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EPILEPSY

Discovery of *DEPDC5* mutations provides further evidence of a genetic link to inherited focal epilepsies

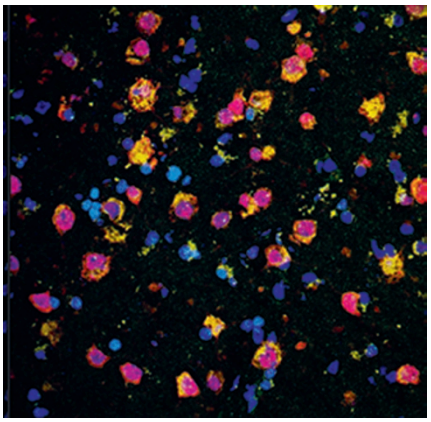
Despite suggestions of genetic involvement, the aetiology of familial focal epilepsies has remained unclear. Now, two new sequencing studies, published in *Nature Genetics*, have identified loss-of-function mutations in *DEPDC5* (which encodes Dishevelled, Egl-10 and Pleckstrin [DEP] domain-containing protein 5) in individuals with familial focal epilepsy, providing evidence for a genetic link to many of these disorders and insight into the molecular mechanism of disease.

"Epilepsy occurs in at least 2% of the population, and about 60% of all epilepsies are focal," says Ingrid Scheffer, principal investigator of the first study. "Finding a gene responsible for a significant proportion of the most common group of epilepsies is extremely important when genetic factors have not previously been considered."

Scheffer and colleagues have been recruiting and studying individuals and families with epilepsy of unknown cause for over 20 years. They first described familial focal epilepsy with variable foci (FFEVF) in 1998 while studying an Australian family in which some individuals had focal epilepsy that emanated from different regions of the brain. "Our hypothesis was that mutations in a single gene could result in different focal epilepsies," she explains.

In their current study, whole-exome sequencing was performed independently in two large families with FFEVF—the Australian family and a Dutch family—in whom the causative locus for disease had previously been mapped to chromosome 22q12. Novel nonsense mutations in the *DEPDC5* gene were identified in both families: c.21C>G in the Australian cohort and c.1663C>T in the Dutch cohort.

Next, Scheffer and colleagues extended their sequencing approach to small families with epilepsy in which only a few members were affected, making diagnosis difficult. "We looked at 82 families with focal epilepsy in two or more individuals,



Confocal images of frozen human brain sample showing expression of DEPDC5 (yellow/green) in neuronal cells (red). Nuclei are shown in blue. Image courtesy of M. Pandolfo.

and identified mutations in *DEPDC5* in 12%," says Scheffer. Identification of mutations in these individuals enabled molecular diagnosis of FFEVF.

In the second study, a team led by Stéphanie Baulac confirmed *DEPDC5* mutations in FFEVF as well as in other inherited focal epilepsies. "Since 2000, our clinician colleagues have collected and phenotyped a series of 19 families with autosomal dominant epilepsies—including FFEVF, autosomal dominant nocturnal frontal epilepsy (ADNFLE) and familial temporal lobe epilepsy (FTLE)—for whom the molecular basis of disease was unknown," says Baulac.

Using whole-exome sequencing, a frameshift mutation in *DEPDC5* was identified in one family with FFEVF. Next, they examined seven families with ADNFLE, five with FTLE and five with FFEVF, and identified five additional mutations in this gene.

"We found *DEPDC5* mutations in a wide spectrum of familial focal epilepsies that, until now, were though to be distinct disorders," says Baulac. "Our discovery indicates that focal epilepsies with different brain localization and electro-clinical expression are, in some cases, due to mutations in a common gene."

The protein encoded by DEPDC5 contains a DEP homology domain that is found in proteins involved in G-protein signalling and membrane targeting, but the exact function of DEPDC5 is unknown. Through immunofluorescence analysis in both mouse and human brain tissue, Scheffer and colleagues found that DEPDC5 is expressed in neurons, which led the team to suggest that the protein is involved in neuronal signal transduction.

The majority of *DEPDC5* mutations observed in the FFEVF cohort of Scheffer and colleagues encoded a premature stop codon, suggesting that haploinsufficiency of the gene is likely to be the underlying pathogenic mechanism. Baulac's group also suggest that haploinsufficiency is the cause of pathology, finding that mutated *DEPDC5* transcripts are degraded by the nonsense-mediated decay system.

"There is now a new player in the landscape of monogenic epilepsy with a function that is not directly linked to excitability," says Baulac. "With no known homology between DEPDC5 and other proteins, new avenues of research in epilepsy are likely to be opened."

Both groups now plan to extend their testing for *DEPDC5* mutations. "Finding mutations in 12% of small families with focal epilepsy suggests that this gene is relevant to a much broader population of people with focal epilepsy," says Scheffer. As both Scheffer and Baulac point out, the new discoveries not only improve our understanding of the neurobiological mechanisms of focal seizures, but also have important implications for diagnosis, genetic counselling and prognostication.

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Original articles Dibbens, L. M. *et al.* Mutations in *DEPDC5* cause familial focal epilepsy with variable foci. *Nat. Genet.* doi:10.1038/ng.2599 | Ishida, S. *et al.* Mutations in *DEPDC5* cause autosomal dominant focal epilepsies. *Nat. Genet.* doi:10.1038/ng.2601