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Mini review article

GATOR1 GENE VARIANTS IN FOCAL EPILEPSY

VARIJANTE U GATOR1 GENIMA U FOKALNOJ EPILEPSIJI

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Abstract

Significant genetic contributions to focal epilepsy have only recently been recognized, despite the well-established hereditary nature of other epilepsy syndromes. In 2013, the significant role of the *DEPDC5* gene in a rare familial focal epilepsy syndrome was described, followed by the discovery of variants in *NPRL2* and *NPRL3* genes in patients with similar clinical features three years later. The genes listed above code the three subunits that comprise the GTPase-activating protein (GAP) activity towards Rags 1 (GATOR1) complex, a negative regulator of the mechanistic target of rapamycin (mTOR) complex 1 (mTORC1). Loss of function of GATOR1 leads to constitutive mTORC1 activation that is linked to various malformations of cortical development (MCD), most notoriously focal cortical dysplasia (FCD), but has also been linked to epilepsy in the absence of overt MCD. Variants in GATOR1 genes have been detected in multiplex families with rare familial focal epilepsy syndromes where they demonstrate an autosomal dominant inheritance pattern with reduced penetrance. More recently, they have also been defined as major contributors in common nonacquired focal epilepsy in which they are detected in 3% of familial and 0.2% of sporadic cases and are particularly common in familial epilepsy associated with FCD where up to 11% of affected subjects carry gene variants. Clinical features of carriers include a propensity for nocturnal seizures, a poor response to antiseizure medication as well and an increased risk of sudden unexpected death in epilepsy, which is why other forms of treatment have been explored, including epilepsy surgery after which GATOR1 gene variant carriers have similar outcomes to other patients with focal epilepsy. A particularly promising avenue of exploration is the utilization of mTOR inhibitors like everolimus in epilepsy treatment, but further investigation into this option is warranted.

Keywords:
focal epilepsy,
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Sažetak

Iako je hereditarna priroda pojedinih epileptičkih sindroma odavno poznata, značaj genetskih faktora u etiopatogenezi fokalnih epilepsija je tek nedavno otkriven. Tako je, na primer, 2013. godine opisana značajna uloga gena *DEPDC5* u retkom sindromu familijarne fokalne epilepsije, što je nakon tri godine praćeno opisivanjem varijanti u genima *NPRL2* i *NPRL3* kod pacijenata sa sličnom kliničkom slikom. Ovi geni kodiraju tri subjedinice proteinskog kompleksa proteina aktivatora GTPaze sa aktivnošću prema Rags1 (engl. *GTPase-activating protein (GAP) activity towards Rags 1* - GATOR 1) kompleksa, negativnog regulatora kompleksa mehanicističke mete rapamicina (eng. *mechanistic target of rapamycin (mTOR) complex 1* - mTORC1). Gubitak funkcije GATOR1 dovodi do konstitutivne mTORC1 aktivacije koja je povezana sa različitim malformacijama kortikalnog razvoja (MKR), od kojih je najpoznatija fokalna kortikalna displazija (FKD), ali je takođe povezana sa epilepsijom bez vidljivih MKD. Varijante u GATOR1 genima su detektovane u familijama sa više članova obolelih od familijarnih sindroma fokalne epilepsije koji se nasleđuju po autozomno dominantnom obrascu sa redukovanom penetrantnošću. U novijim studijama je definisana i njihova velika uloga u nestečenoj fokalnoj epilepsiji, u kojoj su detektovane kod 3% sa familijarnom i 0,2% slučajeva sa sporadičnom epilepsijom, dok su posebno česte kod familijarne epilepsije povezane sa FKD, gde su do 11% obolelih nosioci GATOR1 varijanti. Kliničke karakteristike nosioca obuhvataju sklonost ka noćnim napadima, slab odgovor na antiepileptičke lekove, kao i povećan rizik od naprasne neočekivane smrti u epilepsiji, zbog čega su ispitivane i druge forme lečenja, uključujući hirurgiju epilepsije nakon koje nosioci varijanti u GATOR1 genima imaju slične ishode kao drugi pacijenti sa fokalnom epilepsijom. Posebno obećavajuća mogućnost u lečenju epilepsije je upotreba mTOR inhibitora, poput everolimusa, ali je neophodno dalje istraživanje ove opcije.

