

# A novel GJA1 mutation causing familial oculodentodigital dysplasia with dilated cardiomyopathy and arrhythmia



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## Introduction

Oculodentodigital dysplasia (ODDD) is an autosomal dominant syndrome that presents with craniofacial and limb dysmorphisms caused by mutations in the *GJA1* gene, which codes for connexin 43 (Cx43), a gap junction protein important in cell-to-cell communication. We present for the first time a family with ODDD, progressive cardiac conduction system disease, and dilated cardiomyopathy.

## Case report

The index case presented in infancy owing to dysmorphic features (hypertelorism, thin hair with a receded hairline, prominent scalp veins, cleft chin, pinched nose, small mouth and jaw with dental crowding, and a high-pitched voice). ODDD was suspected and subsequently a *GJA1* sequence variation c.175C>T (p.Pro59Ser) was identified (sequence pherogram shown in [Supplemental Figure 1](#), available online). This sequence variant had not been previously reported as a *GJA1* mutation or polymorphism; however, it was predicted by the reference laboratory (The Johns Hopkins DNA Diagnostic Lab) to be probably damaging, with evidence suggesting that this mutation was the molecular cause of the patient's disease. He was initially found to have conduction system disease (cardiac rhythm varying from sinus rhythm with first-degree heart block and a right bundle branch block [RBBB] to periods of complete heart block) at 5 years of age. He had mild left ventricular dilation at the time, with normal left ventricular systolic function. He was asymptomatic until age 8, when he began to complain of syncope. He had RBBB with infra-His block on invasive testing, which prompted

placement of a permanent pacemaker. The day after his pacemaker was placed he developed an asymptomatic wide QRS tachycardia of 140–150 bpm, consistent with ventricular tachycardia, for which metoprolol was started. Approximately 6 months later, he presented with a right middle cerebral artery stroke, at which time a repeat transthoracic echocardiogram demonstrated severe left ventricular dilation with severely depressed left ventricular systolic function (ejection fraction 11%). His heart failure was initially managed with oral medications, but his clinical status deteriorated 3 months later with worsening heart failure symptoms and he ultimately underwent heart transplantation at 9 years of age. He was doing well until 24 years of age, at which time he was hospitalized for presumed rejection and, unfortunately, died. He was married and had 2 daughters, both of whom have ODDD and manifested a similar cardiac phenotype (family tree depicted in [Supplemental Figure 2](#), available online). His parents both had negative genetic testing. His father, who shared some similar dysmorphic facial features, was found to have coronary artery disease at age 50 after a myocardial infarction and is status post coronary bypass surgery. He currently has severe left ventricular dysfunction with no conduction system disease.

The index case's older daughter had multiple medical issues including ODDD (targeted testing demonstrated the same *GJA1* variant as the father), hypoxic ischemic encephalopathy with a severe seizure disorder, and high-grade second-degree heart block with dilated cardiomyopathy. She had a normal echocardiogram at 1 month of age but by 5 months of age had developed moderate left ventricular dilation and moderate left ventricular systolic dysfunction ([Supplemental Movie 1A–B](#), available online). Her initial electrocardiogram demonstrated sinus rhythm with first-degree heart block, later progressing to high-grade second-degree heart block ([Figure 1](#)) with periods of complete heart block. At 1 year of age, she was admitted for failure to thrive and during her hospitalization had a cardiac arrest leading to a prolonged hospital course, and ultimately she died at 14 months of age.

His second daughter (our patient) was born full-term without complication but did manifest craniofacial and limb

**KEYWORDS** Pediatrics; Dilated cardiomyopathy; Heart failure; Heart block; Oculodentodigital dysplasia

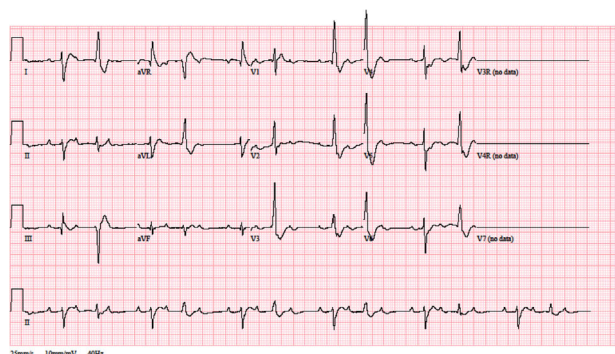
**ABBREVIATIONS** Cx43 = connexin 43; ODDD = Oculodentodigital dysplasia; RBBB = right bundle branch block  
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## KEY TEACHING POINTS

