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Pathogenetic Potential of the Mutations of SPTAN 1

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Recent evidence demonstrates that mutations in numerous genes such as *SPTAN1* are responsible for early-onset epileptic encephalopathies, previously considered as cryptogenic[1]. SPTAN1, located on 9q34.11 chromosome, encodes a subtype of an α spectrin that is specifically expressed in nonerythrocytic cells. Spectrins are a large family of filamentous cytoskeletal proteins that contribute to stabilize the plasma membrane and organize intracellular organelles. They consist of α and β dimers that form tetramers linked in a head-to-head arrangement. The specific protein encoded by SPTAN1 in also implicated in other cellular functions including DNA repair and cell cycle regulation.

As mentioned above, mutations of SPTAN1 are considered responsible for early infantile epileptic encephalopathies and alternate splicing of this gene results in multiple transcript variants. In particular specific in-frame mutation of SPTAN1, altering the sensibility of voltage-gated sodium channels, can determine an elevated action potential threshold that is implicated in the generation of early epileptic events[2]. This effect is due to an abnormal aggregation of α-II mutant/β-II and α-II/β-III spectrin heterodimers. In fact, α-II spectrin consists of α and β subunits, is assembled in an antiparallel side by side manner into heterodimers that can form end-to-end tetramers integrating into the membrane cytoskeleton.

Recently in mouse models it has been shown that αII spectrin is ubiquitously expressed in rodent and human somatodendritic and axonal domains suggesting that αII spectrin is involved in critical aspects of nervous development and synaptogenesis and supporting a dominant-negative mechanism of SPTAN1 mutations in early infancy epileptic encephalopathy[3].

Currently, genetic analysis demonstrated that mutations in the last two spectrin repeats, required for α/β spectrin heterodimer associations, can compromise heterodimer formation between the two spectrins. It has been demonstrated that only in-frame SPTAN1 mutations in the last two spectrin repeats in the C-terminal region can lead to dominant negative effects and severe specific phenotypes[4].

SPTAN1 mutations are associated with various neurodevelopmental phenotypes, ranging from mild to severe and progressive. The typical clinical manifestations are often characterized by epileptic encephalopathy with seizures,

hypsarrhythmia, poor visual attention, acquired microcephaly, spastic quadriplegia and severe intellectual disability, in addition to brainstem and cerebellar atrophy and cerebral hypomyelination, that can be evaluated by magnetic resonance imaging. The most severe mutations typically cause early onset epileptic encephalopathy characterized by infantile spasms or tonic seizures[5].

Imaging studies suggested that the severity of neurological impairment and epileptic phenomena correlates with structural abnormalities and with both mutation type and location. Moreover, this clinical picture is often related to Early Onset West Syndrome, a common infantile epileptic syndrome that in some cases can be associated with SPTAN1 mutation[6].

In particular, according to a recent study[7], the vast majority of patients affected by SPTAN1 mutation exhibit epilepsy and in particular, in the subjects who suffered from an early infantile epileptic encephalopathy infantile, spasms were the most prominent seizure type represented. Infantile spasms manifested at a median age of 4 months (ranging from neonatal onset to 9 months) and occurred in the context of an infantile epileptic encephalopathy or as part of West syndrome accompanied by hypsarrhythmia on EEG. They generally persisted and also were highly refractory to treatment. Hypotonia were also present and could be considered an early sign of abnormal development. In general, most individuals with infantile epileptic encephalopathy exhibit profound developmental delay with quadriplegia and absent speech, often accompained by lack of visual contact and movement disorder, such as opisthotonic posturing or dyskinetic movements.

Therefore, as mentioned above, phenotypes associated with SPTAN1 mutations are various, ranging from mild to severe and progressive. In particular, spectrin aggregate formation in fibroblasts with mutations in the a/b heterodimerization domain seems to be associated with a severe neurodegenerative course and suggests that the amino acid stretch from Asp2303 to Met2309 in the a20 repeat is important for a/b spectrin heterodimer formation and/or aII spectrin function. Moreover, recently four different in-frame *SPTAN1* mutations have been identified in association with different clinical features, from a milder variant characterized by generalized epilepsy with pontocerebellar atrophy to severe phenotypes, generally associated with in-frame *SPTAN1* mutations in the last two spectrin repeats in the C-terminal region.

The functional impact of the identified variants can be predicted by two different methods: the Combined Annotation Dependent Depletion (CADD) and Rare exome variant ensemble learner (REVEL) scoring systems. CADD is a framework integrating multiple annotations into one metric by contrasting variants that survived natural selection with simulated mutations based upon all possible nucleotide variants. The higher the CADD score the more likely the variant has deleterious effects; the score obtained in SPTAN 1 mutations is in most cases highly predictive of pathogenicity[8]. REVEL is an ensemble method predicting the pathogenicity of missense variants with the possibility to distinguish pathogenic from rare neutral variants. The higher the score the more likely the variant is pathogenic[9].

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