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Genetics of idiopathic generalized epilepsy: An overview

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Abstract

Idiopathic generalized epilepsy (IGE) is a common type of epilepsy. Strong support for a genetic role in IGE comes from twin and family studies. Several subtypes of IGE have been reported but families often have members affected with different subtypes. Major advances have been made in the understanding of genetic basis of monogenic inherited epilepsies. However, most IGEs are complex genetic diseases and some susceptible IGE genes are shared across subtypes that determine subtypes in specific combinations. The high throughput technologies like deoxyribonucleic acid microarrays and sequencing technologies have the potential to identify causative genes or loci in non-familial cases.

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Full Text

Introduction

Epilepsy is a chronic neurologic disorder with a prevalence of 3-6/1000 world-wide. [1] There are many types of epilepsies and many factors such as neurotransmitters, transporters, granule cells, voltage gated ionic currents and non-neural proliferation have been suggested to act as major players in this disorder. [2],[3] Idiopathic generalized epilepsies (IGE) are common seizure disorders and represent

electro-clinical syndromes, in which a combination of clinical features such as seizure types, age of onset and electroencephalogram (EEG) features (generalized spike wave) are required for diagnosis. The Commission on the Classification of the International League Against Epilepsy defined IGE as "IGEs are forms of generalized epilepsies in which all seizures are initially generalized (absences, myoclonic jerks and generalized tonic-clonic seizures), with an EEG expression that is generalized bilateral, synchronous, symmetrical discharge (such as is described in seizure classification of the corresponding type). [4] The patient usually has a normal inter-ictal state, without neurological or neuroradiologic signs. In general, inter-ictal EEGs show normal background activity and generalized discharges, such as spikes, polyspike spike-wave and polyspike-waves ≥3 Hz. The discharges are increased by slow sleep. The various syndromes of IGEs differ mainly in age of onset. No etiology can be found other than a genetic predisposition toward these disorders."

IGEs fall into several common and rare recognizable sub syndromes. Among these childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME) and epilepsy with generalized chronic tonic seizures represent the more common sub syndromes of IGE. In addition to this several rare IGE syndromes have been identified, many of which may be associated with some intellectual disability. These syndromes include benign myoclonic epilepsy of infancy (BMEI), early onset epilepsy, myoclonic astatic epilepsy, epilepsy with myoclonic absences, eyelid myoclonic with absences and absence status epilepsy.

Genetics of Idiopathic Generalized Epilepsy

A strong support for the genetic role in epilepsies comes from twin studies, that have shown concordance rates to be consistently higher in monozygotic twins in comparison with dizygotic twins. [2],[5],[6],[7],[8],[9] The IGEs are supposed to be genetic disorders and the research in this direction has allowed the identification of several genetic alterations responsible for the disease. Until date, about 2-8% of IGEs are considered to be monogenic. [10] In majority of the monogenic epilepsies the variants of the genes encoding ion channel subunits (for e.g., voltage-gated Na and K channel subunits) that mediate neuronal excitability and whose loss or gain of function results in abnormal generation and propagation of action potentials, have been reported to be associated with the disease. [11] In addition to this, genes coding for non-ion channel proteins have also been shown to be involved in the development of the disease. However, in these cases identification of epileptogenic mechanisms responsible for seizure induction is not clear and functional interaction with ion-channels is supposed to be involved. However, most IGEs are complex genetic diseases. Although they occur with a greater frequency in relatives of affected individuals yet they do not follow a single Mendelian inheritance pattern. [12] This might be on account of involvement of multiple genes simultaneously. Therefore, diversity of susceptible genes collaborate in determining the disease risk. [13] This article reviews the genetic variants involved in the various types of IGEs.

Childhood Absence Epilepsy and Juvenile Absence Epilepsy

CAE is one of the most common IGEs. The age of onset is between 4 and 8 years peaking at 6-7 years. The reported prevalence of CAE was 10-12% in children with epilepsy younger than 16 years of age. [14],[15] Typical absences are the only seizure type. CAE has been mapped to chromosome 20q where the CHRNA4 gene has been speculated to be responsible. [16] It has also been mapped to chromosome 8q24.3 [17] where the haplotype and recombination analysis of family members reduced the CAE region

