CLINICAL REPORT

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# Long QT, Syndactyly, Joint Contractures, Stroke and Novel *CACNA1C* Mutation: Expanding the Spectrum of Timothy Syndrome

**Jane Gillis,[1] Elena Burashnikov,[2] Charles Antzelevitch,[2] Susan Blaser,[3] Gil Gross,[4] Lesley Turner,[5] Riyana Babul-Hirji,[6] and David Chitayat[6]***

[1]Maritime Medical Genetics Services, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada

[2]Masonic Medical Research Laboratory, Utica, NY

[3]Division of Neuroradiology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[4]Division of Cardiology, Department of Pediatrics, The Hospital for Sick Children, Toronto, Ontario, Canada

[5]Memorial University of Newfoundland, St. John's, Newfoundland, Canada

[6]Division of Clinical and Metabolic Genetics, Department of Pediatrics, The Hospital for Sick Children, The University of Toronto, Toronto, Ontario, Canada

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**Timothy syndrome (TS) is an autosomal dominant condition with the constellation of features including prolonged QT interval, hand and foot abnormalities, and mental retardation or autism. Splawski et al. [2004] previously described two phenotypes associated with TS distinguished by two unique and different mutations within the *CACNA1C* gene. We report on a newborn who presented with prolonged QT interval and associated polymorphic ventricular tachycardia, dysmorphic facial features, syndactyly of the hands and feet, and joint contractures, suggestive of TS. He developed a stroke, subsequent intractable seizures, and was found to have cortical blindness and later profound developmental delay. Initial targeted mutation analysis did not identify either of the previously described TS associated mutations; however, full gene sequencing detected a novel *CACNA1C* gene mutation (p.Ala1473Gly). The clinical and genetic findings in our case expand both the clinical and molecular knowledge of TS.**



**Key words:** arrhythmia; syndactyly; seizure; autosomal dominant; long QT; Timothy syndrome

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## INTRODUCTION

Timothy syndrome (TS) is a rare disorder characterized by cardiac arrhythmia, syndactyly, immune deficiency, intermittent hypoglycemia, and neurologic sequelae including seizure, mental retardation, hypotonia, and autism. First described by Splawski et al. [2004], the same authors showed that TS resulted from a de novo missense mutation in the $Ca_V1.2$ L-type calcium channel *CACNA1C* gene in all 17 originally reported cases [Splawski et al., 2004]. All cases were presented in the newborn period with no other known affected family members, suggesting that the inheritance is most probably autosomal dominant and caused by a de novo mutation in the *CACNA1C* gene. Prognosis is poor with an average life expectancy of 2.5 years, with lethal arrhythmia being the primary cause of death. However, Etheridge et al., [2011] reported two patients with TS type 1 with molecular confirmation of somatic mosaicism and milder clinical manifestations.

We report on a child who presented at birth with dysmorphic facial features, long QT interval with associated polymorphic ventricular tachycardia, syndactyly, and joint contractures consistent with TS. He developed a stroke as a neonate and was found to be cortically blind. Although we could not fully explain his stroke, we presume that his cortical blindness may have been related to it.

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*Correspondence to:
David Chitayat, MD, The Prenatal Diagnosis and Medical Genetics Program, Mount Sinai Hospital, Ontario Hydro Generation Building, 700 University Avenue, 3rd floor, Rm. 3292, Toronto, Ontario, Canada.
E-mail: dchitayat@mtsinai.on.ca
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Interestingly, initial molecular analysis did not identify either of the previously reported mutations in the *CACNA1C* gene. However, complete gene sequencing analysis identified a previously unreported mutation in the *CACNA1C* gene, [c.4418C > G], which predicted an amino acid substitution. We propose that as a result of this novel mutation this child has an expanded and more complex form of TS and that other pathogenic mutations within the $Ca_V1.2$ L-type calcium channel gene, *CACNA1C*, likely exist and should be screened for in any case presenting with long QT interval and digital abnormalities in view of the variability in the clinical manifestations associated with TS.

