Inherited interstitial deletion of 3p22.3—p23 involving *GPD1L* gene

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Abstract

We report the first case of a 294 kb loss, notable for including the entirety of *GPD1L*, on chromosome 3p22.3—p24 in a 3-year-old girl with multiple congenital anomalies including absent left foot, single umbilical artery, bilateral vesico-ureteral reflux, rectovaginal fistula, and imperforate anus. Although *GPD1L* mutations have been associated with cardiac arrhythmias, including Brugada syndrome and sudden unexpected infant death syndrome, full deletions in the *GPD1L* gene have not been reported neither the patient nor her mother, who was later identified to carry the variant, have any signs or symptoms of Brugada syndrome. This may indicate these individuals have findings that have not yet been identified, full gene deletions of *GDP1L* are not necessarily disease causing, or there is incomplete penetrance of this gene or cardiac manifestations can occur at a later age.

Introduction

Deletions on the short arm of chromosome 3 are rare. Most of the deletions appear to fall into two groups: deletions on the 3p25—pter segment and deletions on the 3p11—p21.2 segment.[1] We report the first case of a 294 kb loss on chromosome 3p22.3—p24 in a 3-year-old girl with multiple congenital anomalies including absent left foot, single umbilical artery, bilateral vesico-ureteral reflux, rectovaginal fistula, and imperforate anus. The patient also had language delay. The deletion was notable for including the entirety of *GPD1L* (glycerol-3-phosphate dehydrogenase 1-like), whose pathogenic variants have been reported in Brugada syndrome (an inherited cardiac channelopathy that causes malignant ventricular dysrhythmias and sudden death) and sudden unexpected infant death syndrome. Full deletions in the *GPD1L* gene have not been reported, but neither the patient nor her mother, who was later iden-

tified to carry the variant, have any signs or symptoms of Brugada syndrome. This may indicate these individuals have findings that have not been yet identified, full gene deletions of *GDP1L* are not necessarily disease causing, or there is incomplete penetrance of this gene.

Case Report

The patient was the first born to non-consanguineous Hispanic parents. She was born at 37 weeks of gestation *via* C-section. Pregnancy was complicated by amniotic band syndrome, absent left foot, and single umbilical artery. No genetic testing was performed prenatally. The birth weight was 2600 g (10th centile), and the birth length was 46 cm (10th centile). The newborn screen was normal. Physical examination was notable for non-dysmorphic facial features, amputation of the left lower extremity, and an imperforate anus with a rectovaginal fistula. Surgery was performed to correct these structural defects. Subsequently, she was identified as having vesico ureteral reflux.

Overall, she attained appropriate developmental milestones except for receptive and expressive language skills. She spoke her first word at 8 months. However, at 18 months she could speak only few single words clearly. She started receiving speech therapy and general developmental therapy through the early intervention program.

On examination at the age of 3.5 years, her height was 90 cm (1st centile) and weight was 13.8 kg (23rd centile). She had mild bilateral fifth finger clinodactyly. The left foot was absent, but the long bones of the left lower limb were present. She was able to flex and extend the left knee without any restrictions. There were no other dysmorphic features. She could count to ten with her fingers enunciating the numbers clearly. She could follow basic two and three step commands without any difficulty. The remainder of the physical examination was normal.

The family history was notable for the mother having a prior unilateral nephrectomy. The remainder of the family history was positive for a remote history of sudden death in the mother's paternal grand-aunt, who also had age related heart disease and no known arrhythmias. No further details are known.

Genetic testing

Given the congenital anomalies, genetic testing was performed. An oligonucleotide single nucleotide polymorphism microarray was performed (Genome Browser Assembly hg19, GRCh37, February 2009)

and identified a copy number loss at 3p22.3—p23 of at least 294 kb from base pairs 31946587 to 32240149 (Figure 1). There are three known genes in this region: *OSBPL10* (oxysterol binding protein like 10), *ZNF860* (zinc finger protein 860), and *GPD1L*. *OSBPL10* and *ZNF860* do not currently have associated clinical phenotypes, but pathogenic variants in *GPD1L* gene (base pairs 32106620 to 32168715) have been associated with Brugada syndrome as described previously. Subsequent parental

testing confirmed the deletion was maternally inherited.