to 1.5 MB flanked by D8S554 and D8S502. The LOD score of 4.110 was obtained at D8S534. [18] However, a replication study by Sander et al. could not support this finding. [19] The another study by Delgado-Escueta et al., reported linkage to chromosome 1p in families whose probands had CAE evolving into JAE. JAE has been reported to occur between 9 and 12 years of age and is mainly characterized by typical absences similar to those in CAE but, much less frequent and not as severe. [13] Random infrequent myoclonic jerks and infrequent generalized tonic-clonic seizures (GTCS) occur in most of the patients. A candidate gene study approach reported an allelic association with a GLU R5 kinate receptor gene (GR1K1 polymorphism) in an affected family. A common variant A118G (rs1799971) of human μ-opioid receptor gene (OPRM1) has been implicated in the pathogenesis of idiopathic absence epilepsy (IAE). It results in Asp replacing Asn and the Asp variant displays 3 fold greater affinity for β-endorphin. [20] This polymorphism has also been shown to affect the expression of OPRM1. [21] A significant association of this polymorphism with IAE was reported. [22],[23] Barratt et al. investigated the association of 5 SNPs including A118G with IAE. However, none of these SNPs was found to be associated with the disease. [23]

Genome-wide association studies (GWAS)

A GWAS including 3020 patients with genetic generalized epilepsies (GGE) and 3914 controls of European ancestry was carried out by EPICURE Consortium and EMINet Consortium [24] in order to search for susceptibility genes conferring the risk for genetic absence epilepsy (GAE). A genome-wide Stage-1 association scan was carried out including 702 patients with GAEs of North-Western European origin along with 2461 ethnically matched controls. Four chromosomal regions of strong LD contained at least 4 SNPs with PLMM < 1.0 × 10− 5 at (i) 1q31.1within PLA2G4A gene coding the cytosolic phospholipase A2 group 4A (rs72709849), (ii) at 2q22.3 (rs10496964), (iii) in the 4q31.23 (rs10030601) and (iv) at 2p 16.1 (rs2717068). Based on combined Stage-1 and 2 analysis a significant association of GAEs with 2p16.1 locus (rs2717068) was observed. [24]

Juvenile Myoclonic Epilepsy

JME or Janz syndrome is the most common IGE and is characterized by myoclonic, absence and generalized tonic-clonic seizures and is widely accepted to be genetic in origin. However, its mode of inheritance remains controversial. JME accounts for approximately 12-30% of all epilepsies. [25] Two major and two minor subsyndromes have been identified which account for most of the JME cases. [26] The first major subsyndrome is classic JME with no absences and accounts for approximately 72% of all JMEs. The second major subsyndrome, childhood absence evolves to JME and affects 18% of all JME cases. The two minor subsyndromes consist of adolescent myoclonias and grandmal convulsions with absences which start during adolescence and after age of 18 years.

The role for BRD2-a transcriptional regulator (RING3 belongs to a highly conserved subfamily of double bromodomain-containing proteins) is unclear in humans however, it regulates brain development and errors in regulation might explain the basis of development of JME. Variants in this gene may result in disorganized neuronal connectivity and neocortical hyperexcitability. [27] SNPs in BRD2 (RING3) gene located on chromosome 6p21.3 have been found to be associated with the susceptibility of autosomal recessive JME cases among families from New York. [27]

A study of Greenberg et al. used both case-control and family-based association studies and identified malic enzyme 2 (ME2)-centered, 9 SNPs haplotype on chromosome 18q. [28] In this study an increased risk to IGE was found when ME2- centered, 9 SNPs haplotype were present in the homozygous state. The

results obtained from the above two studies clearly suggest that BRD2 gene in 6p21.3 epistaticaly interacts with ME2 gene in 18q to cause JME phenotypes.

Mas et al. studied susceptibility SNPs in JME families from the UK and Sweden, by sequencing the gene Cx-36 in 29 JME probands previously linked to 15q14 locus and were unable to find any epilepsy causing mutation that segregated with affected members. [29] However, a case-control study found a significant association between JME and c. 588T polymorphism within exon2 of the Cx-36 gene. It was found that subjects bearing TT genotype had a significantly increased risk for JME (OR - 4.3) compared with the subjects with CC genotype. [30]

The susceptibility polymorphisms i.e., BRD2 in chromosome 6p21.3; Cx-36 in chromosome 15q14; and ME 2 in chromosome 18 were also hypothesized to interact epistaticaly as minor epilepsy genes in the homozygous state, necessary but not sufficient alone to produce a JME phenotype.

