COPY NUMBER VARIATIONS IN THE ETIOLOGY OF EPILEPSY

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[Le Copy Number Variations nell'eziologia dell'epilessia]

ABSTRACT

Epilepsy is one of the most common neurological disorders in humans with a prevalence of 1% and a lifetime incidence of 3%. Idiopathic epilepsies occur in the absence of identifiable causal factors, but recent evidences show the role of genetic factors in the developing of these disorders. In particular, several studies focused their attention on the role of copy number variations (CNVs) in the etiology of epilepsy.

In recent years, many CNVs have been identified, like 15q11.2, 15q13.3 and 16p13.11 microdeletions, 22q11.2 microduplication and many others. Possible candidate genes included in these regions were also studied and they seem to be involved in neuronal transmission and ion transport.

The possibility to identify new rare CNVs allow a greater understanding of the mechanisms of epilepsy and other neurodevelopmental disorders.

***Key words*:** *Epilepsy, a-CGH, genomic variants.*

Received *March 05, 2013;* ***Accepted*** *April 22, 2013*

Introduction

Epilepsy is one of the most common neurological disorders in humans with a prevalence of 1% and a lifetime incidence of 3%[1]. Epilepsy can strike at any time of life, from infancy to old age. It is characterized by recurring seizures resulting from abnormal cell firing in the brain.

It is important to distinguish the term "seizure" from the term "epilepsy": the last one indicates a condition characterized by recurrent seizures due to a chronic underlying disease.

Epilepsy varies widely in type and severity and, today, over 50 distinct epilepsy syndromes are recognized. As regards a pediatric setting, a broad range of different epilepsy syndromes can be distinguished.

Seizure disorders can be divided into idiopathic or symptomatic epilepsies. Symptomatic epilepsies (approximately 30% of cases) have a clear cause, such as metabolic disorders, brain trauma, intracranial tumors, stroke or infections[2,3,4]. Idiopathic epilepsies occur in the absence of identifiable causal factors, but recent evidence suggests that genetic factors are important in the developing of these diseases. Several genes have been identified in rare autosomal dominant and severe sporadic forms of epilepsy, but the genetic cause is unknown in the vast majority of cases. In proof of this, just think that mendelian epilepsies account for only 1% of the cases.

Some genetic syndromes can occur with seizures or epilepsy, for example tuberous sclerosis, neurofibromatosis, Sturge-Weber syndrome and Tay-Sachs disease[5].

Furthermore, some epileptic syndromes have a monogenic etiology (the disease is caused by mutation of a single gene)[6,7]. CHRNA4 (20q13.2-q13.3) and CHRNB2 (1p21) genes are responsible for autosomal dominant nocturnal frontal lobe epilepsy. Mutations of KCNQ2 (20q13.3) and KCNQ3 (8q24)

genes give an inherited epilepsy of newborns. An autosomal dominant form of juvenile myoclonic epilepsy is due by mutation of GABRA1 gene (5q34). All these genes encode for proteins involved in the formation of ion channels.

Modern research in genetics focused their attention on the role of copy number variations (CNVs), that are submicroscopic alterations of the genome in excess or defect (microdeletions and microduplications). CNVs are known to play an important role as susceptibility factors for complex neurodevelopmental disorders of unknown etiology, including intellectual disability (ID), autism spectrum disorders (ASDs), and schizophrenia.

Recent studies are revealing that rare CNVs significantly contribute even to the genetic etiology of epilepsy.

Discussion

Several studies are increasingly recognized CNVs as a source of phenotypic variation among humans. The CNVs in the etiology of intellectual disability, autism and schizophrenia have been extensively investigated[8]. Today the role of genomic rearrangements in epilepsy is emerging too.

These findings were possible thanks to the introduction of array-CGH (comparative genomic hybridization) in the genetic researches. Array-CGH represents the most useful method to simultaneously detect and locate the loss or gain of genetic material. For this reason, its application in the study of genetic diseases is rapidly increasing.