## CLINICAL REPORT

The proband was born to a 28-year-old healthy primigravida mother of Caucasian descent and a 30-year-old father of the same descent. The couple was healthy and non-consanguineous and their family histories were non-contributory. The pregnancy was uncomplicated and there was no history of maternal illnesses or exposures. Delivery was via emergency cesarean for fetal distress at 38 weeks gestation. Apgar scores were 7 and 9 at 1 and 5 min, respectively. Birth weight was 3.257 kg (25th centile), length was 48 cm (25th centile), and head circumference measured 35.5 cm (90th centile). On physical examination he had facial dysmorphism with fair and sparse scalp hair. Both anterior and posterior fontanelles were wide and the cranial sutures were splayed. His face was round with a high forehead and frontal bossing. Eyes were deep-set with downslanting palpebral fissures and ears were fleshy and low-set. His mouth was small with downturned corners. Lips were thin and there was micrognathia (Fig. 1). The neck was short with a low nuchal hairline, but no webbing. Shoulders were sloped, the chest was normally shaped and clear on auscultation and the cardiac examination was normal. His abdomen was neither tender nor distended and there was no organomegaly. He had normal male genitalia with both testes descended. He had seemingly normal muscle bulk but demonstrated contractures and decreased range of motion at many joints. Specifically, the upper limbs were held in pronation with limitation in flexion of both elbows and in extension of both wrists. Both hands were clenched with contractures involving the metacarpophalangeal and interphalangeal joints of digits 2–5 with all held in ulnar deviation and both thumbs were adducted (Fig. 1). There were no flexion creases present over the distal interphalangeal joints of fingers 2–5 on both hands with syndactyly between digits 2–3–4–5 on the right hand and digits 2–3–4 on the left. Both hip joints were dislocated. His feet were held in plano-valgus position and his calcanei were prominent. There was partial syndactyly of the 2nd–3rd toes bilaterally and syndactyly of the 1st–2nd toes on the right (Fig. 1). Neurological examination revealed abnormal posturing and movements with arching, fisting, facial grimacing, moaning, and lip smacking. Neonatal reflexes including Moro, sucking, rooting, stepping, and walking could not be elicited. The baby gazed preferably to the right and did not respond to loud noise. Tone was increased, more notably the lower extremities with brisk deep tendon reflexes and clonus, bilaterally. Skin was soft and somewhat doughy, but had no pigment abnormalities.

The baby developed episodes of hypoglycemia, hypocalcemia, seizures, and arrhythmia with self-limited episodes of polymorphic ventricular tachycardia, 2:1 AV block and marked ventricular repolarization delay (prolonged $QT_C$) with striking QT interval prolongation with a raw measurement of 464ms rate—corrected to 640 ms using Bazett's formula at 2 days of life (Fig. 2). Further episodes of arrhythmia continued until rate control was eventually achieved with propranolol (3 mg/kg/day). ECGs performed on both parents were reported as normal.

Magnetic resonance imaging of the brain demonstrated acute infarction involving the left cerebral hemisphere, but no other vascular or structural abnormality (Fig. 3). Echocardiogram revealed a small patent ductus arteriosus (PDA) and a small patent foramen ovale (PFO), with otherwise normal cardiac anatomy and

