

SUSCEPTIBILITY GENE FOR JUVENILE MYOCLONIC EPILEPSY RINGS TRUE

BRD2 (RING3) Is a Probable Major Susceptibility Gene for Common Juvenile Myoclonic Epilepsy

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Juvenile myoclonic epilepsy (JME) is a common form of generalized epilepsy that starts in adolescence. A major JME susceptibility locus (EJM1) was mapped to chromosomal region 6p21 in three independent linkage studies, and association was reported between JME and a microsatellite marker in the 6p21 region. The critical region for EJM1 is delimited by obligate recombinants at HLA-DQ and HLA-DP. In the present study, we found highly significant linkage disequilibrium (LD) between JME and a core haplotype of five single-nucleotide-polymorphism (SNP) and microsatellite markers in this critical region, with LD peaking in the BRD2 (RING3) gene (odds ratio, 6.45; 95% confidence interval, 2.36–17.58). DNA sequencing revealed two JME-associated SNP variants in the BRD2 (RING3) promoter region but no other potentially causative coding mutations in 20 probands from families with positive LOD scores. BRD2 (RING3) is a putative nuclear transcriptional regulator from a family of genes that are expressed during development. Our findings strongly suggest that BRD2 (RING3) is EJM1, the first gene identified for a common idiopathic epilepsy. These findings also suggest that abnormalities of neural development may be a cause of common idiopathic epilepsy, and the findings have implications for the generalizability of proposed pathogenetic mechanisms, derived from diseases that show mendelian transmission, to their complex counterparts.

gene has finally been identified. Why did it take so long? Genes for common, complex disorders are proving notoriously hard to track down, and very few successes have been recorded. Genetic heterogeneity was a major hurdle for the identification of *EJM1*. The gene was initially localized to the human leukocyte antigen (HLA) region on chromosome 6p (1). Subsequent mapping in additional families revealed that probably two different loci are located on chromosome 6p. With the development of a dense linkage marker set and the analysis of additional families, the chromosome 6p region appeared to separate into two distinct loci: one on chromosome 6p12, centromeric to the HLA region (2,3), and one on chromosome 6p21 (4,5). The 6p21 locus is the region where Pal and colleagues found association to *BRD2*. Unlike the previously identified epilepsy genes, *BRD2* or *RING3* (RING is an acronym for “really interesting new gene”) has been associated with a common form of epilepsy. Almost all of the previously identified epilepsy genes were found in rare families with relatively high penetrance of the phenotype. Most families with JME show a complex inheritance pattern, suggesting that several genes and/or environmental factors are involved.

Pal and colleagues analyzed 20 single nucleotide polymorphisms (SNPs) within the 6p21 region, in 20 probands with JME, and found strong association with eight SNPs in or adjacent to the *BRD2* gene. The associated SNPs did not lead to a change in the amino acid sequence; therefore Pal and colleagues went on to sequence *BRD2* in search of possible disease-causing mutations. No significant mutations were found. Does this mean that *BRD2* is not the JME gene, despite the strong linkage evidence? Not necessarily, because it was found that two of the SNPs are located in the promoter region of *BRD2*. Polymorphisms occurring in promoter regions upstream of genes may potentially affect the process of transcription, whereby RNA polymerase is recruited to the gene and messenger RNA (mRNA) is synthesized. This complex process requires the coordinated action of multiple regulatory proteins through complex protein–DNA and protein–protein interactions. Variation in the DNA sequence may potentially alter the affinities of existing protein–DNA interactions or even recruit new proteins to bind to the DNA, altering the specificity and kinetics of the transcriptional process. The effect of the *BRD2* SNPs on promoter function is currently unknown, but they may alter the timing, tissue specificity, or level of *BRD2* expression.

COMMENTARY

The juvenile myoclonic epilepsy gene (*EJM1*) was one of the first human epilepsy genes to be mapped (1). Fifteen years after this first report of linkage between juvenile myoclonic epilepsy (JME) and chromosome 6p, a possible susceptibility

BRD2 (a bromodomain containing protein) is a putative nuclear transcriptional regulator that is found in the human brain and is believed to play an important function in the development of the central nervous system. Imprecise regulation of brain development is an attractive hypothesis for the cause of JME, given recent evidence of subtle cerebral structural abnormalities in JME patients (6). These abnormalities may result in disorganized neuronal connectivity and regions of neocortical hyperexcitability, leading to clinical seizures.

It is likely that a “pool” of JME susceptibility genes exists, and that inheritance of two, three, or more of these genes is required to develop JME. Altered transcription of *BRD2* may not have severe consequences by itself but could lead to JME when combined with variants at interacting loci; hence the complex inheritance pattern. Although the precise function of the bromodomain remains to be elucidated, it has been suggested that it may mediate protein–protein interactions. Pal and colleagues suggest that the other JME susceptibility loci may be genes that produce proteins that interact with BRD2. The development of the human brain is an incredibly complex process, precisely regulated by hundreds of genes. It is possible that slight variation in just a few of these genes is sufficient to cause epilepsy.

In conclusion, Pal and colleagues have provided convincing evidence that subtle variation in *BRD2* results in increased susceptibility to JME. The exact mechanism involved remains to be determined, and many questions still remain regarding the genetics of JME. What are the other genes involved in increasing susceptibility to JME; how many susceptibility genes will there be? Will they be associated with other forms of idiopathic generalized epilepsy? As more epilepsy families are studied and SNP genotyping technologies continue to improve, the answers

will follow. This is an exciting discovery for the field of epilepsy, as *BRD2* is the first susceptibility gene identified for a common type of epilepsy with complex inheritance.

by Robyn Wallace, Ph.D.

References

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