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Genetic characterization and long-term management of severely affected siblings with intellectual developmental disorder with cardiac arrhythmia syndrome

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ABSTRACT

We report two brothers with severe global cognitive and motor delay, cortical visual impairment and sick sinus syndrome who were born to consanguineous parents. Standard genetic evaluations did not reveal the cause of their mental retardation. As expected, chromosomal microarray (CMA) revealed extensive regions of homozygosity. Exome sequencing revealed that both affected boys were homozygous for a nonsense mutation in the G-protein β5 (*GNB5*) gene (NM_016194.3:c.1032C > G; Tyr344Ter), and that the parents were carriers of this mutation. No other DNA variants that were explanatory for the sick sinus or the developmental delay/intellectual disability were identified, and no other clinical parameters are likely to have contributed to this unusual combination of phenotypes. The neurologic features of our patients are more severe than those of most of the other patients previously reported with *GNB5* variants, probably because of the homozygous, complete loss-of-function (nonsense/stop-gain) nature of their variant, and their clinical course has been monitored for longer duration.

1. Introduction

GNB5 is one of the more recently characterized genes that plays an important role in neurologic function and development. This gene and its protein product, Gβ5, had initially been studied in both mouse and human, and appear to be important in autonomic regulation of the nervous system with a variable effect on a multitude of neurologic functions and growth as discussed in more detail in this article [1,2].

In humans, Lodder et al. first identified 9 individuals (six females and three males) from six unrelated families with *GNB5* variants demonstrating a spectrum of neurologic and cardiac manifestations [3]. The affected individuals' phenotype included global developmental delay, seizure, nystagmus, hypotonia, and sinus bradycardia, with no clear funduscopic or brain structural abnormality. This condition has been named Intellectual Developmental Disorder with Cardiac Arrhythmia (IDDCA) Syndrome. As predicted, individuals with loss-of-function alleles had more severe symptoms than those with missense variants. To the best of our knowledge, to this date 24 cases of IDDCA syndrome with various levels of cognitive, vision, cardiac and motor dysfunction ranging from mild to severe, and a wide variety of variants in the *GNB5* gene have been reported [3–9].

We report the phenotype and clinical course of two brothers, currently 18 and 22 years of age, from a consanguineous marriage with homozygous loss-of-function variant in *GNB5*. Both individuals have been followed at our institution since the younger sibling's birth. The duration and continuity of our direct observation, as well as the severity and certain nuances of their presentation, provide a broader understanding of this unusual and rare syndrome. Furthermore, we discuss a possible treatment for the seizure disorder found in this genetic anomaly that may be of therapeutic value to others.

2. Case report

2.1. Sibling 1

The index case is a 22-year-old male, first of two similarly affected boys born to healthy parents who are first cousins of Pakistani origin.

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He was delivered at 41 weeks of gestation *via* C-section due to breech presentation with Apgar scores of 9 each. His birth weight was 3.0 kg (15th–25th percentile). His newborn exam was normal with no gross abnormalities or dysmorphic features. However, he had difficulty feeding after birth and required nasogastric tube feeding.

His first neurodevelopmental issues were noticed at 3 months of age when his parents became concerned about his development and eye conjugation. His strabismus, lateral gaze nystagmus, and lack of fixation led to further evaluation and eventual diagnosis of cortical blindness by ophthalmology. His most recent funduscopic exam at age 22 demonstrated normal retina. However, further evaluation of his retinal function is pending possible electroretinogram in the future.

He continued to show slow developmental progress until one year of age when he reached the peak of his developmental progress. At that time, he was able to sit and scoot. He was subsequently diagnosed with cerebral palsy, spasticity of upper and lower extremities, and progressively lost almost all cognitive, speech (receptive and expressive), gross- and fine- motor functions. Presently, his motor function is limited to semi-purposeful arm movements. He also has an erratic sleep pattern with cycles of prolonged insomnia lasting up to 36 h, followed by long bouts of uninterrupted sleep for about 16 to 18 h.

