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The epileptology of GNB5 encephalopathy

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Summary

Pathogenic variants in *GNB5* cause an autosomal recessive neurodevelopmental disorder with neonatal sinus bradycardia. Seizures or epilepsy occurred in 10/22 previously-reported cases, including six children from one family. We delineate the epileptology of *GNB5* encephalopathy.

Our nine patients, including five new patients, were from seven families. Epileptic spasms were the most frequent seizure type, occurring in 8/9 patients, and began at median age of 3 months (2 months – 3 years). Focal seizures preceded spasms in three children, with onset at 7, 11 days and 4 months. One child presented with convulsive status epilepticus at 6 months. Three children had burst-suppression on EEG, three hypsarrhythmia and one evolved from burst suppression to hypsarrhythmia. Background slowing was present in all after age three years. MRI showed cerebral atrophy in one child and cerebellar atrophy in another. All nine had abnormal development prior to seizure onset and ultimately had profound impairment without regression. Hypotonia was present in all, with contractures developing in two older patients.

All individuals had biallelic pathogenic variants in *GNB5*, predicted by *in silico* tools to result in protein truncation and loss-of-function. *GNB5* developmental and epileptic encephalopathy is characterized by epileptic spasms, focal seizures and profound impairment.

Key words

GNB5, Epilepsy, Intellectual disability, Developmental and epileptic encephalopathy, Recessive

Introduction:

Biallelic pathogenic variants in *GNB5* have recently been associated with an autosomal recessive neurodevelopmental disorder with sinus bradycardia and retinal dysfunction¹. Twenty-two affected individuals from ten families were reported in 2016-2018^{1,2,3,4,5}. Homozygous and compound heterozygous truncating variants are found in a severe phenotype with hypotonia, visual loss, early-onset sinus node dysfunction, epilepsy and profound impairment. A milder cognitive phenotype without seizures is seen in individuals with non-truncating mutations.

GNB5 encodes guanine nucleotide-binding protein subunit beta-5 (Gβ5) and has widespread expression⁶. Gβ5 downregulates central nervous system G protein signaling via interactions with G-protein coupled receptors. These receptors regulate numerous cellular functions including neurotransmission⁴. *GNB5* knockout mice have impaired neurological, cardiac and retinal function¹.

Here we delineate the epileptology of *GNB5* developmental and epileptic encephalopathy in five new and four previously reported patients¹, enabling earlier recognition of *GNB5* developmental and epileptic encephalopathy (DEE).

Methods:

Two individuals with *GNB5* pathogenic variants were identified in a DEE cohort. Following a search of the literature, GeneMatcher and Clinvar, three additional patients were identified via GeneMatcher⁷. We contacted clinicians of four previously-reported patients with *GNB5* pathogenic variants and epilepsy in whom there had been no or limited description of their epilepsy¹. For each patient, we obtained a detailed seizure and medical history, examination findings, MRI and EEG data. The New Zealand Health and Disability Ethics committee approved the study. Informed consent was obtained for each patient from parents or legal guardian.

GNB5 variants were detected via clinical exome sequencing (patients 2-5) or research exome sequencing (patient 1, 6-9¹). Segregation testing was performed in all parents.

Results:

Nine individuals (seven female) aged two to 24 years from seven families were identified with a history of seizures (Table 1).

Epilepsy

Median age of seizure onset was 3 months (1 week to 3 years). Three children presented with focal seizures (age 1 to 16 weeks) and developed epileptic spasms two to three months later. Five children presented with epileptic spasms as their first seizure at a median of 3 months (2 months – 3 years). The remaining 3-year-old child presented with tonic-clonic status epilepticus (6 months) and has had no further seizures.

Eight children developed multiple seizure types including focal tonic (4), focal motor (3), tonic-clonic (3), focal autonomic (2) and tonic (1). Myoclonic, atonic and absence seizures were not seen. Seizures were pharmacoresistant in seven children. Three children became seizure free by age 5 years.

EEGs showed burst-suppression and/or hypersarrhythmia in 7/9 children (burst-suppression range 2 months – 5 months, hypersarrhythmia range 2 months – 3 years). 8/9 developed multifocal discharges at median 3 years (1 month – 20 years). Background slowing was present by age 3 years.

Brain MRI was normal in five. Two had subtle anomalies, one mild cerebral atrophy and one cerebellar atrophy (Table 1).

Development

All individuals had developmental delay noted by four months of age, prior to seizure onset. Five were definitely abnormal from birth. They all showed minimal developmental progress without clear regression. All had profound global impairment and were non-verbal and non-ambulant.

Cardiac

Eight children had bradycardia with sinus pauses (Table 1) which was identified prior to genetic testing. Four presented with apnea by 11 months, while four were asymptomatic with bradycardia identified on cardiac monitoring at age 1–2 years. Patient 3, not known to have cardiac disease, died in her sleep aged 13 years.

