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# Idiopathic epilepsy of childhood and potassium ion channels

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## Abstract

The etiology of common idiopathic epileptic syndromes is genetically determined, but the complex pattern of inheritance suggests an epistatic interaction of several susceptibility genes. Mutations in over 70 genes now define biological pathways leading to rare monogenic forms of epilepsy in humans and animals. Recognizing the molecular basis of an ion-channel disease has provided new opportunities for screening, early diagnosis, and therapy of these conditions.

Potassium can affect the development of common seizure type and can be defined seizure susceptibility allele. The existence of inward-rectifying potassium (Kir) channels was first recognized half a century ago. The biophysical fingerprint of Kir channels is inward rectification in the current-voltage relationship, which limits potassium efflux at depolarizing membrane potentials. Kir channels are essential in the control of resting membrane potential, coupling of the metabolic cellular state with membrane excitability, and maintenance of potassium homeostasis. The critical interval contains several candidate genes, one of which, KCNJ10, exhibits a potentially important polymorphism with regard to fundamental aspects of seizure susceptibility. Deletion of KCNJ10 as a seizure susceptibility gene that code for inward rectifier potassium ion channels imparts protection against seizures results in spontaneous seizures and increased seizure susceptibility. The unique role of Kir channels in membrane physiology coupled with previous strong association between ion channel gene mutations and seizure phenotypes puts even greater focus on KCNJ10

The major challenge of the future will be to recognize the molecular basis of a Kir-mediated channelopathy in order to screen, diagnose and treat these ion channel diseases.

## Review

Epilepsy is a general term that includes over 40 different types of human seizure.<sup>1</sup> Interaction between individual genetic variation and environmental influences is the most likely causative factor of several types of epilepsy. Autosomal dominant nocturnal frontal lobe epilepsy<sup>2</sup>, generalized epilepsy with febrile seizure plus<sup>3</sup> benign

neonatal familial convulsions<sup>4</sup>, Lafora progressive myoclonic epilepsy and Unvericht-Lundborg types can be given as examples of causative gene variations.

Idiopathic generalized epilepsies (IGE) affect about 0.3% of the general population and account for approximately 30% of all epilepsies. The etiology of common IGE syndromes is genetically determined, but the complex pattern of inheritance suggests an epistatic interaction of several susceptibility genes.<sup>5</sup> Twin and family studies indicate an over-lapping genetic component that is shared across the common IGE subtypes<sup>6</sup>, but also provide evidence that specific gene configurations determine the particular IGE subtype.<sup>7</sup>

Mutations in over 70 genes now define biological pathways leading to rare monogenic forms of epilepsy in humans and animals.<sup>8</sup> Many of the identified human epilepsy genes encode voltage-gated or ligand-gated ion channels. Inherited forms of idiopathic epilepsies indicate that "channelopathies" represent frequent functional pathways of paroxysmal network synchronization and epileptogenesis.

Several types of human epilepsy are caused by single gene variations that are inherited in a predictable Mendelian fashion. Furthermore an understanding of the basic mechanism causing these rare seizure disorders is complicated by genetic heterogeneity. Nevertheless, the success achieved in isolation gene variations involved in several of these rare forms of seizure disorder has broadened the focus of seizure research from studies on GABA and glutamate pathways to studies on ion channels and other genes that directly affect ion flux across excitable membranes.<sup>5,8</sup>

Mutations in genes encoding calcium and potassium channels as well as a sodium/hydrogen exchange protein are associated with spontaneous and recurrent seizure in mice. In humans, rare Mendelian epilepsy syndromes have been linked to mutations in genes for potassium and sodium channels. Evidence has been presented to support the specific involvement of inward-rectifying potassium ion channels in epilepsy and current strategies for anticonvulsant drug discovery recognize them as a new group of biological targets for treating epilepsy.<sup>3,7</sup>

Single gene related epileptic disorders are rare and represent less than 1% of all cases of epilepsy seen in the clinic.<sup>1</sup> Association between idiopathic generalized epilepsy and mu opioid receptor, juvenile myoclonic epilepsy and variations in the BRD2 gene, temporal lobe epilepsy and variations in the interleukin 1 beta and prodynorphin genes are the examples of single nucleotide polymorphism.<sup>8</sup> On the other hand, the search for genetic variations that is associated with common forms of epilepsy, such as idiopathic focal epilepsy has been less successful.<sup>9</sup>

An association of idiopathic generalized epilepsy and variations in the mu opioid receptor gene was reported in one case. Genetic linkage between idiopathic generalized epilepsy and markers on human chromosomes 3, 5, 6, 8 and 15 has also been reported.<sup>9</sup> Strong association between juvenile myoclonic epilepsy and variations in the BRD2 gene on chromosome 6 has also been observed. Temporal lobe epilepsy and variation in the interleukin 1 beta and prodynorphin genes have been associated. The interleukin 1 beta polymorphism was seen in cases with febrile convulsions, a condition long thought to be associated with some cases of temporal lobe seizure.<sup>2,3</sup> Further work is needed to elucidate the functional consequences of the variations identified.