Ključne reči:
fokalna epilepsija,
genetska epilepsija,
DEPDC5,
NPRL2,
NPRL3,
GATOR1

Introduction

Epilepsy has been recognized as a hereditary disease since antiquity and well established as such in familial studies in the early twentieth century (1). While the genetic basis of generalized epilepsy has been extensively investigated, focal epilepsy has, until recently, been widely considered a disorder associated with radiologically definable lesions and as such mostly an acquired disease. However, a large proportion of focal epilepsy patients have normal magnetic resonance imaging (MRI) (2). Additionally, the emergence of large families with multiple affected family members with clinical features of focal epilepsy has prompted suspicion of an underlying genetic cause of focal epilepsy.

In 2013, two publications described variants in the gene coding Dishevelled, Egl-10 and Pleckstrin domain46 containing protein 5 (*DEPDC5*), a previously unrecognized epilepsy gene, in familial focal epilepsy with variable foci (FFEVF). Dibbens et al. identified *DEPDC5* variants in two large multiplex families, and then, subsequently detected *DEPDC5* in 5/6 previously described families with the same syndrome, as well as 10/82 of families that were too small for clinical diagnosis of the syndrome (3). Ishida et al. found *DEPDC5* gene variants in a single multiplex family with FFEVF and subsequently detected additional *DEPDC5* variants in 5/15 families with focal epilepsy (4). The two articles were the first to establish *DEPDC5* as an epilepsy gene and were published in the same issue of Nature Genetics. The same year a third publication described the role of GTPase-activating protein (GAP) activity towards Rags 1 (GATOR1) complex, consisting of three subunits, DEPDC5, nitrogen permease regulator-like 2 (Nprl2) and nitrogen permease regulator-like 3 (Nprl3) in the mechanistic target of rapamycin (mTOR) molecular pathway (5). Three years later, variants in genes *NPRL2* and *NPRL3*, coding the other two subunits of GATOR1, were also described in patients with focal epilepsy (6). Thus, an important contribution of GATOR1 genes in focal epilepsy was established.

The molecular role of GATOR1 complex

The mTOR is a serine/threonine kinase that acts as a regulator of cell growth, proliferation, differentiation, and survival. It is ubiquitously expressed in all mammalian cells and can be found in particularly high concentration in brain tissue. Combined with other accessory proteins, mTOR forms mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Activated mTORC1 promotes cell growth and survival by regulating mRNA synthesis and autophagy (7). Additionally, it affects synaptic transmission and plasticity, neural network activity and neurogenesis in the brain (8).

mTORC1 receives input from upstream regulatory proteins that are in turn controlled by levels of growth factors, ATP concentrations or nutrients. High levels of amino acids inhibit the activity of the GATOR1 complex, which acts as a negative controller of mTORC1, resulting in activation of mTORC1 (9). Loss of function of GATOR1 subunits leads to mTORC1 resistance to amino acid deprivation and subsequent constitutive mTORC1 activation. However, unlike variants in mTORC1

repressors, *TSC1* and *TSC2* are responsible for tuberous sclerosis complex (TSC), variants in GATOR1 genes appear to only affect brain tissue (10).

Epileptogenesis in GATORopathies

Pathogenic GATOR1 gene variants are inactivating and lead to a reduction or complete loss of protein function that results in constitutive mTOR1 activation (7). However, the precise mechanism by which excessive mTORC1 activation causes neuronal hyperexcitability remains elusive. Epilepsy in GATORopathies is linked to various epileptogenic malformations of cortical development (MCD), such as focal cortical dysplasia (FCD) (11), hemimegalencephaly (HME) (12), polymicrogyria (PMG) (6) or subcortical band heterotopia (13) that in themselves are the cause of epilepsy and could be explained by mTORC1 hyperactivity.