Molecular findings

Four patients have novel homozygous truncating variants (Table 1), including a sibling pair (patients 3, 4). No other likely pathogenic variants were identified. Patients 2 and 8 had a recurrent mutation; patient 5 was homozygous for a different variant at the same residue. All novel variants are pathogenic according to American College of Medical Genetics and Genomics guidelines (Supplementary table)⁸.

Illustrative case histories (Figure 1a)

Patient 1, a 10-year-old boy, developed cyanotic episodes with bradycardia at 5 hours of age. Holter study showed sinus arrhythmia with sinus pauses up to 4.2 seconds. On day 11 he had hemiclonic seizures responsive to carbamazepine. EEG at 4 weeks showed frequent multifocal spikes. At 3 months he represented with clusters of focal epileptic spasms and burst-suppression. Spasms stopped with steroids. At 21 months he had a febrile tonic-clonic seizure. He continued to have occasional

focal tonic and focal to bilateral tonic-clonic seizures, often triggered by illness until 5 years, and has been seizure free since.

Development was abnormal from birth. He smiled at 4 months. Tone was initially normal but he was hypotonic by 3 months. At 10 years, he is profoundly impaired with poor head control and unable to sit. He has cortical visual impairment and bilateral optic atrophy. He was failing to thrive by 3 weeks. Following surgery for pyloric stenosis at 7 weeks he continued to have poor feeding. A gastrostomy tube was inserted and growth normalized (25th centile).

Patient 2, a 3.5-year-old boy, developed apneic episodes with bradycardia on day 3. Holter study at 3 weeks showed sinus pauses of up to 6.9 seconds. At 2 months he had head lag, did not fix or follow and was not smiling. He presented at 3 months with epileptic spasms and burst-suppression unresponsive to prednisone but responsive to vigabatrin. At 18 months, he developed daily tonic-clonic seizures resistant to topiramate, clonazepam and valproate. At 23 months, he had daily clusters of extensor epileptic spasms more frequent with eating and during sleep. These were partially responsive to levetiracetam.

He now has profound developmental delay; unable to sit and no socially responsive smile. He only sleeps for 3 hours at a time. He developed roving eye movements by 6 months and vertical nystagmus by 9 months. There were neonatal feeding difficulties and now he has pureed food orally. He has acquired microcephaly. By 4 months he was hypotonic. MRI brain showed mild posterior fossa atrophy, particularly affecting the cerebellar vermis at 2 years.

Summaries of epilepsy in other patients

Patients 3 and 4 are sisters who had abnormal development from birth. Both had epileptic spasms at 6 months however Patient 3 had upper limb clonic seizures prior (4 months) and developed generalised tonic-clonic seizures at 11 months. Her spasms resolved at 14 months but recurred at 3 years. EEGs performed as part of a work up for delay showed multifocal discharges (6 weeks) evolving to burst suppression (2 months) and hypsarrhythmia (6 months). She died, 13-years-old, in her sleep. Her sister is now 2-years-old. Her epileptic spasms quickly resolved and she developed focal impaired awareness and clonic seizures at 2 years which responded to levetiracetam. EEGs showed multifocal discharges and slowing.

Patient 5, a 3-year-old girl, presented with nystagmus and abnormal motor development at 4 months and now has profound impairment. At 6 months she had a single tonic-clonic seizure lasting 90 minutes. EEG showed multifocal discharges.

Patient 6 and 7¹ are sisters who had abnormal development from birth and now, at 24 and 22 years have profound impairment. They developed epileptic spasms with hypsarrhythmia on EEG at 3 months however patient 7 first presented with focal motor seizures at 1 week. They both developed focal autonomic (13 months, 2 years respectively) and pharmaco-resistant ongoing focal tonic and clonic seizures (4 years, 5 years) with multifocal discharges on EEG.

Patient 8¹, a 15-year-old girl with profound disability had abnormal development by 3 months. Epileptic spasms and focal tonic seizures developed at 3 years and were pharmaco-resistant. EEG at 3 years showed hypsarrhythmia which evolved over time to multifocal discharges.

Patient 9¹, a 8-year-old girl with profound impairment had abnormal development from birth. She had epileptic spasms from 2 to 24 months and EEG showed burst suppression. EEG evolved to multifocal discharges by 3 years but she had no further seizures until 6 years when she developed ongoing tonic seizures.

Discussion:

Here we describe the epileptology of *GNB5* encephalopathy. *GNB5*-DEE is characterized by abnormal development prior to infantile-onset seizures but children can first present with developmental delay, seizures, nystagmus or bradycardia. Seizure onset occurs at a median age of 3 months; focal seizures occur initially in some with almost all cases evolving to epileptic spasms within a few months. They develop multiple seizure types including focal, tonic-clonic and tonic seizures. Burst-suppression and hypsarrhythmia are usual in the first year of life, and later EEGs show generalized slowing and multifocal discharges. The outcome is extremely poor with profound impairment.