The relationship between neuronal excitability and extracellular potassium ion concentration has been well established.<sup>10</sup> Neurons become hyperexcitable when extracellular potassium concentrations are above 5 mM or below 2 mM. Thus, subtle variation in the inward rectifying channel may have an appreciable effect on extra-cellular potassium ion concentration during and after neuronal excitation. The inward rectifier family contains 16 different genes with an average 42% homology at the amino acid level.

The relationship between neuronal excitability and extracellular potassium ion concentration has been well-known.<sup>11</sup> There is a difference in K allele frequencies from population to population in different parts of world. Heterogeneity can exist in the people from different geographic locations or countries.

Mutations in genes encoding ion channels have increasingly been identified to cause disease conditions collectively formed channelopathies. Recognizing the molecular basis of an ion channel disease has provided new opportunities for screening, early diagnosis, and therapy of such conditions. This channelopathy is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) and is associated with defective chloride conductance, which leads to pulmonary and pancreatic insufficiency, long QT syndrome associated with sudden cardiac death in

otherwise healthy young individuals and also molecular defects in inwardly rectifying K (Kir) channels.<sup>12</sup>

Recognizing the molecular basis of an ion-channel disease has provided new opportunities for screening, early diagnosis, and therapy of these conditions.<sup>13</sup> The existence of Kir channels was first recognized half a century ago. This family of potassium channel genes encodes proteins in the range of 360-500 amino acids.<sup>14,15</sup> Kir channels have a structure that is simpler than that of other ion-channel families.<sup>16,17</sup> Further diversity is achieved through association of Kir subunits with additional structurally unrelated proteins that play important roles in the expression distribution or regulation of the channel activity.

Kir channels are expressed and serve functions as diverse as regulation of resting membrane potential, maintenance of K<sup>+</sup> homeostasis, control of heart rate, and hormone secretion, in humans. The association of Kir subunits with additional structurally unrelated proteins can play important roles in the expression, distribution or regulation of the channel activity. Kir channels are essential in the control of resting membrane potential, coupling of the metabolic cellular state with membrane excitability, and maintenance of potassium homeostasis.<sup>18</sup>

The biophysical fingerprint of Kir channels is inward rectification in the current-voltage relationship, which limits potassium efflux at depolarizing membrane potentials. Kir channels are essential in the control of resting membrane potential, coupling of the metabolic cellular state with membrane excitability, and maintenance of potassium homeostasis.<sup>19-21</sup> Kir4.0 is a strong inward rectifier expressed in the brain. It is expressed mainly in glia, where it may be responsible for potassium buffering.<sup>19</sup>

K can also affect the development of common seizure type and can be defined seizure susceptibility allele. This gene contains a coding region single nucleotide polymorphism variation in the mouse that correlates with seizure susceptibility. The most compelling positional candidate gene in the critical chromosomal segment of 6.6 Mb is the glial inward-rectifying potassium channel gene KCNJ10.<sup>12</sup> The KCNJ10 protein shows a widespread expression in the brain and mediates various physiologic functions, such as the maintenance of the resting membrane potential, responsiveness to synaptic inputs and neurotransmitter release.<sup>10</sup> Haplotype analyses of positional candidate genes revealed an amino acid substitution polymorphism (Threonine262Serine) in the KCNJ10 gene that discriminates high and low seizure susceptibility. Buono et al.<sup>13</sup> reported an allelic association of a common missense variation (Arginine271Cysteine) in the human KCNJ10 gene with focal and generalized epilepsy syndromes.

