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CLINICAL REPORT

Monochorionic twins with 15q26.3 duplication presenting with selective intrauterine growth restriction and discordant cardiac anomalies: A case report

Suraj Kannan[1] | **Joann N. Bodurtha**[2] | **Ada Hamosh**[2] | **Christopher Jordan**[3]

[1]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[2]Department of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[3]National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA

Correspondence
Suraj Kannan, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
Email: skannan4@jhmi.edu

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Abstract

Background: Duplication of the distal end of chromosome 15q has been previously implicated in a characteristic overgrowth syndrome. Additionally, many patients have other congenital malformations, including cardiac, renal, genital, and musculoskeletal anomalies. However, some patients may present with intrauterine growth restriction and short stature. Different breakpoints within 15q, as well as different environmental factors, may underlie these varied presentations.
Case Presentation: We discuss monochorionic-diamniotic twins with a ~345 kb maternally inherited duplication in 15q26.3. The twins presented with discordant pathology—one twin with a single umbilical artery, selective intrauterine growth restriction, and multiple cardiac defects including aortic coarctation, aortic valve stenosis, and ventricular septal defect, whereas the other twin was unaffected. To our knowledge, this case represents the smallest reported duplication of distal 15q.
Conclusion: The discordant phenotype seen in the twins is likely due to a complex interplay between genetic and environmental causes. The affected infant presented prenatally with growth restriction and a single umbilical artery rather than overgrowth, potentially due to a unique breakpoint within 15q. This, in turn, may have produced hemodynamic perturbations between the twins, leading to discordant cardiac disease. Our report thus highlights the importance of genetic and non-genetic mechanisms underlying discordant anomalies in monochorionic twins.

KEYWORDS

discordant cardiac anomalies, distal 15q duplication, genetic testing, monochorionic-diamniotic twins

1 | BACKGROUND

Trisomy and tetrasomy of the distal end of chromosome 15q have been previously implicated in an overgrowth syndrome characterized by macrosomia, intellectual disability, and distinctive facies (Cannarella et al., 2017; Faivre et al., 2002; Tatton-Brown et al., 2009). Putative mechanisms for these anomalies include inappropriate gene dosage of the insulin-like growth factor 1 receptor *IGF1R* (OMIM*147370), which plays a key role in mitogenic

signaling pathways and cell growth (Nagai et al., 2002). In addition to overgrowth, patients may present with other congenital malformations, including craniosynostosis, cardiac and renal malformation, genital anomalies, and limb abnormalities (Cannarella et al., 2017). Patients with distal 15q duplications have also presented with intrauterine growth restriction (IUGR) and short stature rather than the classic overgrowth (Burada et al., 2021; Roggenbuck et al., 2004). These variable presentations may be due to different breakpoints within 15q, leading to differential regulation of *IGF1R*.

Here, we present monochorionic-diamniotic (mono-di) twins with a small (~345 kb), maternally inherited interstitial duplication in 15q26.3, overlapping with exons 3 through 21 of *IGF1R*. Notably, only one twin presented with a detectable disease in the prenatal and perinatal periods. The affected twin presented with a single umbilical artery, selective IUGR (sIUGR), and multiple cardiac defects including aortic coarctation, aortic valve stenosis, and ventricular septal defect (VSD). Previous reports of 15q duplications were typically large (>3 Mb); thus, to our knowledge, this case represents the smallest reported duplication of distal 15q. The discordant phenotype in the twins likely indicates a complex interplay between genetic and environmental factors.

2 | CASE PRESENTATION

The patient's mother was a 31-year-old, gravida 1 para 0 woman with no significant medical history who was followed for prenatal management of mono-di twin pregnancy. Routine ultrasound at 13 weeks gestation was significant for a two-vessel umbilical cord and suspected small left ventricle and VSD in Twin A. Repeat ultrasounds at 15 and 18 weeks gestation identified several pertinent findings for Twin A, including sIUGR, missing right umbilical artery, and complex cardiac anomaly. In particular, Twin A's heart was noted to have a conoventricular-type VSD with the overriding aorta and right ventricle larger than the left ventricle. Fetal biometry identified 28% weight discordance at week 15. However, there were no abnormal umbilical dopplers in either infant. Both fetuses presented with visible bladders, without evidence of fetal hydrops or other indicators for twin–twin transfusion syndrome. Additionally, weight discordance improved somewhat over the course of gestation. First-trimester screening showed decreased risk (1:>10,000) of trisomies 13, 18, and 21.