Our new cases bring the number of individuals with a *GNB5*-related disorder to 26 (from 13 families), with epilepsy in 15. In addition to our five new cases, we obtained additional epilepsy phenotyping data on four individuals from three published families, to delineate the picture of *GNB5*-DEE¹. There is one additional published family from Turkey with six affected individuals; the DEE was described in one child and mirrors our cases².

Two of our nine patients presented with apnea and cardiac arrhythmia at 5 hours and day 3 of life. The predominant cardiac arrhythmia is bradycardia with sinus pauses, which is frequently

asymptomatic and may become more prolonged in sleep. Eight of our nine patients had bradycardia. The remaining child died in her sleep at 13 years; her death may have been cardiac or due to sudden unexpected death in epilepsy (SUDEP). Although SUDEP occurred in sleep in two members of a family with a different *GNB5* variant², the cardiac manifestations could potentially cause or contribute to death.

Our five new cases confirm the previously hypothesised *GNB5* genotype-phenotype correlation, in which patients with biallelic loss-of-function variants have a more severe neurodevelopmental phenotype than those with non-truncating variants¹. All nine of our children had biallelic variants predicted to result in protein truncation and a profound DEE. Conversely, individuals without epilepsy all have at least one missense or splice site variant (Figure 1b). Homozygosity for the same missense variant has been seen in three families with non-epileptic, milder phenotypes, with either speech delay or mild intellectual disability^{1,4}. Two siblings without seizures were homozygous for a variant that was predicted to affect splicing, but this was not proven *in vitro*¹. Interestingly, two recently reported children who were compound heterozygous for frameshift and missense variants had an intermediate phenotype^{3,5}. In both cases there was significant developmental delay at a year of age. Neither child had seizures, but one had an abnormal EEG showing multifocal sharp waves³. Two of our nine cases had atypical seizure presentation: Patient 5 a single episode of status epilepticus; patient 8 epileptic spasms at 3 years. Their genotype did not provide an explanation for this. They had the same amino acid change as patient 2 who had a typical epilepsy phenotype.

GNB5-DEE is distinctive and recognizable with neonatal cardiac manifestations in some, abnormal development, focal seizures and epileptic spasms. Early genetic diagnosis is important, as bradycardia is almost universally present, and 5/15 patients with DEE have died. In those with a diagnosis of *GNB5*-DEE, modifiable cardiac and epilepsy risk factors should be considered.

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Disclosures:

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figure 1

- a) Pedigrees of patients 1 and 2. Variants relate to NCBI reference sequence NM_006578.3. Plus symbol indicates wild type sequence.
- b) Schematic representation of the GNB5 protein. Variants causing developmental and epileptic encephalopathy (DEE) shown above; variants causing developmental encephalopathy without epilepsy (DE) shown below. Red symbols indicate variants predicted to result in protein truncation, green symbols indicate missense variants. Homozygous variants are indicated by a circle around the colored symbol. Arcs represent compound heterozygous variants. Recurrent variants are shown in bold. Novel variants are underlined. Numbers in brackets indicate references of reported cases.

Table 1. Clinical features of patients with *GNB5*-DEE.

