Minireview

Chipping away at the common epilepsies with complex genetics: the 15q13.3 microdeletion shows the way

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Abstract

The idiopathic epilepsies are genetically heterogeneous with more than 50 clinical classifications. They are characterized by episodic seizures arising from erratic neuronal discharge in susceptible individuals. The most common predisposing genetic cause is the recently discovered chromosome 15q13.3 microdeletion. Other disorders previously attributed to the same lesion include autism, intellectual disability and schizophrenia. This phenotypic spectrum is most easily imagined as a contiguous gene syndrome with idiopathic generalized epilepsy as the most common clinical manifestation. Expressivity of the microdeletion in carriers is too variable for antenatal prediction of phenotype to be possible; however, when it is detected in living affected cases, it can be taken as the major predisposing cause for the observed phenotype. The discovery of this small 15q13.3 lesion barely scratches the surface that conceals what we ultimately need to know about the molecular genetic mechanisms behind the common epilepsies with complex genetics, but it provides valuable insight into how to proceed toward that goal.

Genetic epilepsies

Helbig and colleagues [1] have recently described the most common inherited cause of epilepsy detected so far. Such progress has reminded us of Ryan's eloquent 1995 review [2] on the mapping of genes for familial idiopathic epilepsies to chromosomes, which he likened to creating "chinks in the(ir) armor". The 'armor' he was referring to was the enormity of the human genome, which effectively shields the underlying molecular defects from detection. The timing of Ryan's article was impeccable: epilepsy gene hunters, assisted by rapid technological developments in molecular genetics and bioinformatics as the Human Genome Project gained momentum, were at the threshold of uncovering the channelopathy paradigm for the familial epilepsies showing Mendelian inheritance. The first genes for the monogenic idiopathic epilepsies were about to be identified [3-7].

Epilepsy as a family of channelopathies

Most of the known pathogenic culprits in epileptogenesis are mutations in genes encoding components of neuronal ion channels [8]. The question from the beginning was whether knowledge of the genes underlying these familial epilepsies would provide the clues to uncover the susceptibility genes for common, polygenic or multifactorial epilepsies, with their complex genetics and complex genotype-environment interactions.

Gargus [9] suggested that multiple neuronal ion channels might be involved in seizure susceptibility through the additive effects of genetic variants that contribute to the channelopathy load. Even the simple 'monogenic' epilepsies show a certain level of genetic complexity, as they are genetically heterogeneous [8]. Add to this the incomplete

penetrance of mutations and variable expressivity, and one can imagine a continuum between the apparently monogenic and the polygenic epilepsies [8].

A few rare and polymorphic variants in ion channel genes have been identified that result in changes to channel properties consistent with an increased predisposition to seizures [8,10]. To this list of susceptibility genes we could add the calcium channel gene *CACNB4* [11], given that we have posited previously that genetic modifiers in 'monogenic' epilepsy and susceptibility alleles in the common epilepsies are the same [12]. Kryukov and colleagues [13] proposed that most low frequency alleles are at least mildly deleterious, so their association with disease can be deduced when the proportion of low-frequency alleles is significantly greater in cases than in controls. Results of large-scale resequencing of ion channel genes are not yet available as a test of that hypothesis; however, manual mutation screening of extended gene families relevant to known mechanisms of epileptogenesis has detected little coding genetic variation in ion channels [14].

The most prevalent risk factor for the genetic epilepsies yet: the 15q13.3 microdeletion

Helbig and colleagues [1] have recently reported recurrent 15q13.3 microdeletions in 1% of common idiopathic generalized epilepsy (IGE). Most of their cases were free of the co-morbidities of intellectual disability, autism and schizophrenia that have previously been associated with the 15q13.3 lesion. They did not detect 15q13.3 microdeletions in a large cohort of controls. The consortium was steered in the direction of 15q13.3 after the same lesion had been implicated in three other major groups of disorders. The first group is intellectual disability and seizures, sometimes with mild dysmorphic features and growth retardation. The detection rate for the microdeletion in this cohort was 0.3% and it was not present in a large control cohort [15]. The second group is autism, with or without intellectual or learning disability and a range of other psychiatric disorders, not with epilepsy, but sometimes with mild dysmorphic features. The detection rate among cases was 0.4% with a large set of negative controls [16]. The final group is schizophrenia, with a detection rate of 0.2-0.3%. The microdeletion was found in controls, but only in one of the two studies at a frequency of 0.02%, representing a single individual [17,18].

The basis for the recurrent 15q13.3 deletion mutation is most likely non-allelic homologous recombination [19] in an unstable region of the genome flanked by two highly homologous segmental duplication regions. The reciprocal product, the microduplication, has been detected in both the patient cohorts and the controls, but it has not been implicated in any of the disorders associated with the microdeletion. The rarity of the 15q13.3 microdeletion in controls strongly suggests that it is under strong natural selection and maintained at low frequency by the balance between recurrent mutation and selection.