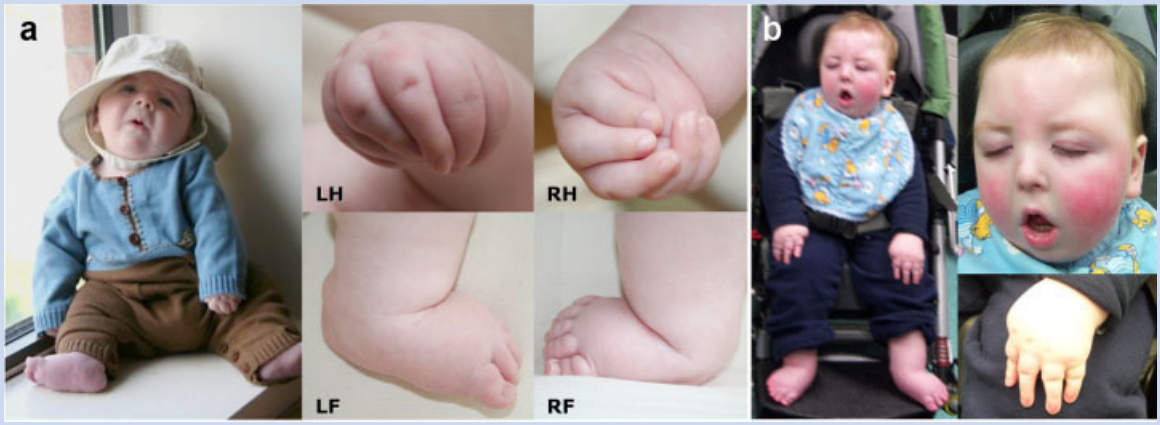


**FIG. 1. a: Photographs of our patient at 3 months of age showing dysmorphic facial features, sloped shoulders, and joint limitation. To the right note the syndactyly and contractures of hands and feet bilaterally (LH, left hand; RH, right hand; LF, left foot; RF, right foot). b: Photographs of our patient at 4 years of age showing myopathic facies, downslanting palpebral fissures, and same hand and foot anomalies as previous.**