But how does a germline mutation that is present throughout the entire brain explain a focal anomaly? And is haploinsufficiency alone enough to cause malformations considering that GATOR1 genes are negative regulators? A possible explanation may be a second-hit mechanism in which an additional somatic mutation both explains how some cortical cells are affected while others aren't, and how the allele unaffected by the germline mutation fails to achieve the necessary level of protein function. Knudson originally described a primary inherited mutation and a secondary somatic mutation as the genetic basis of retinoblastoma (14). Similarly, somatic second hit mutations have been found in resected brain tissue of patients with MCD-associated epilepsy and germline GATOR1 gene mutations (15), which is not surprising, considering isolated somatic mutations in mTOR regulators have already been well described as causes of MCD (16). Additionally, a germline and somatic *DEPDC5* mutation in trans-position were described in resected FCD tissue (17) which suggests a biallelic gene inactivation. In this sense, somatic variants occurring earlier in development can account for more extensive MCD while those occurring later would result in small, bottom of sulcus FCD. Additionally, the so-called "variant allele fraction gradient" may be correlated with cytoarchitectural changes, such as the dysmorphic neuron density gradient, and epileptogenicity (11, 16).

However, most patients with germline GATOR1 gene variants so far have not been found to have a secondary somatic mutation (15), suggesting either somatic mutation at frequency below detectable thresholds, variants of different mechanisms, such as copy number variants and intronic variants or that secondary somatic mutations are not essential in all cases of GATOR1 gene associated epilepsy. Additionally, most GATOR1 gene carriers have normal brain MRIs. It is currently unclear whether subtle and MRI-undetectable malformations underlie epilepsy in these patients or whether there are other mechanisms in play (18).

Phenotypic spectrum of epilepsy in GATORopathies

The GATOR1 gene variants have been identified in a wide array of focal epilepsy syndromes and constitute a genetic contributor to a heterogeneous phenotypic population. None the less, there are certain traits in common in carriers that could serve as clinical markers for identifying patients with GATOR1 associated epilepsy, most notably the association with MCD, intractable epilepsy, as well as an increased risk of sudden unexpected death in epilepsy (SUDEP). A brief overview of characteristics of GATOR1 associated epilepsy is provided in **table 1.**

Rare familial focal epilepsy syndromes

Familial focal epilepsy with variable foci

FFEVF is the prototypical GATOR1opathy and the first syndrome in which *DEPDC5* gene variants were described (3, 4). However, only 10% of variant carriers meet the criteria for FFEVF diagnosis (22), in part because of it being a familial, rather than individual diagnosis. FFEVF

Table 1. Characteristics of GATOR1 associated focal epilepsy.

Characteristic		
Prevalence in common focal epilepsy cohorts	Familial focal epilepsy (19)	3%
	Sporadic focal epilepsy (20)	0.2%
	Focal epilepsy with FCD (21)	11%
Penetrance (22)		66%
Age at seizure onset (9)		$\bar{x}$ = 9 (0 - 52) years
Infantile spasm risk (18)		5 - 10%
Frequency of MCD (9)		23%
Frequency of intractable epilepsy (22)		54%
Psychiatric comorbidities (22)		43%
Cognitive comorbidities (22)		46%
Frequency of SUDEP (9)		9.3%

is an autosomal dominant disorder with a 60% penetrance in which different members of the same family suffer from focal epilepsy of variable location (13). A vast majority of patients suffer from temporal or frontal lobe epilepsy, but posterior quadrant epilepsy is not rare. What is typical is that there is no clinical or radiological feature of FFEVF patients distinguishing them from patients with common focal epilepsy syndromes of the same location (23), which is probably why at least some of these patients fall under the clinical radar and the syndrome is considered to be much more common than has so far been described.

Most patients have normal intellectual function, but patients with intellectual disability, as well as autism and psychiatric comorbidities, such as obsessive-compulsive disorder or psychosis, have been described (24). Epilepsy severity varies from intractable cases with high seizure burden to mild epilepsy cases with late-onset and few seizures (23). Intractable cases have proven to be good surgical candidates (25), but not enough cases have been analyzed so far to make a definitive conclusion.

Autosomal dominant sleep-related hypermotor epilepsy

Autosomal dominant sleep-related hyper motor epilepsy (ADSHE), previously autosomal dominant nocturnal frontal lobe epilepsy, is a rare familial focal epilepsy with autosomal dominant inheritance and 70% penetrance (26). The clinical hallmark of the disorder are hypermotor seizures clusters arising from sleep, but some patients have other seizure types as well. Around a third of patients have associated non-REM parasomnias such as somnambulism or pavor nocturnus, as well as relatives with parasomnia without epilepsy (24).