- Dilated cardiomyopathy is the most common cardiomyopathy worldwide and has many causes, all leading to dilation and impaired contraction of the left or both ventricles. It can be primary (genetic, mixed, or predominantly familial nongenetic) or secondary (eg, infiltrative or autoimmune), with the familial type accounting for 20%–48% of all cases. Novel gene mutations leading to the development of dilated cardiomyopathy continue to be discovered.
- Oculodentodigital dysplasia is an autosomal dominant syndrome that presents with craniofacial and limb dysmorphisms caused by mutations in the *GJA1* gene, which codes for connexin 43, a gap junction protein important in cell-to-cell communication. As connexins are essential for cardiac action potential propagation, their modification in pathologic states has been hypothesized to serve as a potential arrhythmogenic substrate.
- The inherited disorder of oculodentodigital dysplasia may cause cardiac conduction system disease and dilated cardiomyopathy, which can ultimately result in cardiac arrest and death or progressive heart failure and need for heart transplant. It is important to be observant of external clues that can guide physicians in correctly diagnosing this rare disorder.

dysmorphisms characteristic of ODDD (targeted testing demonstrated the same *GJA1* variant as the father), including unusual curvature of the fingers, syndactyly of the toes, and sparse hair with prominent scalp veins (a finding that her father shared), which are depicted in [Figure 2](#). Neonatal electrocardiogram ([Figure 3A](#)) demonstrated an atrial rhythm (likely sinus) with normal cardiac intervals (PR interval 120



**Figure 1** An electrocardiogram done at 6 months of age demonstrating second-degree heart block with 3:2 conduction with alternating QRS morphology due to aberration.

msec, QRS duration 54 msec), although overall voltages were low. Neonatal echocardiogram demonstrated normal left ventricular size (left ventricular end diastolic diameter 1.5 cm) and systolic function (ejection fraction 59%) ([Supplemental Movie 2A–B](#), available online).

At follow-up evaluation 4 months later, her electrocardiogram had significantly changed ([Figure 3B](#)), showing a regularly irregular rhythm with multiple QRS morphologies, the mechanism of which was difficult to discern. On close inspection ([Figure 3C](#)), some P waves can be identified in V3 (arrows) and others can be suspected (vertical lines) where they would be, assuming regular atrial activity (rate 150–155 bpm). Therefore, this likely represents an unusual form of 8:6 second-degree heart block with variable atrioventricular and intraventricular conduction disturbance; ectopy is difficult to exclude. Her echocardiogram demonstrated moderate dilation of her left ventricle (left ventricular end diastolic diameter 2.6 cm) with moderately depressed left ventricular systolic function (ejection fraction 36%) ([Supplemental Movie 3A–B](#), available online).

Over the next 2 years she remained asymptomatic, with repeated electrocardiograms and Holter recordings showing first- and second-degree heart block, likely some ventricular ectopy (difficult to quantify owing to varying intrinsic QRS morphology), and mildly low average heart rate without significant pauses.

At age 2.5 years, diagnostic catheterization and electrophysiology study were performed. Hemodynamic parameters were normal except for an elevated pulmonary capillary wedge pressure of 12 mm Hg. The predominant QRS morphology was RBBB with left axis deviation, although intermittently complete left bundle branch block was present. No convincing His potential was ever identified, although during periods of first-degree block there was at times a small deflection approximately midway in an A-V interval of ~600 msec. Various pharmacologic and autonomic maneuvers were undertaken, with results generally favoring intranodal block. Nonsustained but rapid (~300 bpm for up to 5 seconds) polymorphic ventricular tachycardia was repeatedly elicited with double extrastimuli ([Figure 3D](#)).

Dual-chamber pacemaker placement was recommended on the basis of the conduction system disease and to permit beta-blockade. Epicardial biventricular pacing (cardiac resynchronization therapy) was selected, as right ventricular pacing might worsen the cardiomyopathy. In the operating room, bipolar epicardial steroid-eluting leads were placed. Despite multiple attempts, no reliable atrial sensing could be achieved, and atrial pacing thresholds were very high (5 V bipolar and 3 V unipolar, with pulse width 2 msec). Atrial lead function normalized gradually over the next several days, and metoprolol was initiated. Telemetry showed a monotonous paced rhythm without any ventricular ectopy. A repeat echocardiogram (with biventricular pacing, QRS duration 100 msec) prior to hospital discharge showed improvement in left ventricular systolic function, although not to normal ([Supplemental Movie 4A–B](#), available online), with subjective improvement in left ventricular synchrony.