One of seven contiguous genes deleted in the smallest interval common to all 15q13.3 microdeletions associated with IGE [1] is the α7 gene of the acetylcholine receptor (*CHRNA7*). Mutations in three acetylcholine receptor subunits (α2, α4 and β2) are causative for epilepsy [8]. Helbig and colleagues [1] therefore postulated that *CHRNA7* is the likely culprit in the IGE cohort, just as others have suggested it to account for epilepsy where it occurred in the intellectually challenged cohort [15]. *CHRNA7* was also an attractive candidate for schizophrenia on the basis of previous linkage results [17].

The IGE subsyndromes found to be associated with the 15q13.3 lesion are childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE) and juvenile myoclonic epilepsy (JME) [1]. It is tempting to use this to support the notion that the same genetic determinants can be causal in different subsyndromes of the common epilepsies, and indeed more broadly between epilepsy and other complex brain disorders, such as autism, intellectual disability and schizophrenia. However, this argument holds true only if the entire spectrum of associated phenotypes can be attributed to haploinsufficiency of only one of the missing genes, for example *CHRNA7*. The microdeletion removes a copy of seven genes [1] and may affect transcription of other structurally unaffected genes; any of these genes alone or in combination could be involved in the genesis of the multifaceted phenotype arising from this lesion.

The finding of Helbig and colleagues [1] demonstrates the potential role of structural variation in accumulating a genetic load predisposing to IGE, in addition to single nucleotide polymorphisms (SNPs) in ion channel or other brain-expressed genes. High-density probe arrays are now available for high-resolution interrogation of the entire genome for lesions, such as the one at 15q13.3, for any disorder with complex genetics. Furthermore, the wealth of structural variations known throughout the entire human genome represents a pool of potential genetic modifiers for any number of genes that might participate in molding the final phenotype associated with the 15q13.3 deletion.

A contiguous gene syndrome at 15q13.3 or a single-gene *CHRNA7* disorder?

As exciting as this new finding of an association between the 15q13.3 microdeletion and IGE is for the genetics of epilepsy, it raises unanswered questions. The contiguous genes always missing from the chromosome 15 homolog with the deletion are those encoding the Rho GTPase activating protein 11B (*ARHGAP11B*), myotubularin-related protein 10 (*MTMR10*), myotubularin-related protein 15 (*MTMR15*), transient receptor

potential cation channel (*TRPM1*), Krüppel-like factor 13 (*KLF13*), OTU domain-containing deubiquitinating enzyme (*OTUD7A*) and *CHRNA7* [1]. Given the range of phenotypes associated with this microdeletion from cohorts originating from different medical disciplines, it is highly possible that more than just the one gene, *CHRNA7*, is pathogenically involved. But of the six other genes, only *OTUD7A* is known to be expressed in the brain, and it encodes a de-ubiquitinating enzyme. Such enzymes are generally involved in multiple biochemical pathways.

A variety of potential mechanisms could be invoked to explain the observed range of disease phenotypes. Pathogenicity of the deletion could be explained by: (i) a position effect arising from a juxtaposition of genes creating new promoter relationships; (ii) deregulation of transcription of nearby genes that are not structurally deleted themselves but for which some or all regulatory elements are deleted; (iii) haploinsufficency for any of the deleted genes; (iv) exposure of deleterious recessive alleles at any of the seven genes present on the normal chromosome 15 homolog; or (v) a combination of mechanisms involving any of the above.

Two of the deleted genes have been knocked out in mice. The *CHRNA7* mouse knockout has neocortical electroencephalogram abnormalities suggestive of predisposition to epilepsy [20] and mild impairment of working/episodic-like memory, which fits within the human schizophrenia spectrum [21]. *KLF13* is a transcription factor, and mouse knockouts show that it is necessary for normal control of erythropoiesis [22], while other members of this Krüppel-like factor family are known to have roles in development. These animal models fail to resolve the question of whether defective *CHRNA7* alone could account for the entire range of phenotypes associated with the human 15q13.3 microdeletion. Ultimately, *CHRNA7* will need to be resequenced in the cohorts in which the 15q13.3 microdeletion was detected to determine whether DNA sequence mutations in *CHRNA7* alone can account for the same range of phenotypes.