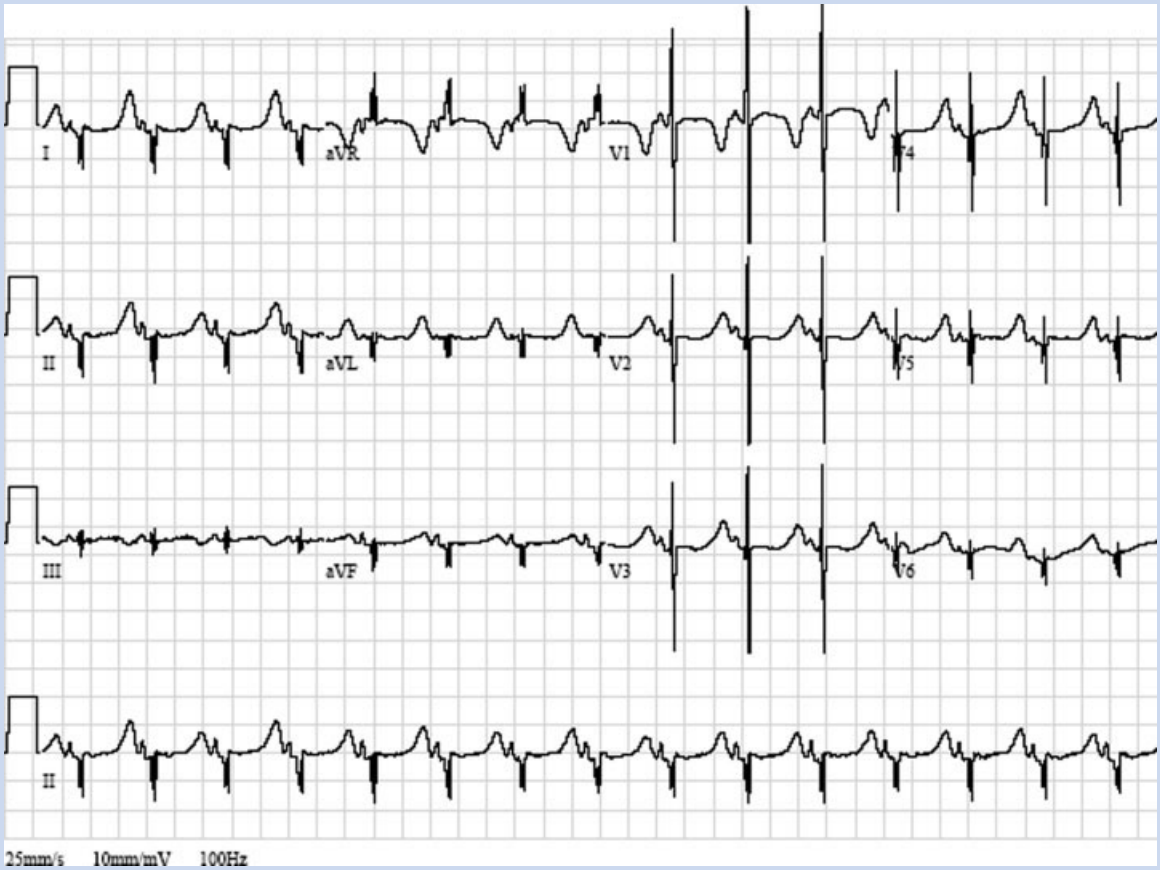


**FIG. 2. Standard 12-lead ECG recorded at 2 days of age showing rightward QRS axis deviation, incomplete right bundle branch block, and striking QT interval prolongation with a raw measurement of 464 ms rate-corrected to 640 ms using Bazett's formula. There is a subtle T-wave alternans most apparent in leads I and II.**

good biventricular function. X-rays of the upper extremities showed ulnar deviation of the 2nd through 5th digits on both hands and syndactyly of the 4–5th fingers (Fig. 4). X-rays of the lower limbs showed dislocations of both hip joints and ultrasound of the hip joints confirmed bilateral hip dislocations and steep acetabular roofs. X-rays of the feet showed vertical talus and horizontal calcanei (Fig. 4). X-rays of the back showed a mild scoliosis convex to the right over the upper thoracic spine.

Immunological studies were normal with no evidence of immune deficiency. Metabolic investigation including urine organic acid analysis, urine mucopolysaccharides and oligosaccharides as well as plasma amino acids, ammonium, and serum lactate levels were also within the normal laboratory values. Investigation for coagulopathy and bleeding disorders (including INR, anti-thrombin III, PTT, and fibrinogen) showed no abnormalities.

Chromosome analysis revealed a balanced chromosome rearrangement inherited from his father [46,X,der(Y)t(Y;15)(q12;p11.2)pat]. ArrayCGH (Signature Genomics®, Spokane, WA) confirmed the balanced nature of this rearrangement in both the patient and his father who is healthy and holds a university degree. Further, due to the involvement of chromosome 15, an imprinting defect was ruled out via Multiplex Ligation-dependent Probe Amplification analysis which showed a normal methylation pattern.

Based on the patient's clinical features suggestive of TS targeted mutation analysis of the two previously reported *CACNA1C* gene mutations associated with the *CACNA1C* gene, mapped to chromosome 12p13.3, reported in association with TS, failed to identify one of these mutations.

On follow-up at 3 months of age the patient had ongoing apneic spells; he required a Pavlik harness for bilateral hip dysplasia and his seizures continued despite medical treatment with Phenobarbital (4.5 mg/day). He continued on a β-blocker and salicylic acid (ASA) at discharge and his parents were provided with an automatic external defibrillator.

Sequencing of the *CACNA1C* gene done a few years later when it became available, identified a novel mutation c.4418C > G in exon 38, predicting an amino acid substitution of glycine for alanine at codon 1473 (p.Ala1473Gly; Fig. 5). Assessments of the pathogenicity of the p.Ala1473Glu mutation was performed on two sites, PolyPhen-2 and SIFT (http://genetics.bwh.harvard.edu/pph2/ and http://sift.jcvi.org/). The results from both sites indicated a very high probability of a damaging effect of the mutation. A score of 0.999 out of 1 was obtained with PolyPhen-2 and 100% probability

