Section IV
Symptomatic Epilepsies of Genetic or Developmental Origin

Chapter 21
Familial Focal Epilepsy with Variable Foci
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The Causal Disease
Familial focal epilepsy with variable foci (FFEVF) is an autosomal dominant disorder typically characterized by different electroclinical focal seizure patterns in different family members. The disease was first mapped to chromosome 22q11-q12 in 1999 [1]. The causative gene, DEPDC5, was identified 14 years later through exome sequencing [2,3]. Mutations in DEPDC5 are also identified in up to 16% of families with focal epilepsies [2–5]. Mutations in DEPDC5 have also been identified in a variety of other defined familial focal epilepsy syndromes, including autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [6], familial mesial temporal lobe epilepsy [3] and autosomal dominant epilepsy with auditory features (ADEAF, also called familial lateral temporal lobe epilepsy) [7,8], as well as in rare cases of rolandic epilepsy [5] and severe infantile-onset epilepsies [5,9,10]. DEPDC5 contains 43 exons and codes for the protein DEP domain-containing protein 5 [11]. DEPDC5 is a subunit of the GATOR1 complex, a negative regulator of the mechanistic target of rapamycin complex mTORC1 in response to decreased amino acid availability (Figure 21.1) [12]. mTORC1 is a kinase complex involved in pivotal neuronal functions, including cell proliferation, survival, growth and plasticity [13]. Recently, heterozygous mutations have also been identified in NPRL2 and NPRL3 in patients with various types of focal epilepsies [10,14–16]. NPRL2 and NPRL3 encode the proteins nitrogen permease regulator-like 2 and 3, respectively, the two remaining components of the GATOR1 complex. Subsequently, malformations of cortical development were identified in some of the individuals carrying mutations in DEPDC5, NPRL2 and NPRL3 [16–19]. Expression studies in human and mouse tissues have demonstrated that DEPDC5, NPRL2 and NPRL3 are ubiquitously expressed, with higher levels in brain regions in comparison to other organs [2,10]. The genes are expressed in all brain regions and throughout brain development. In-vitro studies have demonstrated disruption of the DEPDC5-dependent inhibition of mTORC1 for some of the mutations, lending support to the hypothesis that excessive mTORC1 signalling is responsible for the epilepsy in these [20]. Hyperactivation of mTORC1 was also demonstrated in brains of Depdc5 homozygous knockout rats [21]. Similarly, resected dysplastic brain tissue from patients with truncating mutations in DEPDC5, NPRL2 and NPRL3 showed a significant decrease in expression, consistent with haploinsufficiency, as well as evidence of activation of the mTOR pathway [14,16,19]. These observations are reminiscent of tuberous sclerosis, in which mutations in TSC1 and TSC2 are also associated with excessive activation of the mTORC1 pathway, suggesting common pathogenic mechanisms underlying these disorders. Similar to a ‘second hit’ in tuberous sclerosis complex giving rise to cortical tubers in the presence of a germline TSC1 or TSC2 mutation [22], it is hypothesized that a second hit somatic mutation in a GATOR1 gene or another gene gives rise to the focal epilepsy and/or the associated brain malformation in these patients. A recent report described one patient from a family with a germline DEPDC5 mutation carrying an additional somatic mosaic DEPDC5 variant in resected dysplastic brain tissue [18]. Collectively, these findings establish mutations in GATOR1 complex genes as the most common cause of familial focal epilepsy identified to date.

Epilepsy in the Disease
FFEVF is characterized by focal seizures emanating from different cortical regions of the brain in different members of a family. Each individual in the family has, however, one specific focal seizure type and electroclinical semiology in a given individual is not different from that of focal epilepsy due to other causes (Figure 21.2). FFEVF is, therefore, a diagnosis at the level of the family, not at the level of the individual. Inheritance is autosomal dominant. Age of onset, seizure frequency and drug response may vary considerably.
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within a family. Asymptomatic heterozygote carriers are common. Penetration is reduced and may be as low as 60% [2,3]. Age of seizure onset ranges from the neonatal period to adulthood. Seizure symptomatology depends on the focal region of the brain in which seizures originate. Frontal lobe and temporal lobe seizures are most common, however seizures with parietal, occipital, multifocal and central onset are also seen [23]. Nocturnal seizures are common, and some families may have an electroclinical phenotype resembling that of ADNFLE [24]. Psychomotor development and cognition are usually normal; however, some individuals with mild intellectual disability have been described [17,23]. Neuropsychiatric problems, including autism spectrum disorder, obsessive-compulsive disorder and psychosis are reported in a minority of patients [17,23,25]. Neurologic examination is usually normal. Epilepsy severity is variable, ranging from good response to AEDs to refractory epilepsy. Individuals with concomitant malformations of cortical development usually present with early-onset drug-resistant seizures. Of note, some studies have reported a seemingly increased incidence of sudden unexpected death in epilepsy (SUDEP) in members from families carrying mutations in DEPDC5, NPRL2 and NPRL3 [16,26]. Moreover, a whole exome study of 61 SUDEP cases identified six probably pathogenic DEPDC5 mutations [27]. Further studies are needed to determine whether GATOR1 complex mutations indeed confer an increased risk of SUDEP, and if so what the underlying mechanism is.