A synthesis of results from all cohorts in which the 15q13.3 lesion has been detected - pending the outcome of large scale *CHRNA7* resequencing, which might challenge the following interpretation - strongly suggests a new and as-yet unnamed contiguous gene syndrome with highly variable expression. The cohort in which expression is primarily restricted to epilepsy alone probably represents the phenotype close to the milder end of the disease spectrum associated with this microdeletion. Non-penetrance, in which the lesion has been found in asymptomatic carriers in family studies [1], represents the extreme end of the spectrum. Just as the highly variable expressivity incorporated into the clinical concept of 'genetic (generalized) epilepsy with febrile seizures plus' (GEFS+) [23] was validated by the discovery of a familial mutation responsible for the phenotypic variations [7], the microchromosomal deletion is the genetic diagnostic marker for, and thus validates, the 15q13.3-related clinical syndrome with its multiple clinical manifestations. The concept of the spectrum solves the dilemma of how to clinically classify individuals into their respective disease cohorts in the presence of complex overlapping morbidities. We do not have to do this classification if we regard the multiple clinical manifestations as one contiguous gene syndrome. The corollary to this concept of a single multigenic syndrome is that phenotype cannot be predicted from antenatal detection of the lesion, making its utility as a genetic test uncertain other than as a postnatal marker to explain symptoms.

Perspectives and predictions

So where are we at for the epilepsies with complex genetics? Mullen and colleagues [24] have reviewed the principles of genome-wide association studies (GWASs) with great clarity and optimism in the context of the epilepsies. An alternative view is that the frequency of most susceptibility SNPs in epilepsy could be so rare, or individually could make such small contributions toward raising the seizure threshold, that GWASs are not sensitive enough to detect them. We have previously expressed this view as the Realistic Model [12] and as later renamed the Polygenic Heterogeneity Model [10]. This model remains lacking in detail pending the accumulation of additional real data and was formulated in the limited context of coding SNPs within ion channel genes. However, evidence is now mounting from other brain disorders with complex genetics (schizophrenia and autism) that large numbers of rare or novel structural chromosomal variants may be responsible for the major fraction of disease risk [17,25,26]. The polygenic heterogeneity model may be correct in principle, but it may now require the inclusion of copy number variants (CNVs) as its dominant feature, with SNP variation relegated to a secondary role. The greater potential of multiple, rare structural variants as effectors in disorders with complex genetics is highlighted by the fact that the differences between all of us at the CNV level is about double that at the SNP level [27].

IGE comprises only about 20-30% of all epilepsy [28], and only about 1% of IGE has the most common predisposing lesion at 15q13.3 [1]. There are now far more sophisticated molecular technologies to direct at Ryan's armor analogy [2], now in the context of the epilepsies with complex genetics, but our understanding of their molecular genetic basis remains very limited despite the significant advance reported by Helbig and colleagues [1]. Piercing the armor to dissect out the genetic architecture underlying the common epilepsies might require more than a few 'artillery shots' aimed at the bigger targets such as common polymorphic variants (as in GWASs looking for associations in populations that have so far eluded the gunner's aim [29,30]). Instead of or in addition to this, it might require a comprehensive peppering of affected individuals examined

one at a time with a 'scattergun' approach (as in array comparative genome hybridization (array CGH), in which the causative defects in most affected individuals with genetic epilepsies could be different structural variants possibly involving blocks of genes, as in the 15q13.3 microdeletion). CGH hits have uncovered multiple rare structural variants for autism and schizophrenia [17,25,26] where GWASs had made little progress toward uncovering common susceptibility alleles. We suggest the same CGH approach is now the way forward for the genetic epilepsies, with the report of Helbig and colleagues [1] representing a tantalizing preview of what is yet to come. Some time ago for the same 15q13.3 region Taske and colleagues [31] examined *CHRNA7* as a positional candidate for JME following an earlier linkage study [32] and predicted the possibility of disease-causing genomic rearrangements in this unstable region after they were unable to find unequivocal DNA sequence mutations in *CHRNA7*. The gene content of each new structural lesion or CNV polymorphism to be associated with epilepsy would represent an accumulation of the 'chips off the armor' slowly uncovering the presently concealed complex genetic architecture underlying the common genetic epilepsies.

Abbreviations

ARHGAP11B, Rho GTPase activating protein 11B; *CACNB4*, calcium channel β4 subunit; CAE, childhood absence epilepsy; CGH, comparative genome hybridization; *CHRNA7*, acetylcholine receptor α7 subunit; CNV, copy number variant; GEFS+, genetic (generalized) epilepsy with febrile seizures plus; GWAS, genome-wide association study; IGE, idiopathic generalized epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; *KLF13*, Krüppel-like factor 13; *MTMR10*, myotubularin-related protein 10; *MTMR15*, myotubularin-related protein 15; *OTUD7A*, OTU domain-containing deubiquitinating enzyme; SNP, single nucleotide polymorphism; *TRPM1*, transient receptor potential cation channel.

Competing interests

The authors declare that they have no competing interests.

Author contributions

Both authors contributed to the concept, design, writing and editing of this article. Both authors have read and approved the final version.

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