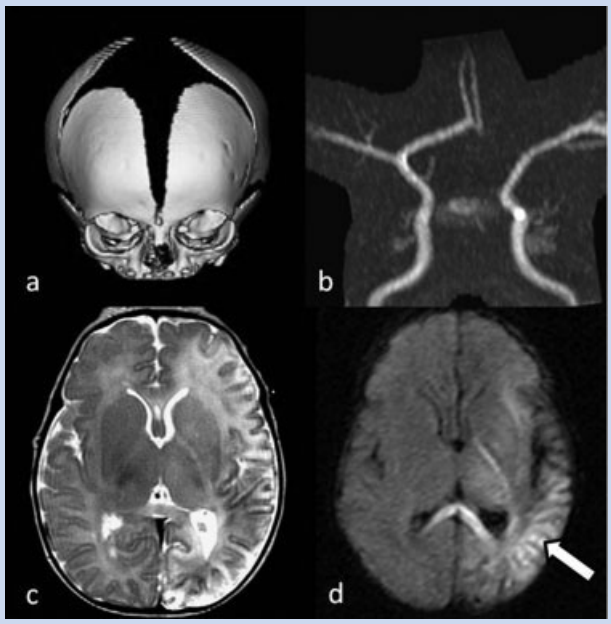


FIG. 3. Patient's CT scan and MRA: (a) CNS and craniofacial montage: CT 3D reconstruction at 4 days of age reveals markedly enlarged sutures and anterior fontanel for gestational age. b: MRA at 9 days of age demonstrates incidental dominant right anterior cerebral artery and bilaterally patent middle cerebral arteries. c: Axial T2W image and DWI (d) at 9 days of age reveal subacute left hemispheric stroke with persistence of diffusion restriction (arrow).

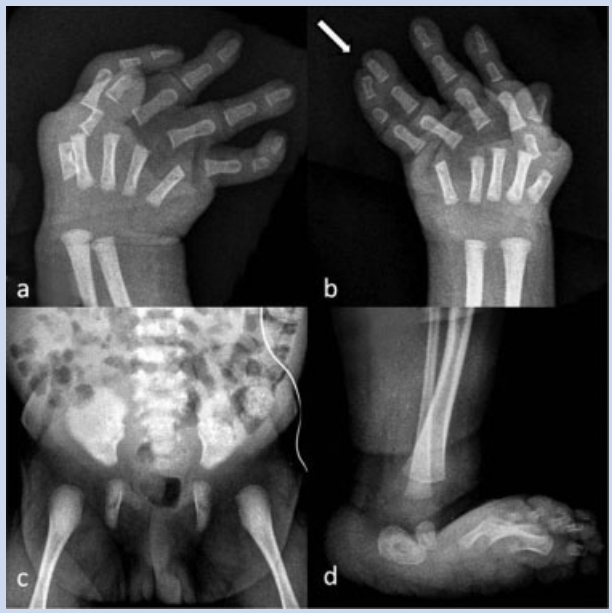


FIG. 4. Radiographs of the hands (a,b) demonstrate bilateral ulnar deviation, adduction of the thumbs, and unilateral soft tissue syndactyly of digits 4 and 5 (arrow). Pelvic AP radiograph (c) reveals shallow steep acetabuli and femoral head dislocation. Lateral foot radiograph (d) demonstrates vertical talus and pes planus deformity.

of a damaging (1 out of 1) with median info 3.19 was obtained on SIFT. Multiple sequence alignments of the mutated region of $Ca_v1.2$ protein (OMIM: Q13936-12) showed a high homology and conservation with many available species on both databases. The topological position of the mutation in channel architecture is three amino acids away from the end of segment 6. This is very similar to the position of the original TS mutation G402S only in a different domain (Domain I in case of G402S and Domain IV of A1473G). Although these data point to a very high probability of a damaging effect of the mutation, functional expressional studies are planned in the future to definitively confirm the disease-causing effect of the A1473G mutation. Genetic testing on both parents did not identify the mutation in either of them.

