subgroups that are likely to share susceptibility genes. We review two types of studies that have been utilized to advantage to elucidate shared and distinct genetic influences on various clinically defined subsets of epilepsy. This lack of clear information about the relationship between phenotype and genotype significantly impedes efforts to discover genes because it results in samples with uncontrolled heterogeneity and

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reduced statistical power. Additionally, each of these methods can be used to investigate the possibility of a genetic link between epilepsy and other disorders like depression or migraine [7,8].

Although the results of GWA studies have not yet been made available for the majority of epilepsy types, evidence from other complex disorders suggests that common variants probably only make a small contribution to the epilepsy genome as a whole. On the other hand, structural variation studies have shown that epilepsy genetic architecture is heavily influenced by rare genetic variants. The majority of rare variants are not represented on the panel of SNP genotypes investigated, either directly or indirectly (through high linkage disequilibrium), limiting the ability of GWA studies to identify rare variants with a frequency of less than 2%. Next generation sequencing (NGS), which can be applied to whole genomes or protein-coding regions (whole exome sequencing) at costs that are not prohibitive (at least on a small scale, to date), can now be used to investigate rare variants. Several recent studies have succeeded in identifying genes for Mendelian disorders, using very small numbers of patients or families. The majority of these studies focused on extremely rare Mendelian disorders with high penetrance, which is an ideal situation for disease gene detection (just However, the use of NGS is rapidly expanding to include disorders with more complex characteristics like locus heterogeneity and ambiguity regarding the definition of the phenotype. We are currently working on a study of whole genome sequencing in families with multiplex epilepsy, and another significant project is in the process of developing a collaborative NGS study of the epilepsies.

The development of study designs and statistical methods for the analysis of the large number of NGS-identified variants is one of the challenges in this field. In our current study of multiplex epilepsy families, we sequence two affected people in each family who are chosen to be as far apart from one another as possible and “connected” by family branches that also contain affected people. Genomic variants with a strong risk-raising effect are likely to be present in families with multiple affected members, and affected members of the same family are likely to have the same pathogenic variants. The sharing of variants between sequenced family members can be used as a "filter" to reduce the number of potentially causative variants for further analysis because it is unlikely that distant relatives will accidentally share rare variants. The possibility that two relatives have distinct genetic causes for their epilepsy is prevented by restricting access to distant relatives who are connected by family branches that also contain other people with the condition [9,10].

Conclusion

We have completed whole genome sequencing to an average coverage of 38 xs in two affected individuals from each of nine families with various forms of non-acquired epilepsy (an average of 6.2 affected individuals per family). The total number of variants averaged about 4.4 million per individual, but the number was reduced to an average of 108 per family by restricting to rare, shared, potentially functional (missense, protein truncating, or splice site-disrupting) variants. Genotyping of other family members to assess co-segregation with epilepsy and case-control analyses of larger cohorts are the planned follow-up studies.

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