EFHC1 (EF hand containing calcium binding protein) gene encodes for EF hand containing calcium binding protein which might play a role in calcium homeostasis. Myoclonin 1/EFHC1 is one of the most common genes involved in cell division, apoptosis and survival as well as postsynaptic calcium homeostasis through R-type voltage - dependent calcium channels. Several missense, nonsense, frameshift-deletion and deletion mutations in EFHC1 gene have been identified in 6 separate cohorts causing JME. [31]

GABRA1 are ligand gated chloride channels responsible for inhibitory functions in the central nervous system. [32] The GABAa receptor is a heteropentameric protein complex consisting of 19 different classes of subunits. The mutations in the GABARA1 receptor gene have been confirmed in one absence family from France and a large French Canadian JME family. [33]

A study evaluating the association of GABRA1 Ala322Asp mutation in JME families from India, found that this mutation is not associated with JME in these families. [34] They further compared allele frequencies at two marker loci D5S2118 and D5S422, flanking GABRA1, in probands and matched controls. One of the allele frequencies at D5S422 was significantly different between the cases and controls suggesting an association between the genes located in the proximity of the deoxyribonucleic acid (DNA) marker with JME. [34] Another study from North India has evaluated the association between Bromodomain-containing protein 2 (BRD2), Linkage Group 14 (LG14) and GABRG2 gene variants with JME and provided an evidence for an association between - 198A/T polymorphism of BRD2 gene and JME. In addition to this, a positive association for the dinucleotide polymorphism 1914GC/AT of the LG14 gene with JME was also established. [35]

Chloride currents have also been reported to get altered in case of chloride channel (CLCN2) gene mutations because anomalies of CLCN2 channels determine the impairment of chloride efflux, with intracellular accumulation of chloride. Several mutations in CLCN2 gene have been found to be segregated in affected members of a large German JME family. Mutations in CLCN2 have also been observed in rare families from Brussels and Belgium. [36]

Calcium channel beta 4 subunit (CACNβ4) has not been identified to be a putative JME gene because its mutation did not segregate in affected family members and was found in only a single member of JME family from Germany. This has not been replicated further. [37]

GWAS

A genome wide Stage-1 association scan was carried out in 586 JME patients of North-Western European origin and 2461 ethnically matched controls to determine the susceptible genes conferring the risk for

JME. The gene located on chromosome 1q43 (rs12059546) encoding the M3 muscarinic acetylcholine receptor (CHRM3) and MAST4 gene located on chromosome 5q12.3 encoding the microtubule-associated serine/threonine kinase 4 (rs39861) showed a prominent association. Further Stage-2 replication analysis was carried out for five top-ranked Stage-1 SNPs with PLMM <1.0 × 10− 5 including 166 parent-off-spring trios of children with JME and a case-control sample consisting of 382 European JME patients and ethnically matched controls. The combined Stage-1 and 2 analysis revealed a significant association of JME with Chr1q43 (rs12059546) which codes for CHRM3. [24]

Copy number variants

Apart from SNPs, copy number variations (CNVs) have increasingly been recognized in IGE/GGE including JME. The CNVs contain submicroscopic deletions and duplications of chromosomal material, including rearrangements at genomic hotspots and also duplications and deletions with unique breakpoints. [38] Although Lemke et al., in their study had reported some cases of JME due to structural genomic variations including microdeletions in 22q11.2, [39] the interest in CNVs gained momentum only after the first descriptions of 15q13.3 microdeletions in intellectual disability and epilepsy [40] Taken together the data from existing epilepsy studies, 15q13.3 microdeletion has been identified to represent a significant risk factor for IGE/GGE with an odds ratio of 68. [41],[42],[43] 56% of the IGE/GGE probands had JME including one patient with CAE evolving to JME. After the identification of 15q13.3 microdeletions, some other microdeletions like recurrent variants at 15q11.2 and 16p13.11 were identified in JME. [43],[44] However, the risk conferred by these variants is smaller compared to 15q13.3 microdeletions. All these three variants share a common genetic architecture and represent the so-called "genetic hotspots." [45] In addition to these, several large genetic rearrangements have also been identified in up to 6% patients with JME. [46] Genetic findings from monogenic families have always supported the channelopathy concept of IGEs. [47] However, the current studies on both recurrent and non-recurrent structural genomic variations have found only few ion channel genes covered by pathogenic variants. The 15q13.3 microdeletion spanning the Neuronal acetylcholine receptor subunit alpha-7 gene (CHRNA7) represents the only recurrent structural genomic variation associated with JME covering an ion channel gene. The 15q13.3 microdeletion has been found to be absent in large cohort of patients with temporal lobe epilepsy [44] which suggests novel phenotypic boundaries, which can be unraveled through genetic studies. Although GWAS have been successful in identifying the genes associated with wide range of common human diseases, this has been less successful in seizure disorders. [48] Since the genetic contribution of monogenic variants as well as common variants has been found to be limited, the rare variants with an intermediate risk are expected to account for a larger part of the so-called "missing heritability" of human disease. [38] The CNVs provide first insight into the genetic properties of these variants. The risk conferred by the recurrent microdeletions including variants at 15q13.3, 15q11.2 and 16p13.11 appears exceedingly large in comparison with the small risk conferred by many variants identified through GWAS. [49] Therefore, CNVs have a vast potential to probe the genetic architecture and identifying the rare genetic variants in JME. Emerging high-resolution platforms have a lot of potential to identify the smaller CNVs and therefore, increase the yield of CNV studies in JME.