Currently at 4 years of age, the child continues to have prolonged QT interval, is G-tube dependant for feeding, has cortical blindness, intractable seizures, is profoundly developmentally delayed and has very little spontaneous movement and possible myopathy. His glucose and calcium levels have remained stable and within normal laboratory limits and he has not had any significant bouts of illness or hospital admissions.

## GENETIC TESTING

Blood was collected from the proband and family members after obtaining informed consent. Genomic DNA was extracted from

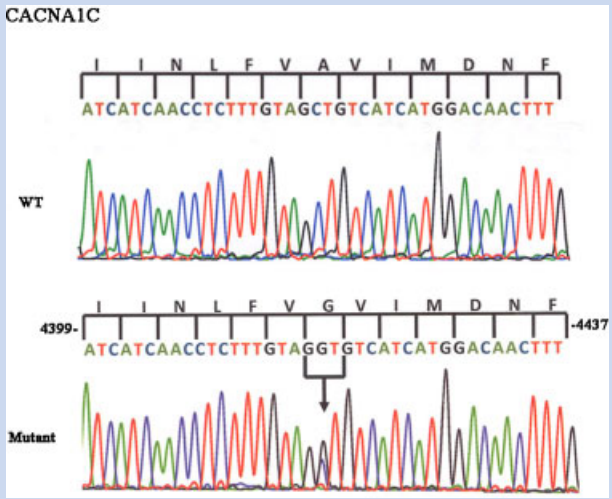


FIG. 5. Sequencing of the *CACNA1C* gene identified a novel mutation c.4418C > G in exon 36, predicting an amino acid substitution of a glycine for an alanine at codon 1473 (p.Ala1473Gly). The same analysis done on both parents did not identify the mutation in either of them.

peripheral blood leukocytes using a commercial kit (Puregene, Gentra Systems, Inc. Minneapolis, MN) and amplified by polymerase chain reaction (PCR) on GeneAmp® PCR System 9700 (Applied Biosystems, Foster City, CA). Fifty-five primer pairs were used to amplify 55 exons including exon–intron borders of the *CACNA1C* and analyzed by direct sequencing on ABI PRISM 3100 Automatic DNA Analyzer (Applied Biosystems). Electropherograms were visually examined for heterozygous peaks and compared with reference sequences for homozygous variations (GenBank accession number NM_000719) using CodonCode Aligner Ver. 2.0.4 (CodonCode Corporation, Dedham, MA). The variation was absent in 400 reference alleles obtained from 200 healthy individuals of similar ethnicity. The mutation was named based on the Human Genome Variation Society's guidelines for nomenclature. Assessment of the pathogenicity of the p.Ala1473Glu mutation was performed on two sites, PolyPhen-2 and SIFT (http://genetics.bwh.harvard.edu/pph2/ and http://sift.jcvi.org/).

## DISCUSSION

Timothy syndrome and its associated *CACNA1C* gene mutations were first described by Splawski et al. [2004] as a novel genetic calcium channel-related disorder with a constellation of features including congenital heart anomaly, lethal arrhythmia, immune deficiency, intermittent hypoglycemia, webbing of fingers and toes, and cognitive abnormalities including autism. Marks et al. [1995a,b] and others [Levin et al., 1992; Reichenbach et al., 1992] had previously reported a similar condition in infants with prolonged QT interval and syndactyly involving the 3rd–5th fingers and 2nd–3rd toes in both males and females. In the absence of family history it was suggested that the condition may be inherited in an autosomal dominant fashion. Lo-A-Njoe et al. [2005] subsequently identified the classic *CACNA1C* mutation in a patient presenting with hypertrophic cardiomyopathy and further expanded the phenotype associated with this specific gene mutation.