Cardiac evaluation

Due to the deletion of the *GPD1L* gene and its association with Brugada syndrome, both the patient and the mother underwent further cardiac evaluation. The mother reported that she had a normal echocardiogram and normal electrocardiograms. She was completely asymptomatic from a cardiovascular standpoint. She has not had provocative drug testing for Brugada syndrome. The patient has also been completely asymptomatic. Her serial electrocardiograms, including the ones performed with lead V1 and V2 placed higher up in the chest, were completely normal without concerns for Brugada syndrome (Figure 2). Her 48-h Holter monitor and echocardiogram were also normal. Given her young age and absence of cardiac signs and symptoms, provocative drug challenge for Brugada syndrome was deferred. The mother was encouraged to seek further cardiology testing with drug provocation. The patient will continue to be followed longitudinally. The mother was instructed to obtain an electrocardiogram should the patient develop fever.

Discussion

GPD1L and Brugada syndrome

Brugada syndrome is an autosomal dominant inherited channelopathy characterized by distinct right bundle branch block and ST-segment elevation patterns in the precordial leads V1 and V2 and a structurally normal heart.[2] Brugada syndrome patients are susceptible to sudden death due to ventricular dysrhythmias. Brugada syndrome is diagnosed when a typical Brugada *coved* ST elevation pattern is observed either spontaneously or after intravenous administration of a sodium channel blocker in at least one right precordial lead (V1, V2), placed in a standard or superior position (up to the 2nd intercostal space).[3] The prevalence of Brugada syndrome is dependent on geography and sex. Asia has the highest prevalence (0.9%) while North America has the lowest prevalence (0.2%).[4] The mean prevalence in male is about 9 times greater than in female (0.9% *vs* 0.1%).[4]

Brugada syndrome is rare in children. The typical Brugada electrocardiogram patterns were found in 0.01%-0.02% of asymptomatic children from Japan suggesting that Brugada syndrome may exist in children but becomes clinically unmasked with increasing age.[5] Moreover, the majority of children are asymptomatic at presentation with 14% presenting with syncope, 13% presenting with dysrhythmias, and rarely aborted sudden death (1%).[6] The syncopal episodes usually occur at rest.[7]

SCN5A (sodium voltage-gated channel alpha subunit 5) was the first gene implicated in Brugada syndrome and contains the majority of all pathogenic variants.[8] This gene encodes the alpha subunit of the cardiac sodium channel Nav1.5. This sodium channel subunit is responsible for phase 0 of the cardiac action potential. A minority of other potentially pathogenic variants have been reported in other genes including *GPD1L*.[8] Yet, all pathologic variants combined can only explain about 35% of all reported cases of Brugada syndrome.[8]

To date, three mutations in *GPD1L*, which encodes an enzyme that is homologous to the glycerol-3-phosphate dehydrogenase 1, have been associated with Brugada syndrome: A280V, I124V, and R189X.[9-12] Another mutation, E83K, has been associated with unexpected sudden infant death syndrome.[13] Full gene deletions of *GPD1L* for individuals diagnosed with Brugada syndrome have not previously described in the medical literature. The enzyme *GPD1L* catalyzes the conversion of glycerol-3-phosphate to dihydroxyacetone phosphate. Mutations causing loss of function of this enzyme, may be responsible for the loss of function of the sodium channel (and hence reduced the amplitude of sodium current I_{Na}). Indeed, London *at al.* showed then that the co-expression of the missense mutation A280V reduced inward Na^+ current approximately by 50%, and decreased *SCN5A* surface membrane expression.[10] Moreover, Liu *et al.* demonstrated that the A280V mutation in *GPD1L* can elevate the concentration of NAD(H), which can downregulate I_{Na} acutely through a Protein Kinase C activation and increased superoxide.[14] Valdivia *et al.* showed that the *GPD1L* mutation itself causes a loss function and decreased *GPD1L* activity.[15] This
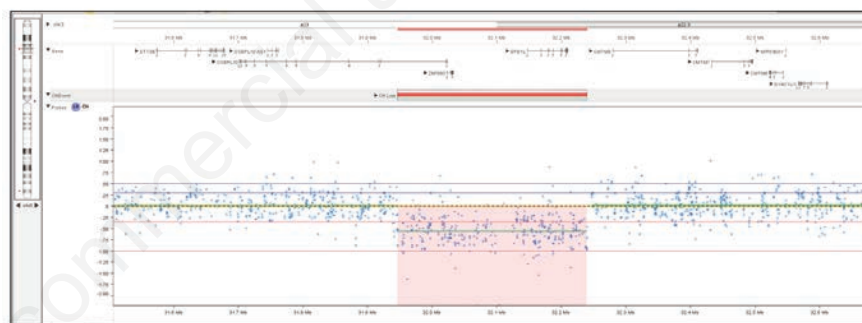