At three months of age, an electroencephalogram (EEG) testing was done to examine his spastic movements, which demonstrated epileptiform sharp waves and spikes that were frequently associated with slow waves, mainly during drowsiness and sleep. The abnormalities were most pronounced in the right central temporal region, although there were also independent bursts in the left side. The patient continued with similar movements during sleep until 7 years of age. The frequency and intensity of these movements significantly improved after 2 years of age with occasional nighttime spasms that were triggered by insomnia or randomly spontaneous excitement of his mood. Brain magnetic resonance imaging (MRI) obtained at 4 years of age was normal. Due to low intensity and frequency of his seizures and poor response to various treatments that caused severe somnolence, all of his seizure medications were discontinued at 4 years of age. However, during his 18th year of life he began demonstrating spastic movements of the upper extremities during his sleep, lasting up to 30 s. Subsequent EEG showed mild to moderate diffuse slowing with no epileptiform features. His seizures are typically exacerbated by poor or erratic sleep that continues to be poorly controlled despite a multitude of pharmacologic interventions. He was subsequently treated with levetiracetam with significant improvement and rare breakthrough seizures. However, due to parental concerns for side effects such as somnolence, and low frequency and intensity of his seizures, he is maintained at a low levetiracetam dosage of 6 mg/kg/day dispensed daily.

Not unlike previously reported cases, at 30 months of age he was diagnosed with sick sinus syndrome with frequent pauses lasting 6 s that led to the placement of a pacemaker. His parents eventually decided to allow the pace maker battery to run out. Subsequently this patient has had no cardiovascular-related events despite the continuation of his sick sinus syndrome and no functioning pacemaker since the age of 17 years.

At 21 years of age, he developed intermittent urinary retention requiring occasional catheterization for relief. This is believed to be more likely due to the progression of his neurologic symptoms since it does not correlate with the initiation or change in dosage of his medications or treatment regimen.

He has continuously depended on gastric-tube feeding due to poor bulbar function and aspiration risk since 5 years of age. He has multiple food allergies causing both gastrointestinal and skin reaction that were confirmed with food allergy testing, and has had multiple admissions for severe bouts of reflux and repeated emesis leading to admission for dehydration and occasional esophageal bleeding.

2.2. Sibling 2

His younger brother was diagnosed at birth but has had an overall milder gastrointestinal and cardiac course with some differences in neurologic manifestations. His Apgar scores were 2 and 8 at birth while his weight was 2.54 kg (3rd-15th percentile). He had no dysmorphic features. His brain MRI, obtained shortly after birth, and as recently as 13 years of age, have been consistently normal. During infancy, he demonstrated episodic leg and arm stiffness that would last 10–15 s followed by post-ictal sleep. His EEG demonstrated bursts of generalized slowing intermixed with spikes and paroxysmal fast activity during sleep, with no evidence of any seizure activity while awake. These symptoms gradually resolved after the first two years of life. He presently has no clinical signs of seizure, and has never been on anti-seizure medications. He also has cortical blindness with strabismus, lateral gaze nystagmus, and poor eye fixation. His funduscopic exam is significant for bilaterally small, anomalous, tilted, pale discs and peripapillary atrophy indicating optic nerve atrophy. Similar to his brother, evaluation of the extent of retinal dystrophy is pending possible electroretinogram in the future.

His developmental course, cognition and ability to communicate are the same as his brother. Because of the observed sick sinus syndrome in his older brother, he was carefully observed by ECG and revealed to also have sick sinus syndrome during the first week of life that has remained mild and asymptomatic; thus, no intervention has been performed. Unlike his brother, with some feeding assistance (food or water placed inside the mouth), he is able to chew and swallow independently in order to maintain adequate hydration and nutrition without a gastric tube. He rarely experiences mild reflux, and has no food allergies.

3. Methods

3.1. Sample collection and genomic DNA extraction

Both siblings and mother were consented for participation in the UCLA IRB-approved research study for Molecular Genetic Studies of Degenerative Disorders (IRB#11-001087). Blood samples were collected from the unaffected mother and the two affected siblings. Unaffected father was not available at the time. High molecular weight genomic DNA was extracted at the UCLA Molecular Diagnostics Laboratories using QIAcube.

3.2. Chromosomal microarray

Chromosomal Microarray (CMA) was performed twice using Affymetrix SNP array platforms, SNP 6.0 (for clinical diagnostics) and CytoScan HD (for confirmation) at the UCLA Molecular Diagnostics Laboratories. Data was analyzed following the standard procedures and the ACMG guidelines for interpretation and reporting. A UCLA-customized annotation track containing regions reported to have position effect on well-characterized genes was used for the analysis [10,11].