Today we are showing that many of those patients who, in the past, received a clinical diagnosis of sporadic autosomal recessive syndrome or de novo autosomal dominant syndrome, are actually carriers of cryptic chromosomal imbalance responsible for their condition. Many studies report that about 15% of these patients have a cryptic chromosomal anomaly, detected by array-CGH with a resolution of 1Mb[9,10,11,12,13].

All these conditions play an important role in determining morbidity and mortality rates, and this is even more important in neonatal age[14,15]. Indeed, in this age of life many other risk factors, such as congenital malformations, prematurity, nosocomial infections and chemical mediators, may add their cumulative effect influencing short- and long-term outcome[16-30].

In the last years, array-CGH allowed the identification of many CNVs associated with mental retardation, autism spectrum disorders, schizophrenia and epilepsy. It is also important to note that CNVs can be detected even in normal population.

The molecular genetic pathogenesis is shared between most of these rearrangements. They are usually flanked by duplicons, or low copy repeats (LCRs), that are blocks of few repeated sequences, with very high mutual homology (from 90% to 100%) and large hundreds of kilobases (200-400 Kb). LCRs give to the region of DNA a high instability and predispose to homologous recombination events, which mediate nonallelic homologous recombinations (NAHR) resulting in inversions, translocations, duplications or deletions.

It's important to underline that microdeletions are more frequent than microduplications and they generally result into specific and more severe signs and symptoms, compared to the mild clinical features due to microduplications.

Among the most important CNVs associated with epilepsy, recent studies revealed recurrent deletions at 15q11.2, 15q13.3 and 16p13.11[31]. They seem to play a role in idiopathic generalized epilepsies (IGEs).

An analysis of 1234 IGE patients showed that a microdeletion at 15q11.2 is the most common rearrangement in this cohort of patients, occurring in 1% of cases.

A 15q13.3 microdeletion syndrome has been identified in 0.2-0.3% of individuals with mental retardation and epilepsy, schizophrenia, autism and other neuropsychiatric features[32,33]. The critical region of the 1.5-Mb deletion on 15q13.3 contains at least seven genes. CHRNA7 gene, coding for the α7 subunit of the nicotinergic acetylcholine receptor, is considered a plausible candidate gene for the epileptic phenotype.

Deletions at 16p13.11 are associated with schizophrenia, mental retardation, and most recently idiopathic generalized epilepsy. CNVs on chromosome 7q34–36.1 were observed in three unrelated patients with epilepsy and schizophrenia. This region includes CNTNAP2 gene, that has previously been associated with epilepsy. CNTNAP2 encodes Caspr2 (contactin-associated protein 2), a member of the neurexin superfamily, a group of transmembrane proteins that mediate cell-cell interactions in the nervous system. Caspr2 is essential for the localization of voltage-activated K+ channels in the juxtaparanodal region of axons, which may function to stabilize conduction and help to maintain the intermodal resting potential.

So, a loss of function of this gene could determine an abnormal cell firing in nervous system.

A recent Italian study identified 28 rare CNVs in 26 patients with epilepsy. Among these, we want to mention: 22q13.32qter deletion, 19q13.43 deletion and duplication, 6q22.31 duplication, 15q24.1 deletion, 6q26qter deletion, 9q34qter deletion, 15q11-q13 duplication and Xp22.31 deletion. Patients analyzed in this study had heterogeneous clinical features, but genotype-phenotype correlations showed that having mental retardation or other neuropsychiatric disorders in association with epilepsy was significantly associated with the occurrence of CNVs compared with not having them[34].

CNVs on chromosome 22q11.2, that has long been implicated in several genomic disorders, were also associated with epilepsy[35].

Conclusions

Modern knowledge shows the role of genetic factors in the etiology of epilepsy. In particular, CNVs are emerging as genetic alterations predisposing to the onset of these disorders, especially when they are associated with mental retardation or other neuropsychiatric features.

The possibility to identify new rare CNVs allows a greater understanding of the mechanism of epilepsy and other neurodevelopmental disorders.

In addition, the identification of cryptic chromosomal abnormalities can help to make a more accurate genotype-phenotype correlation. It will be possible to plan an appropriate global evaluation of the patient and organize targeted follow-up and therapies.

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