ADSHE was first associated with a variant in the acetylcholine nicotine receptor subunit, *CHARNA4*, and the first pure epilepsy syndrome with a described monogenetic cause (27). Soon after, variants in genes of the same family, like *CHRNA2* and *CHRNB2* were also described. In recent years, ADSHE has been linked to variants in GATOR1 genes, frequently associated with MCD (28). In an analysis of 103 patients with clinical features of the syndrome, GATOR1 gene variants were detected in around 5% (29). Furthermore, some families with FFEVF have members who phenotypically resemble patients with ADSHE (30). What distinguishes ADSHE associated with GATOR1 gene variants from "classical" ADSHE is epilepsy severity that is frequently intractable and requires surgical treatment, especially when associated with MCD (28).

Autosomal dominant epilepsy with auditory features

Autosomal dominant epilepsy with auditory features (ADEAF) is a rare autosomal dominant epilepsy disorder with penetrance varying from around 70% (31) to below 50% (32). Seizures typically arise as focal aware seizures with elementary auditory symptoms, what used to be classified as a "primary auditory aura", but can evolve into more complex symptoms such as receptive aphasia, complex visual or vertiginous, sensitive, or psychological symptoms. Focal to bilateral seizures are also common (33). The epileptogenic zone is believed to be localized in Heschl gyri of the temporal lobe (34). Seizure onset is in childhood or early adolescence, and neurological and cognitive functions are normal (24).

ADEAF is primarily associated with *LGI1* and *RELN* gene variants (35), but GATOR1 gene variants are detected in a few families as well (36). Extensive evaluation of these subjects so far has not revealed an association with MCD, or other traits distinguishing them from patients with other genetic causes of the syndrome.

Familial mesial temporal lobe epilepsy

Familial mesial temporal lobe epilepsy (FMTLE) is a benign epilepsy syndrome with late-onset and typically normal brain MRI findings with focal aware seizures and dysmnestic symptoms. The disorder demonstrates a pattern of complex inheritance and encompasses close to 20% of newly diagnosed mesial temporal lobe epilepsy (37). Seizures are typically drug-responsive, and many patients go into spontaneous remission, although some family members have more severe epilepsy and even hippocampal sclerosis (HS) (38). The genetic basis of this disorder has not been very well described, but anecdotal reports of *DEPDC5* variants have been made (36, 39).

Common focal epilepsy

Whole exome sequencing in large epilepsy cohorts has identified *DEPDC5* as one of the major genetic contributors to common nonacquired focal epilepsy. Nonacquired focal epilepsy is a fairly new term, coined to signify focal epilepsy with a presumed genetic basis. The term has arisen from the recognition that many patients with few or no affected family members, as well as patients with brain MRI lesions, suffer from genetically determined epilepsy. Its definition varies between authors but always excludes patients with known acquired insults associated with epilepsy, such as brain trauma, tumors, infection, or stroke. In the first in a series of these reports, the EPI4K and Epilepsy Phenome/Genome Project cohort, the only gene in which variant enrichment reached statistical significance was *DEPDC5* in patients with a familial occurrence of focal epilepsy (19). The GATOR1 gene variants were detected in a combined 3% of the entire cohort, suggesting they are major genetic contributors to focal epilepsy. The greatest portion of genetic contribution was described in familial epilepsy associated with FCD where up to 11% of affected individuals carried inactivating GATOR1 gene variants (21). Conversely, only 0.2% of patients with sporadic focal epilepsy were carriers of variants in these genes (20), which is somewhat surprising, considering that around half of GATOR1 gene variant carriers have no affected family members (22). Similar results were found in other studies (40).

Infantile spasms

Tuberous sclerosis complex, another mTORopathy, is a well-known major genetic cause of infantile spasms (41). It is therefore no surprise that infantile spasms are frequently associated with GATOR1 gene variants (42), and up to 10% of carriers present with infantile spasms (22). They are usually associated with intellectual disability and high seizure burden, and, like other GATOR1 gene-associated epilepsy syndrome, some patients have accompanying MCD, mostly FCD. Infantile spasms have been described in the absence of hypsarrhythmia, which significantly delays diagnosis as well as treatment that is vital to ensure cognitive development (42).

