INTRODUCTION

Juvenile myoclonic epilepsy is the most common subtype of genetic generalized epilepsies formerly called idiopathic generalized epilepsies. It represents about 30% of all epileptic syndromes [1]. Clinical features of juvenile myoclonic epilepsy are characterized by onset in adolescence of recurrent unprovoked myoclonic seizures of shoulders and upper members. Often, generalized tonic-clonic seizures can be associated and, less often, absences seizures. The seizures usually occur after awakening and can be provoked by fatigue, alcohol intake and sleep deprivation. Its electroencephalography findings show generalized 4-6 Hz irregular spike- or polyspike- wave activity, with a maximum in frontocentral regions [2]. Among genetic generalized epilepsies, juvenile myoclonic epilepsy is the most studied by geneticists despite its various heredity and transmission modes. Mendelian autosomal dominant and autosomal recessive trait and non-Mendelian Complex genetic trait were reported [3-5]. Juvenile myoclonic epilepsy-associated genes involve ion-channels, and non ion-channel genes.

Here, we present a resume of ion channels polymorphisms associated to juvenile myoclonic epilepsy and we describe briefly, the engendered functional deficits.

Chloride channel 2 (CLCN2)

In a retracted paper of Haug and colleagues [6], a heterozygous 1-bp insertion 597G (M200fsX231) mutation of the voltage-gated chloride channel gene CLCN2 (chromosome 3q26), was detected in affected members of one large German autosomal dominant juvenile myoclonic epilepsy family. It was reported that this mutation results to a truncated protein lacking major sequence determinations of the chloride ionic pore. The complementary electrophysiological analyses demonstrated that this mutation cause a loss of function.
of ClC-2 channels, suggesting that resultant intracellular chloride accumulation would reduce an inhibitory GABA response, resulting in epileptic seizures [6].

A re-examination of the same family realized few years later, have revealed that only one member of the studied family had juvenile myoclonic epilepsy. The re-sequencing of the CLCN2 gene, revealed the published mutation c.597insG (M200fsX231) in three family members: the index case, and her unaffected father and sister. So, it was not possible to consider the c.597insG mutation as a candidate major gene effect in the studied German juvenile myoclonic epilepsy family but it still believed that it may contribute to the epileptic phenotypes and could represent a susceptibility factor for idiopathic generalized epilepsies [7]. This latest deduction was hardly criticized by Niemeyer and colleagues whom confirmed that there is no evidence for a role of CLCN2 variants in idiopathic generalized epilepsies [8]. They have already demonstrated that the truncated protein did not exert any dominant negative effect on the function of normal chloride ion channel-2 in epileptic patients [9].

The R235G is a novel mutation of CLCN2 gene which was identified in affected sibling pairs presenting JME and inherited from their unaffected father. This variation was also absent in the French control population and in the ethnically-matched populations. The R235Q residue is located in the inner portion of the G transmembrane domain of the channel and affects the kinetics of channel deactivation [10]. This finding, according to the authors, may contribute to an accumulation of intracellular chloride or neuronal hyperexcitability and in consequence it predicts a loss of function of chloride channel-2 in these patients [7, 10].

**Calcium channel voltage-dependant β4-subunit (CACNB4)**

The CACNB4 gene encodes for the β4-subunit of voltage-dependant calcium channel. It’s mapped on chromosome 2q22-23. The C-terminus domain of the β4-subunit protein interacts with α1-subunit for modulating channel kinetics in neurons [11]. Escayg and colleagues [12] screened for mutations in small pedigree with familial epilepsy and ataxia. A premature termination mutation R482X, (C->T; Arg>Stop) was identified in one patient with autosomal dominant juvenile myoclonic epilepsy of the studied family. The truncated protein lacks the 38-C-terminal amino-acids leading to a small decrease in the fast time constant for inactivation of the cotransfected α1 subunit [12].

The results of a genome-wide linkage study realized in a Tunisian Family with autosomal recessive form of juvenile myoclonic epilepsy have revealed a putative locus on chromosome 2q23-24 which harboring the CACNB4 gene. Promoter region, splice junctions and all exons of this later were sequenced in juvenile myoclonic epilepsy family members but no nucleotide variation was detected [13].

Although R482X mutation is functional, CACNB4 gene is not considered as putative juvenile myoclonic epilepsy gene. The published non-sens mutation (R482X) was found until now, in only one member of a juvenile myoclonic epilepsy family from Germany [12], since, it has not been replicated.

**γ-aminobutyric acid receptors GABARs**

GABA receptors are ligand-gated chloride channels that mediate fast inhibition in the mammalian central nervous system. They form a protein complex assembled with different subunits [4, 14]. Juvenile myoclonic-causing mutation have been identified in GABRA1 (gamma-aminobutyric acid alpha-1 receptor) [4, 15] and GABRD (gamma-aminobutyric acid delta receptor) [13].

GABRA1 missense mutation, A322D was identified in an autosomal dominant form of juvenile myoclonic epilepsy. It was reported that it conferred a dominant negative effect: it leads to severe loss of function of GABA receptors by reducing its total and surface expression subsequently and that cells rapidly degrade the misfolded α1 autosomal dominant subunit both proteasome and lysosome mediates processes [16-19].

Recent studies have demonstrated that, although the α1 autosomal dominant subunit did not substitute for wild type α1 subunits on the cell surface, it reduced the surface expression of α1β2γ2 and α3β2γ2 receptors by association with the wild type subunits within the endoplasmic reticulum and preventing them from trafficking to the cell surface. Thus, a reduction of inhibitory postsynaptic current is engendered [20].

**γ-aminobutyric acid receptor gene, GABRD** is located on chromosome 1p36.3. It encodes for the δ subunit of the ligand-gated chloride channel and plays a role in γ-aminobutyric acid neurotransmitter [14, 21]. A homozygous R220H missense mutation that induces a loss of GABRD protein was reported in a patient with juvenile myoclonic epilepsy. But such as CLCN2 and CACNB4 genes, GABRD gene is not considered as a common factor for JME because the cited missense mutation was not detected in any other juvenile myoclonic epilepsy patient until to date.
CONCLUSIONS

Identification of ligand- and/or voltage-gated ion-channels genes linked to juvenile myoclonic epilepsy, confirm that this later is considered as a channelopathy. However, others genes called “non-ion channel genes” were linked to juvenile myoclonic epilepsy. We quote for example: BRD2 (Bromodomain-containing protein 2), EFHC1 (EF-hand calcium-binding motif1) and EFHC2 genes (EF-hand calcium-binding motif2) genes. Proteins corresponding to these genes are involved in varied metabolic processes, others than those in touch with the ion channels [22-26]. In addition, new susceptibility loci for major idiopathic generalized epilepsies were recently identified by high-density microarrays [27, 28] but no genes were linked directly to juvenile myoclonic epilepsy.

REFERENCES

epilepsy phenotypes associated with different EFHC1 mutations.


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