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Short communication

Familial early infantile epileptic encephalopathy and cardiac conduction disorder: A rare cause of SUDEP in infancy

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1. Introduction

GNB5 encodes the G protein b involving in subunit 5 inhibitory G protein signaling and is preferentially expressed in heart, brain and nervous system with a direct role in parasympathetic control of heart rate, motor function and vision [1].

Recently, homozygous or compound heterozygous GNB5 gene mutations have been reported in a rare multisystem syndrome with ocular, cardiac conduction and neurological findings including cognitive disability and epilepsy (MIM: 617173) in 9 patients from 6 families [1]. The spectrum of neurological findings ranged from epileptic encephalopathy and profound developmental delay to only borderline or mild cognitive disability. Concurrently, Shamseldin et al. [2] described a neuropsychiatric phenotype without epilepsy or systemic findings in a consanguineous family with a novel homozygous missense mutation on GNB5 gene (MIM: 617182).

Here we report an extended consanguineous family with early infantile epileptic encephalopathy (EIEE), low birth weight, severe neurological developmental delay, nystagmus, retinal degeneration, cardiac conduction disorder and premature sudden death (SD) with a novel homozygous deletion of GNB5 gene.

2. Case report

Case IV.14: The proband, aged 10 years, is a pair of a monozygotic twin born at 40 weeks with 1800 gr birth weight and admitted to intensive care unit due to poor sucking lasting for 2 weeks. (Fig. 1). Hypomotor seizures started at 6 weeks of age and epileptic spasms at 4 months which ceased with vigabatrin. She had occasional hypomotor seizures which were completely resolved by topiramate at early childhood. She is hypotonic without having any developmental milestones, even at pre-seizures period and severely autistic with midline hand automatisms and lack of eye contact. She has horizontal nystagmus, no eye tracking, prominent forehead and acquired micro-brachicephaly. EEG examinations demonstrate multifocal spikes, disorganized background and lack of sleep spindles. Cranial magnetic resonance imaging and metabolic work-up were irrelevant. Ocular electrophysiological examinations revealed retinal degeneration. Abdominal US examination and echocardiography were normal. Electrocardiography and Holter monitoring identified normal PR and QTc intervals, marked sinus arrhythmia, sinus bradycardia with multiple sinus pauses up to 4.5 s. Transeosefageal electrophysiologic (TOE) study for examination of sinus node function and measurement of sinus node recovery time and subsequent pacemaker implantation was suggested, but refused by parents.

Cases IV.8 and IV.11-13: The phenotype is identical in 4 siblings and proband (Fig. 1). Case IV.8 died when she had a severe acute gastroenteritis at 5.5 months of age. Case V.11 and IV.13 were found

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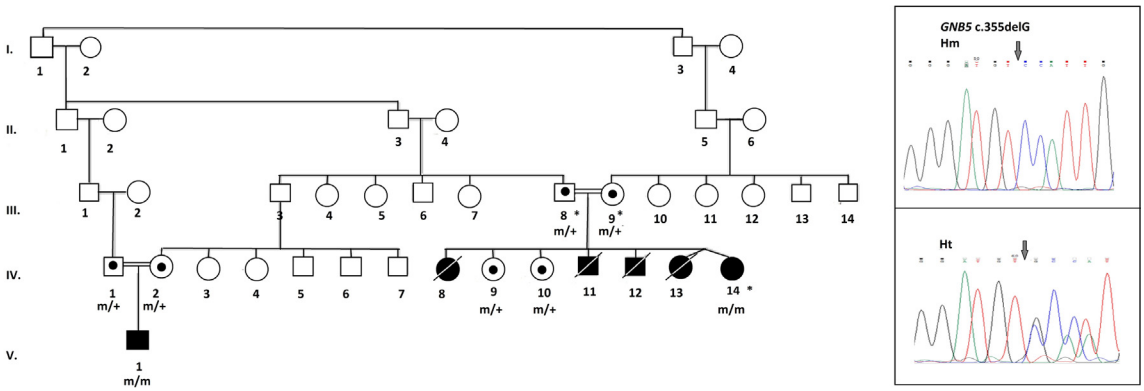

Fig. 1. Family pedigree. Affected individuals are shown as black, mutation carriers are denoted with a black dot. m, represent mutated allele i.e. *GNB5* c.355delG and + represents normal allele. Individuals selected for whole exome sequencing are marked with a star. Right panel is showing the chromatograph of *GNB5* c.355delG single nucleotide deletion in homozygous (upper) and heterozygous (bottom) state.

death during sleep at 7 and 8 months, respectively when they had rare short seizures. Case IV.12 died at 7 years of age with a diagnosis of multiple organ failure at a different hospital. He had a documented sinus bradycardia and sinus arrhythmia in admission. We do not have any postmortem medical reports of these cases.

Case V.1: The proband's second degree cousin, aged 2 years has the same phenotype described for Case IV.14 (Fig. 1). Cardiac evaluation revealed sinus arrhythmia with normal PR and QTc intervals and sinus bradycardia with frequent sinus pauses up to 3.3 seconds without structural abnormalities. TOE study and pacemaker implantation was rejected by the parents.

2.1. Genetic analyses

All experimental procedures were conducted in accordance with recommendations of Ethics Committee of Marmara University. The index patient and her parents were analyzed by whole exome sequencing as a part of a project aimed at genetic analysis of EIEE patients. Details of the analysis are given as Supplementary data.

A novel homozygous single nucleotide deletion on GNB5 (OMIM:604447) gene resulting in a frameshift and premature stop codon was identified (Chr 15: 52439669delC, NM_006578 355delG, A119Pfs*16) in patients IV.14 and V.1 (Fig. 1). Their parents (III.8/9 and IV.1/2 respectively) are heterozygous carriers as like unaffected siblings of patient IV.14 (IV.9 and IV.10)

3. Discussion

The variants leading to biallelic loss of functions on GNB5 gene are associated with serious cardiac conduction disorder, nystagmus, severe intellectual disability and hypotonia and represent the most severe phenotype [1]. Epilepsy was reported in 3 of 4 families with severe phenotype and EIEE was defined in only 1 patient. The presence of the most severe phenotype in our family suggests that the novel mutation causing premature stop codon on GNB5 gene is associated with loss of function.

Patients with EIEE have massive intractable seizures and severe hypotonia and are at increased risk for sudden unexpected death in epilepsy (SUDEP) related with underlying different mechanisms [3]. Patients with relatively well-controlled epilepsy, including those with infrequent seizures also remain at risk for SD. In our family, 2 of 5 affected siblings experienced SD in infancy while seizures were rather controlled. Considering cardiac conduction dysfunctions as a well-known risk factor for SD, profound sinus bradiacardia and prolonged sinus pause intervals suggesting sinus node dysfunction is probably cause of sudden death in our family.

Various neuro-cardiac ion channel genes associated with epilepsy and SUDEP are expressed in both neuro-cardiac and respiratory control pathways and indicates that some variants might predispose to SD through neurocardiac or sole cardiac mechanisms [4]. A clinically confirmed phenotype of epilepsy and cardiac arrhythmia, usually associated with mutations of genes dually expressed in the brain and in the heart is not common. As a novel gene related with neuronal and cardiac signalizing function, GNB5 supports the concept of a combined neurocardiac phenotype and to be kept in mind in patients with EIEE and premature SD. This report also emphasizes the importance of detailed cardiac evaluation in patients with EIEE, especially in families with a history of SD or SUDEP.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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