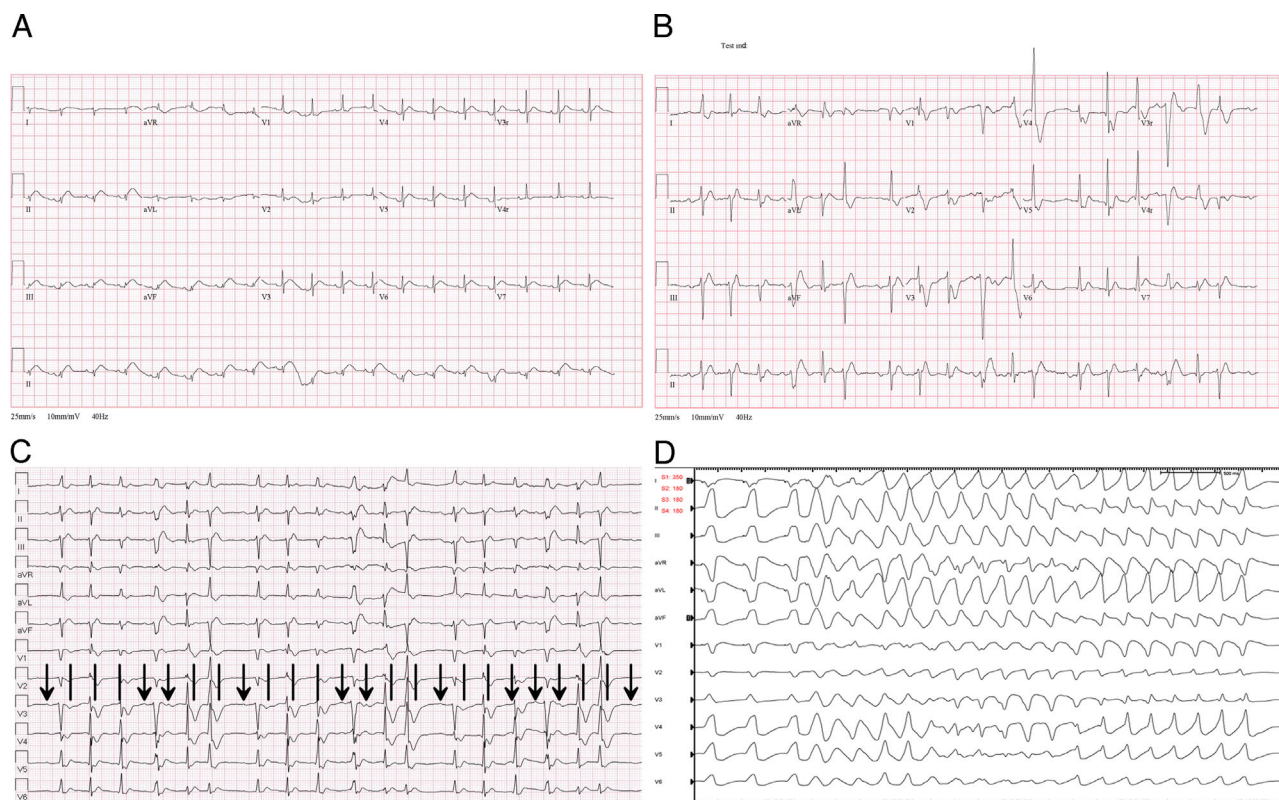
**Figure 2** Dysmorphic features manifested by our patient and felt to be consistent with oculodentodigital dysplasia included **A**: unusual curvature of the fingers; **B**: syndactyly of the toes; and **C**: sparse hair with prominent scalp veins.