3.3. Exome sequencing

Sequencing library preparation was performed using Illumina TruSeq DNA Sample Prep Kit and Illumina TruSeq Exome Enrichment Kit. Sequencing was performed within the UCLA Clinical Genomics Center on Illumina HiSeq2000 as a 100 bp paired-end run. Sequencing data were analyzed using the CAP and CLIA validated UCLA Clinical Exome Sequencing data analysis pipeline as previously described [12]. The variant c.1032C > G was confirmed in the two sibs and both unaffected parents by Sanger sequencing in the UCLA Orphan Disease Testing Center.

Table 1
List of all rare homozygous variants within the ROH segregating with the disorder.

Gene name	Genomic position (hg19/b37)	DNA change	Protein change
TECTA	11: 121061505	NM_005422.2: c.6458C > T	p.Thr2153Met
TBRG1	11: 124493091	NM_032811.2: c.112 T > A	p.Tyr38Asn
ATP8B4	15: 50339635	NM_024837.2: c.114 T > G	p.Tyr38X
LEO1	15: 52230365	NM_138792.2: c.1989A > T	p.Glu663Asp
GNB5	15: 52416814	NM_016194.3: c.1032C > G	p.Tyr344X

4. Results

4.1. Chromosomal microarray

CMA revealed that both affected boys had substantial regions of homozygosity as expected due to consanguinity but no pathogenic copy number variants. The index case had 108 Mb (total) regions of homozygosity (ROH) on chromosomes 7, 10, 11, 13, 14, 15 and 17 while his younger brother had 128.8 Mb (total) ROH on chromosomes 1, 2, 8, 11, 15, and 19. Of this, they shared ~47 Mb of the homozygous regions across the genome including the *GNB5* locus.

4.2. Exome sequencing

Across the RefSeq defined exome, each genomic DNA sample had an average depth of coverage of 45-fold with on average > 87% of the exome covered with at least 10 independent reads. Homozygosity mapping using the exome sequencing data confirmed the findings from CMA. Within the shared regions of homozygosity, rare variants (< 1% MAF in the exome variant server) that were homozygous in the two siblings but heterozygous in the unaffected mother were searched for [13]. In total, 5 such variants were identified across 5 genes (Table 1). Only one of these genes, *TECTA*, had been associated with a human disorder at the time of initial analysis. Variants in *TECTA* are associated with autosomal dominant deafness type 12 (DFNA12) [MIM: 601543], or autosomal recessive deafness type 21 (DFNB21) [MIM: 603629]. While the variant was predicted to be damaging by both SIFT and Polyphen, neither the patients nor either of the parents had evidence of hearing loss. The other 4 genes had not been associated with human disorder. Specifically, no human disease was associated with *GNB5* variants although there was a mouse knock-out model of *Gnb5* reported with substantial neurological defects [14]. *GNB5* mutations in humans are now associated with intellectual disability and in a total of 26 individuals, homozygous or compound heterozygous *GNB5* mutations are reported [3–9]. Our patients are homozygous for the NM_016194.3:c.1032C > G; p.Tyr344Ter mutation. This base position, 1032C, was also mutated in the patient reported by Shao et al. (1032C > A, p.Tyr344Ter) [9]. In both our patients and the one reported by Shao et al., the mutation results in the same premature stop codon. (See Table 2.)

5. Discussion

The *GNB5* gene encodes the G protein β5 [13,14]. Gβ5 is part of a signal-transducing G-protein β subunit family. Gβ5 is preferentially expressed in the brain and the nervous system, and it is unique in its ability to heterodimerize with G-protein signal regulating protein family R7 [15,16]. After binding to the R7 proteins, Gβ5 forms a complex with SNARE-like membrane-anchoring proteins [17]. From work in animal models, we know that the Gβ5 protein is required for normal development of the brain and the retinal photoreceptor layer [2,3,14].

The siblings in this report suffer from IDDCA syndrome with severe neurologic deficiency and cardiac issues, which have been reproduced in knock-out mouse and zebrafish models and reported to varying degrees in 23 individuals [3–8,14]. The two siblings presented here seem to share many of the features seen in the more severely affected individuals that were previously reported, including sinus node problems, blindness and cognitive deficit. Furthermore, there appears to be no structural abnormalities in any of the related organs. However, there appears to be some differences in the type and severity of the clinical presentation of the siblings in this report compared to others. One of the most striking differences is the early presentation of complete central blindness and oculomotor dysfunction in our patients, while the previously reported cases' visual deficit was limited to nystagmus and some retinal disease. Similarly, many of the previous patients presented with hypotonia, while both siblings in our report appear to have severe truncal and limb spasticity with no evidence of hypotonia.

