

Localisation of missense mutations in SCN1A affects epilepsy phenotype severity

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Objective: Many missense mutations in the voltage-gated sodium channel subunit gene SCN1A were identified in patients with generalised epilepsy with febrile seizure plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI), although generalised epilepsy with febrile seizure plus is distinct from severe myoclonic epilepsy of infancy in terms of clinical symptoms, severity, prognosis, and responses to antiepileptic drugs. This study was carried out to clarify the issue.

Methods: We analysed the localisation of all reported missense mutations in SCN1A identified in patients with generalised epilepsy with febrile seizure plus and severe myoclonic epilepsy of infancy to clarify the phenotype-genotype relationships.

Results: Mutations in severe myoclonic epilepsy of infancy occurred more frequently in the 'pore' regions of SCN1A than did those in generalised epilepsy with febrile seizure plus. These severe myoclonic epilepsy of infancy mutations in the 'pore' regions were more strongly associated than mutations in other regions with the presence of ataxia and tendency to early onset of disease. The possibility of participation of ion selectivity dysfunction of the channel in the pathogenesis of severe myoclonic epilepsy of infancy was suggested by a mutation in the pore region identified in a severe myoclonic epilepsy of infancy patient by Fukuma *et al.*¹

Conclusion: We found a significant phenotype-genotype relationship in generalised epilepsy with febrile seizure plus and severe myoclonic epilepsy of infancy with SCN1A missense mutations. We speculated that more severe sodium channel dysfunctions including abnormal ion selectivity, that are caused by mutations in the pore regions, and which are involved in the pathogenesis of severe myoclonic epilepsy of infancy.

Reference

1. Fukuma G, Oguni H, Shirasaka Y, *et al.* Mutations of neuronal voltage-gated Na⁺ channel alpha 1 subunit gene SCN1A in core severe myoclonic epilepsy in infancy (SMEI) and in borderline SMEI (SMEB). *Epilepsia* 2004; 45: 140-8.