Epilepsy with Generalized Tonic-clonic Seizures

This term denotes an idiopathic propensity to mainly or exclusively GTCS that occur mostly within 2 h after awakening from sleep. [50] The seizures may also occur when the patient is awake at times of relaxation and leisure. Neuronal voltage gated sodium channels have been reported to be responsible for the generation and propagation of action potentials in the brain and peripheral nervous system. Mutations in the genes encoding sodium channel α and β1 subunits have been associated with genetic forms of

epilepsy. [37],[51],[52],[53],[54] Several missense mutations in SCN1A gene have been identified in probands affected by the syndrome of intractable childhood epilepsy with generalized clonic tonic seizures (ICEGTC). Rhodes et al. characterized 8 ICEGTC missense mutations by whole cell patch clamp recording of human SCN1A heterogeneously expressed in cultured mammalian cells. [54] Two mutations (G979R and T1709I) were found to be non-functional. The remaining alleles T808S, V983A, N1011I and F1808L were found to exhibit measurable sodium current but, had a heterogeneous biophysical phenotype. The SCN1 mutations associated with ICEGTC resulted in a wide spectrum of biophysical defects including mild to moderate gating impairments, shifted voltage dependence and reduced use dependence.

Benign Myoclonic Epilepsy of Infancy

BMEI is initially characterized by the occurrence of myoclonic seizures in the first 3 years of life in developmentally normal children. No other types of seizures except for simple febrile seizures are usually observed. [55] A family history of epilepsy has been reported in about 30% of the cases. [56] The BMEI account for 2% of all GE and <1% of all the epilepsies in an unpublished data for Centre Saint-Paul in Maseilles. It has been suggested that neurodevelopment outcome depends on early recognition and proper treatment. Treatment is favorable in the great majority but mild mental retardation is observed in some cases and therefore, the real benignity of the syndrome has been questioned. [55] This entity is characterized by partial seizures that appear in the 1 st year of life in otherwise normal infants. [57],[58] A family history of similar seizures is frequent and an autosomal dominant mode of inheritance with incomplete penetrance has been suspected. [59] Linkage to chromosome regions 19q, 2q24 and 16 p12-q12 has been suggested. [59],[60] However, no specific genes have been identified so far.

Genetic influences have been shown to play a major role in GEs than in focal epilepsies. [2] More than two dozen genes have been examined as possible candidates. Most of the studies turned out to be negative and therefore no further replication attempts were made on this. In fact, no clear susceptibility gene has yet been identified for its association with IGE except for opioid receptor μ-subunit gene. [22], [61] Tan et al., have summed up all the studies into 4 groups: (a) Positive studies that are replicated (b) initial positive studies that could not show a positive association in subsequent replication studies (c) weakly positive studies without any replication attempts and finally (d) the negative studies. [62] Further CNVs have been demonstrated to collectively explain a larger portion of IGEs than any single gene. Structural genomic variations have also been associated with IGEs using chromosome microarray analysis. [63]

Heinzen et al. compared the exome sequences of 118 subjects with IGE and 242 controls of European ancestry using next-generation sequencing. The subjects belonged to two forms of IGE, including JME and CAE. [64] The results of the study suggested that moderately rare variants with intermediate effects of the so-called "goldilocks alleles" do not play a major role in the risk of IGE. [64],[65] The results of this study also suggested that the pathophysiology of epilepsy might be far more complex than simply a disorder of disrupted ion channels. [64]

The genetic testing techniques are evolving at a rapid rate and whole genome or whole exome sequencing is being performed at increasingly cheaper costs. This will allow rapid discovery of other mutations, CNVs as well as the variants in non-coding DNA. However, we need to understand how these genetic variations will interact with environmental factors and modulate the clinical spectrum of the disorder.

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