Spectrum of malformations of cortical development

The strong association between GATOR1 gene variants and MCD has challenged the long-standing dualism between "idiopathic" (implied genetic) and "symptomatic" (in this case lesional) epilepsy. In a cohort of 73 patients with GATOR1 gene variant-associated epilepsy, 17 (63%) had associated MCD, the most frequent of which was FCD in 14 (52%) patients. Hemimegalencephaly, subcortical grey matter heterotopia and hemispheric cortical dysplasia were found in one patient each (22), while other authors have described patients with polymicrogyria harboring GATOR1 gene variants (6).

Sudden unexpected death in epilepsy

A particularly daunting discovery is the link between GATOR1 gene variants and SUDEP which was found in over 10% of families carrying variants (22). Cases of autopsy confirmed, what is termed "definitive SUDEP" have also been described in *DEPDC5* gene variant carriers (43).

The precise mechanism underlying a link to SUDEP has not been found, but many SUDEP risk factors are associated with GATOR1 gene variants, such as a propensity for nocturnal seizures, intractable epilepsy and polytherapy, early onset of epilepsy, and frequent focal to bilateral tonic-clonic seizures. However, SUDEP has been reported in GATOR1 variant carriers, even in the absence of typical risk factors (43).

Management

Antiseizure medication

GATOR1 gene associated epilepsy is typically intractable to antiseizure medication. A large cohort study found an association of variant enrichment in *DEPDC5* in patients with intractable epilepsy, while no such link was found in patients with drug-responsive epilepsy (44). Over half of these patients meet the criteria for drug-resistant epilepsy with an average use of four antiseizure drugs, and only around 10% become seizure-free on a single drug (22).

Surgical treatment

Patients with intractable focal epilepsy can in some cases be successfully treated with epilepsy surgery. However, numerous patients with epilepsy associated with ion channel mutations have been found to have poor surgical outcomes (25). The takeaway conclusion was that patients with germline genetic variants might not be good surgical candidates because the underlying cause of epilepsy is present throughout the brain. In contrast, recent studies have found that patients with GATOR1 gene-associated epilepsy have surgical outcomes comparable to typical surgical cohorts with favorable surgical outcome in up to 80% of patients (22), especially in cases with MRI-detected FCD (45). Some authors have even suggested integrating GATOR1 gene sequencing into the presurgical evaluation of nonlesional or FCD surgical candidates because detection of an underlying variant could suggest the existence of an unidentified MCD in nonlesional cases and because specific targeted treatments could then be considered in cases of surgical failure (9). Similar considerations are reflected in the diagnostic algorithm proposed by the International League Against Epilepsy Diagnostic Methods Commission task force where GATOR1 gene sequencing is suggested as part of routine diagnostic work-up of FCD surgical candidates (46).

Precession therapy

A better understanding of the molecular mechanisms underlying epilepsy offers great promise for precision care in which the discovery of genetic contributors has played an important role. Epileptogenesis in GATORopathies is, to some extent at least, driven by mTORC1 hyperactivity, similar to patients with TSC. What remains uncertain in what part mTORC1 hyperactivity plays in generating seizures, once an epileptogenic zone is already formed and how much of this can be reversed by blocking mTORC1 activity.

Everolimus, an mTOR inhibitor, has been proven to be safe and efficacious in treating epilepsy in TSC (47), as well as polyhydramnios, megalencephaly and symptomatic epilepsy, another mTORopathy (48). Similarly, *in vivo* and *in vitro* studies show promise for its use in GATORopathies (49), but very little clinical evidence is available to date. A study investigating the efficacy and safety of everolimus in treating FCD type II-associated epilepsy found an average 33% reduction is seizure frequency, but failed to meet the predefined level of statistical significance (50). However, the small sample (16 patients) and short follow-up (12 weeks) limits the extrapolation of this data, and further investigation on larger samples of patients, both with and without visible MCD with longer follow-up is warranted.

Conclusion

The GATOR1 gene variants are a major genetic contributor to an array of focal epilepsy syndromes including common focal epilepsy. Their role in both

nonlesional as well as focal epilepsy associated with MCD has blurred the distinction between what was previously termed symptomatic and idiopathic epilepsy and broadened our understanding of the complexity of epilepsy etiology. The propensity for nocturnal seizures, intractability to ASM as well as an elevated risk of SUDEP all highlight the urgency of further investigation that would facilitate the identification of these patients, as well as optimize their treatment. Precision treatment with mTOR inhibitors is a promising avenue for future investigation.

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