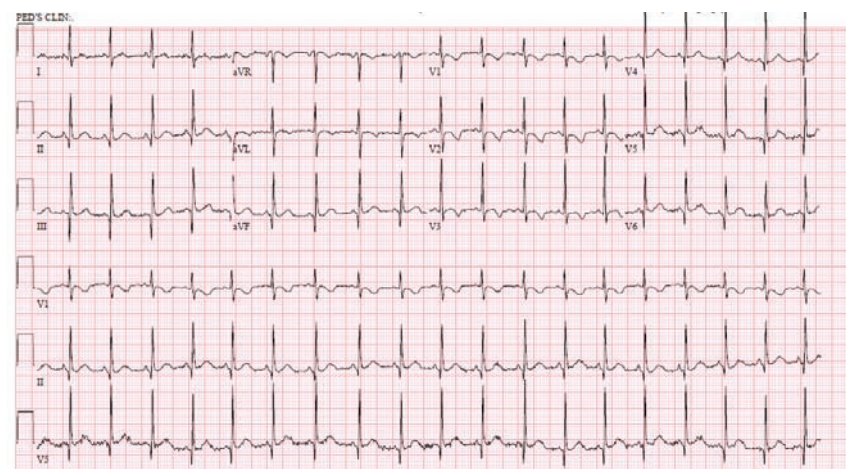**Figure 1. Schematic result of the single nucleotide polymorphism array results.**

Figure 2. Patient's normal electrocardiogram even when leads V1 and V2 were placed higher in the chest.

in turn causes increased levels of glycerol-3-phosphate, promoting the protein kinase C-dependent phosphorylation of the SCN5A that was known to decrease I_{Na}.

While *GPD1L* has been anecdotally showed to account for 11%-12% of Brugada syndrome, other studies showed no pathogenic *GPD1L* mutation, suggesting that *GPD1L* may not be a major cause of Brugada syndrome.[16,17] On the DECIPHER database (https://decipher.sanger.ac.uk/search?q=GPD1L#consented-patients/results), 8 other patients had deletions involving *GPD1L*. These were much larger deletions than in our cases. However, Brugada syndrome, sudden death, and cardiac dysrhythmias were not reported in these patients. Further studies are needed to obtain the accurate prevalence and clinical significance of *GPD1L* variants, particularly full gene deletions, in Brugada syndrome.

3p deletions syndromes

3p25-pter deletions produce a distinct clinical syndrome characterized by low birth weight, mental retardation, ptosis, micrognathia, and notably congenital heart defect in the form of complete atrio-ventricular canal defect.[18] On the other hand, proximal 3p deletions syndromes are more heterogenous depending on the break points. These syndromes involve dysmorphic facial features, early growth retardation, cleft lip and palate, developmental disorders, autistic features, and/or global developmental delay.[19,20]

The deletion in our patient has not been reported in other individuals and is smaller than the previously noted deletion syndromes on 3p. Additionally, the few deletions reported in similar regions to our patient were also larger in comparison, and the primary phenotypes of these patients were intellectual disability without major cardiac findings.[1,21] Our patient's genetic finding is unique given its small size and her presentation of multiple congenital anomalies. Additional research is needed to determine if the genes in this region are potentially associated with these findings, as *OSBPL10* and *ZNF860* do not have known clinical features at this time.

Conclusions

The complete deletion of *GPD1L* in isolation (*versus* within a larger deletion involving many other known genes) may help determine if changes in *GPD1L* are clinically significant, as neither our patient nor her mother have been found to be symptomatic. However, one must also consider the possibility of incomplete penetrance in *GPD1L* or the possibility that cardiac findings will be identified at a later time.

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