Mutations in over 70 genes now define biological

pathways leading to rare monogenic forms of epilepsy in humans and animals.<sup>14</sup> Animal models and quantitative trait loci (QTL) analyses provide powerful tools to dissect key sites of neuronal excitability and to identify the underlying genetic factors.<sup>15,20</sup> The inward-rectifying potassium channel gene *KCNJ10* in mice is the most compelling candidate gene. The *KCNJ10* protein shows a widespread expression in the brain and mediates various physiologic functions polymorphism (Threonine262Serine) in the *KCNJ10* gene that discriminates high and low seizure susceptibility among several inbred mice strains.<sup>14,21</sup>

Studies in humans have suggested an association between generalized epilepsy syndromes and genes for two different inward rectifying potassium channels.<sup>22</sup> In the light of such evidence, there is enthusiasm for the development of anticonvulsant drugs that are targeted to this unique family of potassium channels.<sup>23</sup> The two genetic linkage studies have indicated a linkage between missense variations in *Kir4.1* and seizure susceptibility. The DBA/2 mouse strain exhibits a susceptibility to induced seizures compared to the C57BL/6 strain. Previous QTL mapping identified the seizure susceptibility locus on the distal region of mouse chromosome 1 and further fine mapping studies suggested that a missense variation (Thr262Ser) in *KCNJ10* was the likely candidate for this linkage.<sup>8</sup> In a second linkage study, a variation in the human *KCNJ10* gene (Arg271Cys) was associated with seizure resistance in groups of patients with either focal or generalised epilepsy.<sup>24</sup>

The critical interval contains several candidate genes, one of which, *KCNJ10*, exhibits a potentially important polymorphism with regard to fundamental aspects of seizure susceptibility. The unique role of inward-rectifying potassium channels in membrane physiology coupled with previous strong association between ion channel gene mutations and seizure phenotypes puts even greater focus on *KCNJ10*.<sup>25</sup>

Buono et al.<sup>13</sup> reported *KCNJ10* Cys271 allele associated with seizure resistance to a broad spectrum of focal and generalized epilepsies. Analysis of the human *KCNJ10* gene identified a common *KCNJ10* missense variation (Arg271 Cys) that influences susceptibility to focal and generalized epilepsies. Deletion of *KCNJ10* as a seizure susceptibility gene that code for inward rectifier potassium ion channels imparts protection against seizures results in spontaneous seizures and increased seizure susceptibility

*KCNJ10* is expressed widely in brain, predominantly by glial cells<sup>26</sup>, with particularly high levels of *KCNJ10* mRNA having been noted in brainstem.<sup>20</sup> Insight into the biological role of *KCNJ10* comes from studies of mice with

a targeted deletion of the gene and suggest it has an important role in myelin formation<sup>16</sup>, visual function<sup>17</sup> and auditory processing.<sup>16</sup> The most striking phenotypic feature of homozygous *KCNJ10* knockout mice is a severe demyelinating syndrome associated with multiple neurological defects and short life span.<sup>26</sup>

The human *KCNJ10* Arg271Cys missense variation is nearby the position of the murine *KCNJ10* missense variation (Thr262Ser). Both variations are located in the *KCNJ10* carboxyl terminus, a region which is involved in ion conductance, channel subunit dimerization and anchoring in the plasma membrane.<sup>27</sup> However, the seizure resistance effect attributable to the *KCNJ10* Cys271 variation seems to be small.

It is clear that there are differences in *KCNJ10* allele frequencies in control populations collected in different parts of the world. These differences underscore the importance of collecting controls from the same population as that from which patients are collected or to correct statistically for these population differences when combining patients and controls collected in different geographical regions.<sup>28</sup>

Considering the fact that several genetic factors are involved in the epileptogenesis of common IGE syndromes. It may be difficult to elucidate the underlying functional effect of the *KCNJ10* seizure resistance allele in neurophysiologic studies when interacting genetic background effects are ignored.<sup>20,28</sup> Further studies are needed to evaluate the hypothesis that the *KCNJ10* Cys271 allele confers preferential resistance to IGE-related seizures. Positional evidence of a candidate gene, biological plausibility of the investigated sequence variants with appropriate sample sizes are the major requirements to confirm the evidence of *KCNJ10* Cys271 allele associated with seizure resistance to common IGE syndromes.

The major challenge of the future will be to recognize the molecular basis of a Kir-mediated channelopathy in order to screen, diagnose and treat these ion channel diseases. Despite more than 50 association studies in epilepsy reported so far, most of the susceptibility genes identified could not be replicated in independent samples.<sup>28</sup> In particular, the expected large number of false positive association findings, resulting from multiple testing of many gene polymorphisms and phenotypes, led to skepticism about the prospect of dissecting the genetically complex predisposition of common IGE syndromes by molecular genetic approaches.

Multifactoral etiologies such as replication of initial association findings, positional evidence of a candidate gene, biological plausibility of the investigated sequence variants, appropriate sample sizes in the thousands and

biostatistical methods allowing for epistatic gene interaction will be major requirements to disentangle the genetic basis of epilepsy. Further investigations to verify this allelic association and to specify the underlying phenotype-genotype relationship is required .

We hope that future investigations of the association between these variants and seizure susceptibility phenotypes could examine focus on other candidate genes within this associated chromosomal region.

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