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Genetics of human epilepsies: Continuing progress

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Keypoints

Numerous epilepsy genes have been identified in the last years, mostly in the (rare) monogenic forms and thanks to the increased availability and the decreased cost of next-generation sequencing approaches.
Besides the somehow expected group of epilepsy genes encoding various ion channel subunits (e.g. sodium or potassium channel subunits, or GABA receptors, or glutamate-gated NMDA receptors), more diversity has emerged recently, with novel epilepsy genes encoding proteins playing a wide range of physiological roles at the cellular and molecular levels, such as synaptic proteins, members of the mTOR pathway, or proteins involved in chromatin remodeling.
The overall picture is somehow complicated: one given epilepsy gene can be associated with more than one epileptic phenotype, and with variable degrees of severity, from the benign to the severe forms (e.g. epileptic encephalopathies), and with various comorbid conditions such as migraine or autism spectrum of disorders.
Conversely, one given epileptic syndrome may be associated with different genes, some of which have obvious links with each other (e.g. encoding different subunits of the same receptor) while other ones have no clear relationships.
Also genomic copy number variations have been detected, some of which, albeit rare, may confer high risk to epilepsy.
Whereas translation from gene identification to targeted medicine still remains challenging, progress in epilepsy genetics is currently revolutionizing genetic-based diagnosis and genetic counseling.
Epilepsy gene identification also represents a key entry point to start in deciphering the underlying pathophysiological mechanisms via the design and the study of the most pertinent cellular and animal models - which may in turn provide proofs-of-principle for future applications in human epilepsies.

Points essentiels

Génétique des épilepsies humaines : des avancées permanentes

De nombreux gènes d'épilepsie ont été identifiés ces dernières années, principalement dans les (rares) formes monogéniques, ceci grâce à l'émergence des approches de séquençage de nouvelle génération et à la baisse exponentielle de leur coût.

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Au-delà du groupe des gènes codant, comme cela était prévisible, pour divers types de sous-unités de canaux ioniques (par exemple canaux sodium ou potassium, ou encore récepteurs GABA, ou récepteurs au glutamate de type NMDA), une plus grande diversité fonctionnelle est apparue récemment, de nouveaux gènes d'épilepsie pouvant coder pour des protéines jouant des rôles diversifiés aux niveaux cellulaire et moléculaire, telles que protéines synaptiques, membres de la voie mTOR, ou encore protéines impliquées dans le remodelage chromatinien.

L'image globale de la génétique des épilepsies est compliquée : ainsi, un gène d'épilepsie peut-il être associé à plus d'un phénotype épileptique, ou à une sévérité de degré variable (allant depuis des formes bénignes jusqu'à des formes sévères d'encéphalopathies épileptiques), ou encore à des conditions comorbides telles que migraine ou troubles du spectre autistique.

Inversement, un syndrome épileptique donné peut être associé à plusieurs gènes différents, ayant ou non des liens fonctionnels plus ou moins évidents entre eux.

De plus, des anomalies du nombre de copies du génome ont été détectées, qui, bien que rares, peuvent conférer un risque important de présenter une épilepsie.

Bien que le transfert depuis l'identification d'un gène donné vers une médecine personnalisée reste un défi à relever, les progrès récents bouleversent d'ores et déjà le diagnostic et le conseil génétiques dans un certain nombre de cas.

De plus, cette identification représente un point-clé vers la compréhension des mécanismes physiopathologiques sous-jacents, à travers la génération et l'étude des modèles cellulaires et animaux pertinents – eux-mêmes devant conduire à leur tour à l'obtention de preuves de principe pour de futures applications en épileptologie humaine.

The genetic origin of many epileptic syndromes and the strong genetic component of so-called "idiopathic" epilepsies have been reported for decades. Despite this long-recognized genetic evidence, most known epilepsy genes have been identified in the very last years only. Nowadays it could be mistakenly considered that the majority of epilepsy genes has been discovered. This probably holds true for the rare monogenic epileptic disorders, in which a given genetic variant actually causes the disease; in contrast, little is known on the genetic component of the more frequent epilepsies with complex inheritance, in which a combination of multiple genetic variants, either rare or frequent, and of environmental factors, participates in the emergence of the disease.

Nevertheless success in the genetics of monogenic epilepsies has been achieved thanks to the genetic shift that has occurred at the beginning of the 21st century: the completion of the human genome project and the availability of the human genome sequence, the advent of next-generation sequencing tools and approaches, and the parallel progress that has occurred in bioinformatics, have all been key events in next-generation human genetics. In parallel, this recent burst in epilepsy gene identification has been associated with advances in clinical diagnosis and care, and with an increasing number of precision medicine-based experimental approaches aiming at ultimately improving the phenotypes by targeting the underlying genetic causes.

In the "ancient" days, at the end of the 20th century, old-generation and time-consuming methods that included genetic linkage studies of large multigenerational families and Sanger sequencing of the best candidate genes within the appropriate genomic regions of interest, led to the discovery of a couple of key epilepsy genes. First of those corresponded to the identification in 1995 of one missense pathogenic variant in the *CHRNA4* gene, encoding a subunit of nicotinic acetylcholine receptors, in a large family presenting with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [1]. This was the start of the first era in epilepsy gene discovery: that of the ion channel genes.

Epilepsies as channelopathies

Owing to their pivotal roles in brain development and functioning, genes encoding ion channel subunits had long been considered strong candidates in the pathophysiology of the epilepsies. Following *CHRNA4*, a few more epilepsy genes were identified in the next years. Pathogenic variations of the two *KCNQ2* (Kv7.2) and *KCNQ3* (Kv7.3) potassium channel subunit genes were found in families with autosomal dominant benign familial neonatal convulsions [2–4]; it was rapidly shown that the heterotetrameric association of two Kv7.2 and two Kv7.3 subunits formed the molecular driver of the neuronal M currents. Since then, numerous other ion channel epilepsy genes, either voltage-gated or ligand-gated, have been identified. This