Furthermore, both siblings' seizure disorder appears to correlate with the severity of their clinical presentation, with the more severely affected sibling (sibling 1) continuing to need treatment, and the less severely affected sibling (sibling 2) demonstrating no obvious clinical seizures at this time. Only about half of the previously reported patients in the literature experienced seizures at all, with the others demonstrating homozygous or heterozygous missense variants [4].

We hypothesize that our patients' homozygous nonsense mutation located about 50 nucleotides from the coding terminus of the gene may account for the functional severity, in contrast to most of the other reported patients who were homozygous or compound heterozygous for missense and/or splice-site variants. While the latter class are by definition loss-of-function, their ultimate impact *in vivo* is often modified by the presence of alternative transcripts and “leakiness” of the splice mechanisms, whereas a translation-termination mutation is considered to be absolute [18]. Despite their apparent LoF effects, not all nonsense mutations, even when in the homozygous state, cause severe disease. Their ultimate effect on the organism depends on whether the associated disease is due to loss-of-function or gain-of-function (some of which behave as “dominant-negatives”), and on the potential for other genes (modifier genes) to substitute for the lost function. In fact, population genomic sequencing studies have revealed that so-called “human knockouts”, in which both alleles of a gene are affected, are fairly common in the healthy population [19]. Our study, added to the other patients with homozygous premature stop codons in the literature who are also more severe (Lodder et al. Family B, and Poke et al. patient 2), argues strongly that GNB5 is an essential gene [3,4]. Moreover, most of the more mildly affected patients reported previously have had one or two missense variants, or one missense and one null variant [3,5,8]. Although the siblings reported in the article seem to have significantly worse visual deficit than the family B in Lodder et al. and case 2 in Poke et al., all these individuals are nonverbal, and have severe cognitive deficit and cardiac arrhythmia [3,4]. Therefore, there appears to be an emerging genotype-phenotype correlation with the more severe patients having null mutations compared to missense mutations.

Based on our two-decade experience of managing these patients, levetiracetam may be of use in treating refractory seizures in similar cases.

Table 2
Clinical features of patients with GNB5.

	[3]	[3] Family A II.2	[3] Family B II.1	[3] Family C II.2	[3] Family C II.3	[3] Family D II.2	[3] Family E II.1	[3] Family E II.2	[3] Family F II.1
Maternal allele	c.994C > T p.Arg332*	c.994C > T p.Arg332*	c.249+1G > T p.Asp84Leufs* 31	c.249+3A > G p.Asp84Valfs* 31	c.249+3A > G p.Asp84Valfs* 31	c.906C > G p.Tyr302*	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu
Paternal allele	c.249G > A p.Asp84Valfs* 52	c.249G > A p.Asp84Valfs* 52	c.249+1G > T p.Asp84Leufs* 31	c.249+3A > G p.Asp84Valfs* 31	c.249+3A > G p.Asp84Valfs* 31	c.906C > G p.Tyr302*	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu
Gender, age (Years)	F, 24	F,. 22	F, 8	F, 13	M, 11	F, 14	F, 15	M, 10	M, 25
Cognitive deficit (CD), school issues	Severe CD	Severe CD	Severe CD	Severe CD	Severe CD	Severe CD	Mild CD	Mild CD	Mild CD
Epilepsy	+	+	+	-	-	+	-	-	-
Speech	Severe delay	Severe delay	nonverbal	nonverbal	Severe delay	nonverbal	Mild delay	Mild delay	Mild delay
Motor function	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia	-	Fine motor deficit	-
Vision	Nystagmus	Nystagmus, Retinal degeneration	Nystagmus	Nystagmus	Nystagmus	Nystagmus	-	-	Keratoconus
Cardiac anomalies	Sick sinus syndrome, Escape beats	Bradyarrhythmia, Escape beats, PFO	Sick sinus syndrome	Sick sinus syndrome, Pacemaker implanted	Sick sinus syndrome, Pacemaker implanted	Increased PR interval/ intermittent Wenchebach	Sick sinus syndrome, Escape beats	Sick sinus syndrome, Escape beats	Sick sinus syndrome
Gastrointestinal anomalies	Reflux	Reflux	-	Reflux	Reflux	Reflux	-	-	NA
others									