The $Ca_v1.2$ channel gene *CACNA1C* on chromosome 12p13.3 encodes for the L-type voltage-dependant $Ca^{2+}$ channel pore-forming protein subunit α and is essential for proper cardiovascular and nervous system function. The gene itself is comprised of 55 exons, many of which are subject to alternative splicing to generate the numerous isoforms found in different organ systems [Tang et al., 2004]. The developmental expression patterns of the *CACNA1C* gene and its putative role in the clinical manifestations associated with TS have been well described along with molecular confirmation in 18 affected individuals to date [Splawski et al., 2004; Lo-A-Njoe et al., 2005]. The cardiac L-type calcium channel protein encoded by the *CACNA1C* gene is thought to function primarily in myocardial excitation and contraction coupling [Williams, 1997] with expression mainly in the heart, though the protein has also been shown to exist in other tissues such as brain, digits, bladder, prostate, uterus, and stomach. The *CACNA1C* gene is currently the only gene known to be associated with TS. Two distinct mutations in this gene (G406R and G402S) have been shown to be responsible for the previously described clinical presentations of the disorder, the classic-type 1 and the more cardiologically severe, type 2 [Splawski et al., 2004, 2005]. Type 1 or *classic* TS, has been described in individuals with a rate-corrected QT (QTc) interval of between 480 and 700 ms in conjunction with uni- or bilateral cutaneous syndactyly involving the 2nd–5th digits and bilateral cutaneous syndactyly of the 2nd and 3rd toes. Additional findings of congenital cardiac defect, facial anomaly, and neurologic sequelae including autism, seizures, mental retardation, and hypotonia have also been reported in these cases [Splawski et al., 2004, 2005]. Type 2, reported in two patients so far, is more severe and known to be associated with extremely long corrected QT interval of greater than 500 ms. The originally described p.Gly406Arg amino acid change as well as the second characterized p.Gly402Ser change, have both been found to be associated with the type 2 phenotype [Splawski et al., 2005]. The p.Gly406Arg missense mutation in exon 8A of the *CACNA1C* gene is more common and has been identified in 16 individuals with type 1 (classic) TS [Splawski et al., 2004].

Our patient has features consistent with TS including cardiac defect (PDA and PFO), arrhythmia and long QT. He has dysmorphic facial features including a round face with a high forehead, frontal bossing, sparse hair, myopathic face with deep-set eyes, chubby cheeks, fleshy and low-set ears, micrognathia, and down-turned corners of the mouth with thin lips. Syndactyly of the 4th–5th fingers on the left hand and cutaneous syndactyly of the 1st–2nd toes on the right with bilateral partial syndactyly of the 2nd–3rd toes are also supportive of this diagnosis. He is profoundly developmentally delayed and suffers from intractable seizures. His phenotype appears more severe in some respects than other reported cases with TS, most notably his joint contractures, additional unique facial features, stroke, cortical blindness, and myopathy which have not previously been reported in association with this condition. Moreover, he had episodes of heart block and torsade de pointes at less than 24 hr of age and his QT interval prolongation time was 640 ms. Although he had hypoglycemia and hypocalcemia as a neonate, this resolved spontaneously and he has had no further episodes. Now at 4 years of age he has otherwise plateaued from a medical and developmental perspective and has not required any further hospital admissions or interventions. In particular he has not suffered any significant infections. He demonstrates little spontaneous movement and has gained a considerable amount of weight.

In the investigation of the etiology of our patient's condition we have also considered other syndromes associated with prolonged QT. Unlike with Romano-Ward syndrome, our patient had other abnormalities not typically seen with this condition and had no episodes of syncope. Unlike with Andersen–Tawil syndrome (or LQT7), our patient has not had any episodes of periodic paralysis, clefting of the soft palate, or the typical facial features. Our patient presented in the neonatal period, which is also not typical for Andersen–Tawil syndrome. For thoroughness, molecular testing of the *KCNJ2* gene was undertaken but did not identify a mutation on full sequence analysis. Although our patient has cortical blindness he is not hearing impaired which makes a diagnosis of other syndromes associated with long QT such as Jervell and Lange-Nielsen, unlikely and supported our conclusion that the constellation of findings in our patient is most consistent with TS. Our patient also suffered a stroke in the early postnatal period. Coagulation studies were normal and there was no family history of