Patient characteristics									
Patient (sex, age)	1 (M, 10y)	2 (M, 3y)	3 (F, deceased 13y)	4 (F, 2y)	5 (F, 3y)	6 (F, 24y) ¹	7 (F, 22y) ¹	8 (F, 15y) ¹	9 (F, 8y) ¹
Ethnicity	Cambodia	Pakistan	Algeria	Algeria	Pakistan	Italy	Italy	India	Jordan
Consanguinity	Second cousins	First cousins once removed	First cousins	First cousins	No	No	No	No	First cousins
GNB5 variants (hg19, NM_006578.3)									
Maternal	c.136delG, p.Glu46fs8*	c.906C>G, p.Tyr302*	c.242C>A, p.Ser81*	c.242C>A, p.Ser81*	c.906C>A, p.Tyr302*	c.994C>T, p.Arg332*	c.994C>T, p.Arg332*	c.906C>G, p.Tyr302*	c.249+1G>T, p.Asp84Leufs31*
Paternal	c.136delG, p.Glu46fs8*	c.906C>G, p.Tyr302*	c.242C>A, p.Ser81*	c.242C>A, p.Ser81*	c.906C>A, p.Tyr302*	c.249G>A, p.Asp84Valfs52*	c.249G>A, p.Asp84Valfs52*	c.906C>G, p.Tyr302*	c.249+1G>T, p.Asp84Leufs31*
Epileptology									
Age delay noted	Birth	2m	Birth	Birth	4m	Birth	Birth	3m	Birth
Seizure onset age and type (offset)	11d – FHC (7w)	3m – ES (4m)	4m – C (6m)	6m – ES (7m)	6m – TC - SE (single)	3m - ES (13m)	1w - FM (5m)	3y - ES (7y)	2m - ES (2y)
Other seizure onset age and types (offset)	3m – ES (4m), 21m - FBTC & FT triggered by fever (5y)	18m – TC (23m); 23m – ES	6m – ES (14m), GTCS (11m) 3y – ES	2y – FIAS, FC (2y)	No other	13m – F autonomic; 4y - FT, C	3m ES (6m); 2y – F autonomic (5y); 5y – FT, FC triggered by fever	3y – FT	6y - T
EEG	1m - MFD; 3m - BS	1m – N; 3m – BS, 4m - N	6d – N; 6w – MFD, slow; 2m & 4m - BS; 6m – Hyp; 14m & 3y – Slow	2m & 6m – N; 7m & 2y - MFD, slow	5m – N; 6m; MFD; 2y – slow	3m – Hyp; 9y & 11y - MFD, slow	3m – Hyp; 7y & 20y - MFD, slow	3y - Hyp; 3y & 5y - MFD, slow	5m - BS; 3y – MFD, slow, suppression L hemisphere
Neurological examination	Hypotonia, contractures	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia, decreased reflexes	Hypotonia decreased reflexes	Hypotonia, contractures, decreased reflexes	Hypotonia progressed to spasticity
AED trials	CBZ, PRD	PRD, VGB, TPM,	CZP, PB, VPA, PHT,	CLB, <u>LEV</u>	<u>PB</u>	VPA, VGB, ACTH,	VPA, VGB, ACTH,	VGB, LEV, OX, CLB,	VPA, VGB, TPM,

<u>(current underlined)</u>		CZP, <u>VPA</u> , <u>LEV</u> , <u>NTZ</u>	VGB, PRD, CLB			<u>TPM</u> , <u>PB</u>	<u>TPM</u> , <u>PB</u>	<u>LEV</u> , <u>VPA</u>	<u>PB</u>
Developmental outcome	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA	Profound ID - NV, NA
MRI	2w, 19m, 6y - N	1w, 3m - N; 2y - mild cerebellar atrophy	2w, 7m - N	6m - mild ventricular asymmetry	5m - long posterior corpus callosum	3 y - N	2y - N	3m, 2y, 3y - N	5m - increased signal BG & brainstem ; 21m - cerebral atrophy
Other									
Cardiac findings (presentation and age)	Sinus bradycardia with 4.2s pauses (cyanosis 1d)	Junctional rhythm with 6.9s pauses (apnea 3d)	Normal echocardiogram	Sinus bradycardia, (asymptomatic 2y)	Sinus bradycardia with 4.2s pauses, (asymptomatic 4m)	Sinus bradycardia - exacerbated by fever or sleep (apnea 11m)	Sinus bradycardia – exacerbated by fever or sleep (asymptomatic)	Sinus bradycardia with 2.8s pauses (asymptomatic 2y)	Sinus bradycardia (apnea 3m)
Ophthalmology findings	Cortical visual impairment, optic atrophy; no ERG	Vertical nystagmus; no ERG	Nystagmus; no ERG	Vertical nystagmus, retinopathy on ERG	Nystagmus, retinopathy on ERG	Nystagmus, retinopathy on ERG	Nystagmus, retinopathy on ERG	Nystagmus, retinopathy on ERG	Cortical visual impairment, strabismus; no ERG
Additional features	Pyloric stenosis, G-tube, scoliosis	Microcephaly					Weight <1 st %		Height & weight <3 rd %

M – male, F– female; y – years; m – months; w – weeks; d – days; s – seconds; C - clonic seizure; ES – epileptic spasms; F – focal seizure; FBTC – focal to bilateral tonic clonic seizure; FHC – focal hemiclonic seizure; FIAS – focal impaired awareness seizure; FM – focal motor seizure; FT – focal tonic seizure; GTCS – generalised tonic-clonic seizure; SE – status epilepticus; T – unknown onset tonic seizure; TC – unknown onset tonic clonic seizure; NV – nonverbal; NA – nonambulatory; ERG – electroretinogram; G-tube – gastrostomy tube; ACTH – adrenocorticotrophic hormone; CLB – clobazam; CZP – clonazepam; CBZ – carbamazepine; LEV – levetiracetam; NTZ – nitrazepam; OX – oxcarbazepine; PB – phenobarbitone; PHT – phenytoin; PRD – prednisolone; TPM – topiramate; VGB – vigabatrin; VPA – valproate; ID – intellectual disability; EEG – electroencephalogram; BS – burst suppression; FD – focal epileptiform discharges; Hyp – hypsarrhythmia; MFD – multifocal epileptiform discharges; MRI – magnetic resonance imaging; N – normal.

