

Possible pathogenesis of severe myoclonic epilepsy in infancy: A novel nonsense mutation of GABRG2 leading to aggregation of GABAA receptors in neurons

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Objective: Mutations of genes encoding $\alpha 1$ subunit of a sodium channel (SCN1A) and γ^2 subunit of GABAA receptor (GABRG2) are known to cause severe myoclonic epilepsy in infancy. Here we investigated the pathomechanism of severe myoclonic epilepsy in infancy in dizygotic twin girls.

Methods: We investigated mutations of SCN1A and GABRG2 in the twins and their family members using a direct sequencing method. Electrophysiological studies were conducted to evaluate the function of GABAA receptors reconstituted with γ^1 , β^2 and γ^2 subunits on HEK cells. Brain specimens from one of the twins were examined immuno-pathologically.

Results: A novel nonsense mutation of GABRG2 (c.118C>T, Q40X) was detected in both twins and their apparently healthy father, but not in other family members including their mother, or in 182 volunteers. The twins' mutation was heterozygous and their father's de novo. No other mutations were found. HEK transfected with mutated γ^2 cDNA suppressed GABA-induced current values of GABAA receptors. Immuno-staining with antibodies against $\alpha 1$ and γ^2 subunits revealed partial loss of reactivity and granules in the somas of some neurons and neuropils.

Conclusion: Our findings suggest that the identified mutation interferes with trafficking of the GABAA receptor, and thereby undermines the channel function of the receptor. Precipitation of aggregated channel molecules could induce endoplasmic reticulum stress followed by apoptosis of neurons. However, the full development of severe myoclonic epilepsy in infancy could also involve another putative genetic factor possibly inherited from the mother.