	[5] V:1	[5] V:2	[5] V:3	[5] IV:1	[5] IV:6	[6] V.1	[6] IV.14	[7]
Maternal allele	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.355delG p.Ala119Profs* 16	c.355delG p.Ala119Profs* 16	c.222_226delTAAGA p.Asp74Glufs* 52
Paternal allele	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.242C > T p.Ser81Leu	c.355delG p.Ala119Profs* 16	c.355delG p.Ala119Profs* 16	c.737G > A p.Arg246Gln
Gender, age (Years)	F ,12	F, 11	F, 5	F, 7	F, 11	M, 3	F, 11	M, 2
Cognitive deficit (CD), school issues	Normal IQ, ADHD, academic performance issues	Normal, ADD	NA	Normal IQ	NA, ADHD	Severe CD, autistic (midline hand automatism, no eye contact)	Severe CD, autistic (midline hand automatism, no eye contact)	Severe CD
Epilepsy	NA	NA	NA	NA	NA	+	+	-
Speech	Severe language delay	Severe language delay	Severe language delay	Severe language delay	Severe language delay	Nonverbal	Nonverbal	Nonverbal
Motor function	-	-	Motor delay	Hypotonia, Motor delay	Mild motor delay	Hypotonia	Hypotonia	Central hypotonia
Vision	NA	NA	NA	NA	NA	Retinal degeneration	Retinal degeneration	Severe reduction in cone and rod function
Cardiac anomalies	NA	NA	NA	NA	NA	Sinus arrhythmia/sinus bradycardia	Sinus arrhythmia/sinus bradycardia	Sinus arrhythmia/sinus bradycardia
Gastrointestinal anomalies	NA	NA	NA	NA	NA	-	-	+
others								Left-sided hearing loss, intermittent extremity hypertonia, laryngomalacia, thin corpus callosum

	[8]	[4] Case 1	[4] Case 2	[4] Case 3	[4] Case 4	[4] Case 5	[9]	Current Case Sib 1 I.1	Current Case Sib 2 I.2
Maternal allele	c.242C > T p.Ser81Leu	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.1032C > A/p.Tyr344 * , c.906C > A/ p.Y302 *	c.1032C > G; Tyr344X	c.1032C > G; Tyr344X
Paternal allele	c.222_226delTAAGA p.Asp74Glufs* 52	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.1032C > A/p.Tyr344 * , c.906C > A/ p.Y302 *		
Gender, age (Years)	F, 2.5	M, 10 y	M, 3 y	F, deceased 13 y	F, 2 y	F, 3 y	F,3 y	M, 21	M, 17

(*continued on next page*)

Table 2 (*continued*)

	[8]	[4] Case 1	[4] Case 2	[4] Case 3	[4] Case 4	[4] Case 5	[9]	Current Case Sib 1 I.1	Current Case Sib 2 I.2
Cognitive deficit (CD), school issues	Mild CD	Profound CD	Profound CD	Profound CD	Profound CD	Profound CD	Global delay	Severe CD	Severe CD
Epilepsy	-	+	+	+	+	+	+	+	
Speech	Expressive speech delay	Nonverbal	Nonverbal	Nonverbal	Nonverbal	Nonverbal	-	Nonverbal	Nonverbal
Motor function	Hypotonia	Hypotonia, contractures	Hypotonia	Hypotonia	Hypotonia	Hypotonia	Hypotonia	No purposeful movement, hypertonia (central and extremities)	No purposeful movement, hypertonia (central and extremities)
Vision	Strabismus	Cortical visual impairment, optic atrophy	Vertical nystagmus	Nystagmus; no electroretinogram	Vertical nystagmus, retinopathy on electroretinogram	Nystagmus, retinopathy on electroretinogram	Nystagmus, retinopathy on electroretinogram	Cortical blindness, strabismus, lateral gaze nystagmus	Cortical blindness, strabismus, lateral gaze nystagmus
Cardiac anomalies	Sick sinus syndrome	Sinus bradycardia with 4.2 sec pause	Junctional rhythm with 6.9 sec pause	Normal echocardiogram	Sinus bradycardia	Sinus bradycardia	bradycardia	Sinus bradycardia	Sinus bradycardia
Gastrointestinal anomalies	-	Pyloric stenosis, G-tube						Severe Reflux, esophageal bleeding, Food allergy, G-tube dependent	Mild reflux
others		scoliosis	Microcephaly				Central sleep apnea	Erratic sleep cycle	Erratic sleep cycle

The astrisks were inlcuded as part of the gene nomenclature that is commonly in use indicating, based on its location, a gene vs an allele.

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