stroke or coagulopathies. It is possible that our patient's stroke was the result of his early uncontrolled arrhythmia. However, the Cav1.2 splice variant with exon 9* was found to have a role in the regulation of cerebral artery diameter and thus a mutation in this gene may predispose these patients to intracerebral hemorrhage [Nystoriak et al., 2009]. Now, older than 4 years of age he has not had any further strokes. Nevertheless we cannot rule out the possibility that his stroke, like the previously reported autistic features [Splawski et al., 2004], is related to the identified *CACNA1C* mutation and resulting abnormal protein product.

Targeted molecular analysis was undertaken for the two most common *CACNA1C* gene mutations, Gly406Arg and Gly402Ser in exon 8, which are associated with decreased channel inactivation and the resulting previously described TS phenotype [Splawski et al., 2004, 2005] did not reveal a mutation. Subsequently, full *CACNA1C* gene sequencing became available and a novel, de novo mutation, c.4418C > G was identified allowing us to confirm the diagnosis in our patient. This particular single base pair change predicts an amino acid substitution of alanine to glycine (p.Ala1473Gly) in exon 38 of the *CACNA1C* gene and has not been previously reported. Assessment of the pathogenicity of the mutation was performed on two sites, PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.jcvi.org/). The results from both sites indicated a very high probability of a damaging effect of the mutation. A score of 0.999 out of 1 was obtained with PolyPhen-2 and 100% probability of a damaging (1 out of 1) with median info 3.19 was obtained on SIFT. Multiple sequence alignments of the mutated region of $Ca_v1.2$ protein (OMIM: Q13936-12) showed a high homology and conservation with many available species on both databases. The topological position of the mutation in channel architecture is three amino acids away from the end of segment 6. This is very similar to the position of the original TS mutation G402S only in a different domain (Domain I in case of G402S and Domain IV of A1473G). In comparison with reference sequences, the variation was absent in 400 reference alleles obtained from 200 healthy individuals of similar ethnicity. Although these data point to a very high probability of a damaging effect of the mutation, functional expressional studies are planned in the future to definitively confirm the disease-causing effect of the A1473G mutation.

At least 19 of 55 exons comprising the human *CACNA1C* gene have been reported to be subjected to alternative splicing [Tang et al., 2004]. Of the 55 exons only exon 8 has been implicated in human disease to date. The classic type 1 and milder TS phenotype results from the p.Gly406Arg mutation in exon 8A which is the alternative splice variant of the *CACNA1C* gene and reported to be found in about 20% of all cardiac mRNAs. Type 2 TS is considered the atypical form and presents with a more severe cardiac phenotype. The p.Gly406Arg and the p.Gly402Ser mutations found in exon 8 have been associated with this phenotype. Taken together these two mutations are reported to represent 80% of all cardiac mRNAs found in those affected individuals. In contrast exon 38, the site of the novel mutation reported here is thought not to be alternatively spliced and is therefore likely constitutively expressed. This may account for the more severe phenotype seen in our patient.

We do not know the specific effect of this change, but nonetheless believe that this change likely represents a deleterious mutation and not just a variant of unknown significance, as neither parent carries this change, as confirmed by molecular testing of both parents who are healthy and phenotypically normal. These clinical and molecular findings further expand the clinical and molecular spectrum of TS and emphasize the need to perform sequence analysis when the two common mutations are not identified in a patient otherwise thought to have TS. From the paucity of cases published and seemingly only handful of patients with this condition, our case significantly contributes to our knowledge of this rare condition. It highlights that further studies are needed both to assist in the identification of patients with TS as well as to further delineate the complex role of this gene in embryogenesis and its postnatal function in different body organs and systems. Further investigation is needed to explore the full spectrum of this syndrome and to better understand its true clinical gamut.

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