![Figure 21.2](image-url.com)

- **Figure 21.2** Pedigrees of families and MRI showing malformations. Individuals who have a **DEPDC5** mutation are denoted by m/+ and those negative for mutations are denoted by +/+ . Images are from the individuals with a black circle. (A) Pedigree of Australian Family A, **DEPDC5 c.418C>T** (p.Gln140*). Individual A:III:8 (bottom left): Coronal T1 image showing cortical thickening and loss of gray–white differentiation at the bottom of a sulcus in the right middle frontal lobe. Individual A:III:8 (bottom right): Coronal T1 image showing cortical thickening and loss of gray–white differentiation at the bottom of an abnormal sulcus in the right medial superior frontal lobe. (B) Pedigree of Australian Family B, **DEPDC5 c.21C>G** (p.Tyr7*). Individual B:III:3 sagittal (left) and axial T1 (right) images show cortical thickening and loss of gray–white differentiation involving the depths of two adjacent abnormal sulci in the left superior frontal lobe. (C) Pedigree of Italian Family C, **DEPDC5 c.279+1G>A**. Individual C:IV:1 axial T1 image (upper) shows blurring of gray–white differentiation involving part of the cingulate cortex and left frontal cortex. Coronal T1 image (lower) shows subtle band heterotopia in the white matter adjacent to dysplastic cortex in the left frontal lobe. Reproduced with permission from reference [17].
Diagnostic Testing

No formal diagnostic criteria for FFEVF have been published. The diagnosis should be suspected in cases of familial focal epilepsy, especially when different family members present with seizures arising from different cortical areas. Background EEG is usually normal. Interictal EEG may show focal epileptiform abnormalities that remain constant over time in a given individual. Severity of interictal EEG abnormalities does not correlate with seizure frequency. Serial EEGs are appropriate when seizure frequency increases or when seizures of new symptomatology occur. Asymptomatic carriers may also have interictal abnormalities.

Brain MRI is normal in most individuals; however, some individuals have a malformation of cortical development. These malformations may be subtle and therefore missed on routine imaging (Figure 21.2). Most reported individuals had an FCD type I, IIa or IIb[10,16–19,28]. More rarely, more extensive malformations such as hemimegalycephaly or polymicrogyria have been reported [10,28,29].

Identification of a heterozygous pathogenic variant in any of the GATOR1 complex genes (DEPDC5, NPRL2, NPRL3) confirms a clinical diagnosis of FFEVF. Genes can be sequenced individually or as part of a multi-gene panel [30]. At least 51 distinct mutations have been reported in over 70 probands in the DEPDC5 gene [31]. At least six different mutations have been reported in NPRL2 and 10 in NPRL3 [10,14–16]. The mutations are spread throughout the genes. Most variants lead to a premature stop codon and their transcripts are thought to be degraded by nonsense-mediated decay [3,6]. A few recurrent variants have been reported. Most individuals with malformations of cortical development have nonsense or frameshift variants leading to a premature stop codon, while missense variants have been reported mostly in small families with apparently non-lesional epilepsies. Interpretation of these missense variants is less straightforward, especially in the absence of clear familial segregation, and pathogenicity has not been confirmed by in vitro studies for some of these variants [20]. Mutations in FFEVF are typically characterized by variable expressivity, including differences in age of seizure onset, seizure type, seizure severity, drug response and presence of cortical malformations.

Management

The response to AEDs is variable. While some individuals respond well to first-line AEDs, others have refractory seizures. There is currently no evidence that seizures respond better to one particular AED and management of an individual with FFEVF does not differ from that of any patient with focal epilepsy. Patients with refractory seizures should be referred early for complete surgical work-up, including attentive review of imaging or repeat brain MRI with a higher resolution for the detection of subtle cortical abnormalities. Favorable outcome has been reported after resective surgery, even if the MRI is unremarkable [16,18].

Based on the presumed disease mechanism involving hyperactivation of the mTORC1 pathway, and in analogy with the treatment of tuberous sclerosis, mTORC1 inhibitors including rapamycin analogs such as everolimus are an attractive alternative treatment option in patients with refractory seizures. Of note, prenatal rapamycin treatment was demonstrated to rescue growth delay and embryonic lethality of DePDc5 homoyzogous knockout rats and cortical abnormalities in heterozygous knockouts [21]. Further studies are needed to determine whether patients with GATOR1 complex mutations could benefit from treatment with this class of drugs.

In the absence of specific treatments for FFEVF, the main interest of genetic testing currently lies in genetic counseling. Pathogenic variants may be inherited from a parent or occur de novo. The proportions of inherited and de novo pathogenic variants are currently unknown. Molecular genetic testing of the parents is recommended when a pathogenic variant is identified in an individual. Because of incomplete penetrance, molecular genetic testing of parents and other family members may reveal heterozygosity for a pathogenic variant in asymptomatic individuals or those with a milder phenotype. Germline mosaicism has been reported in one case [18]. Prenatal and preimplantation genetic testing are possible in women with an identified pathogenic variant. It must be noted however that accurate prediction of the specific phenotype, age of onset and disease severity is not possible due to incomplete penetrance and variable expressivity.

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