## Discussion

In 2003, Paznekas et al<sup>1</sup> reported that Cx43 mutations cause the pleiotropic phenotype of ODDD, an autosomal dominant syndrome that presents with craniofacial and limb dysmorphisms, as well as neurologic manifestations such as spastic paraplegia and neurodegeneration. In their study, the authors reported mutations in the *GJA1* gene coding for the gap junction protein Cx43 in all 17 families studied. In a later review, the same group<sup>2</sup> compiled a summary of all known *GJA1* substitutions leading to the ODDD phenotype; the mutation seen in our family has not previously been published. Delmar and Mikita<sup>3</sup> recently reviewed the relationship between nucleotide substitutions in the connexin

genes and the occurrence of cardiac arrhythmias. As connexins are essential for cardiac action potential propagation, their modification in pathologic states has been hypothesized to serve as a potential arrhythmogenic substrate, although these authors emphasize the remarkable absence of a cardiac arrhythmia phenotype in known patients with ODDD. The only electrocardiologic abnormalities reported in a series of 177 individuals with ODDD were RBBB (2 patients, 1 of whom also had first-degree heart block) and premature ventricular contractions (1 patient).<sup>3</sup>

In contrast, *in vitro* studies have reported changes in gap junction channel function consequent to Cx43 mutations,<sup>4-6</sup> and changes in electrical properties and arrhythmias have



**Figure 3** Electrocardiograms done **A**: shortly after birth, demonstrating an atrial rhythm (likely sinus) with low-voltage QRS complexes; and **B**: several months later, demonstrating a regularly irregular rhythm with varying QRS morphology. **C**: Reformatted version of the latter tracing (**B**) shows an atrial rate of 150–155 bpm (visible P waves, *arrows*; inferred P waves, *vertical lines*) with probable second-degree heart block and distal conduction system disease. **D**: An electrocardiogram demonstrating the polymorphic ventricular tachycardia that was induced in the electrophysiology lab (study done at 2.5 years of age).

been reported in murine models of the disease.<sup>7,8</sup> The reason (s) for the lack of a cardiac electrical phenotype in humans with ODDD has remained unclear. However, 2 recent case reports associate Cx43 amino acid substitutions with 2 cases of sudden cardiac death in children: 1 infant and 1 teenager.<sup>9,10</sup> Additionally, the findings in our family suggest that mutations in Cx43 may cause progressive cardiac conduction system disease, as well as dilated cardiomyopathy, both potential manifestations of dysfunction in the cardiac sodium channel complex, with which Cx43 interacts.<sup>3</sup>

The clinical phenotype manifested by the family described in this report is similar to that reported in families with other known genetic mutations, including the cardiac sodium channel (*SCN5A*) gene and lamin A/C (*LMNA*) gene. McNair et al<sup>11</sup> identified a heterozygous mutation in exon 21 of *SCN5A* (substitution of an aspartic acid by an asparagine in the first third of the S3 transmembrane region of domain III) that cosegregated within a large family with the affected phenotype of sinus node dysfunction in adolescence, supraventricular tachyarrhythmia, progressive atrioventricular and intraventricular conduction delay (requiring permanent pacing in most cases), and progression towards atrial dilation, right ventricular dilation, and, in some cases, left ventricular dilation and dysfunction. This phenotype differs from our family in that the family members did not manifest sinus node dysfunction, only 1 family member had supraventricular tachycardia, and the cardiomyopathy that developed affected primarily the left ventricle.

Mutations in the *LMNA* gene have also been linked to the phenotype of dilated cardiomyopathy. Carriers of *LMNA* gene mutations when compared to noncarriers (all having dilated cardiomyopathy) had a younger age of disease onset, were more likely to be female, were more likely to have a supraventricular arrhythmia and/or conduction system disease (requiring permanent pacing), and were more likely to have skeletal muscle involvement. Taylor et al<sup>12</sup> reported on the natural history of dilated cardiomyopathy due to *LMNA* mutations and found that the majority of subjects with this disease were deceased, required heart transplant, or had severe worsening of myocardial function between the third and fifth decade of life. Although there are some striking similarities to the family we describe, skeletal muscle involvement was not present and it seems that the age of onset of cardiac disease was significantly younger (the proband at 5 years of age and both daughters at less than 1 year of age).

In conclusion, the inherited disorder of ODDD may cause cardiac conduction system disease and dilated cardiomyopathy,

which can ultimately result in cardiac arrest and death or progressive heart failure and need for heart transplant. It is important to be observant of external clues that can guide physicians in correctly diagnosing this rare disorder. Ultimately, diagnosing such a disorder can be important not only for diagnosis and management of the patient but also to make families aware of inherited traits that may be passed on to future generations. The role of cardiac resynchronization therapy in these patients warrants further consideration.

## Appendix

### Supplementary data

Supplementary material cited in this article is available online at <http://dx.doi.org/10.1016/j.hrcr.2015.08.013>.

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