With multiple anomalies in one of the twins, the family was referred for prenatal genetic counseling. The mother's family history was significant for unilateral renal agenesis (in the mother's mother and maternal aunt), learning disability (mother's maternal half-brother), and bipolar disorder (mother's maternal cousin). The father's family history was also notable for unilateral renal agenesis (in the father's paternal grandmother) and bipolar disorder (father's maternal aunt). After discussion, the family opted to pursue amniocentesis for single nucleotide polymorphism (SNP) microarray testing, alpha-fetoprotein level, and carrier screening for 421 autosomal recessive and X-linked disorders (Natera Horizon). SNP microarray found an interstitial duplication of unknown significance in the long arm of chromosome 15 (arr[hg19] 15q26.3(99282850_99627413)x3, ~345 kb) in both twins (Figure 1). This duplication partially overlaps the *IGF1R* gene (OMIM*147370), from exons 3 to 21. Further testing of both parents found that the duplication was maternally inherited. Notably, the mother was negative for any history of cardiac or renal disease but had not had ultrasounds.

Delivery was performed by the primary cesarian section at 35 weeks due to premature rupture of membranes. Delivery was otherwise uncomplicated; APGAR scores were 8 and 9 at 1 and 5 min, respectively, for both twins. At birth, Twin A weighed 2.04 kg, whereas Twin B weighed 2.69 kg. Twin A was transferred to the pediatric cardiac intensive care unit for initiation of prostaglandin treatment, whereas Twin B was transferred to the newborn nursery.

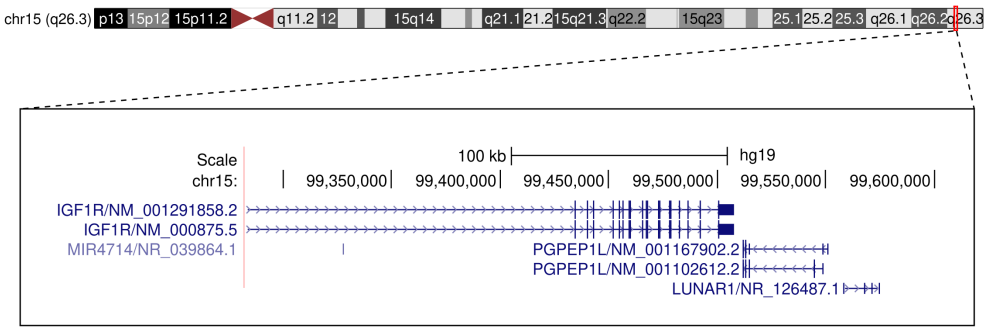

FIGURE 1 Region of duplication reported in this study. The patients presented with a maternally inherited interstitial duplication of chromosome 15q26.3. Figure is made using the UCSC Genome Browser (http://genome.ucsc.edu) with assembly GRCh37/hg19 (Feb 2009) (Kent et al., 2002; Navarro Gonzalez et al., 2021). The session can be accessed through https://genome.ucsc.edu/s/skannan4/SK_15q26.3_casereport

A postnatal echocardiogram confirmed cardiac abnormalities for Twin A, including transverse aortic arch and isthmus hypoplasia, bicommissural stenotic aortic valve, and large posterior malalignment VSD but normal ventricular size and function. Twin B presented with no cardiac anomalies. Abdominal ultrasounds with two functional kidneys were normal in both. On examination, both infants presented with brachyclinodactyly of the fifth finger and microretrognathia, though this was more pronounced in Twin A and accompanied by a sloping forehead. Twin A additionally presented with the widened distance between the first and second toes bilaterally. Other features demonstrated typical variation.

3 | DISCUSSION

Here, we discuss the case of a pair of mono-di twins with a maternally inherited distal 15q26.3 microduplication and discordant cardiac anomalies. The affected twin presented prenatally with sIUGR and missing right umbilical artery, and cardiac anatomy significant for transverse aortic arch and isthmus hypoplasia, aortic valve stenosis, and malalignment VSD. Congenital heart disease is notably more common in twin pregnancies, with a reported prevalence of 20 in 1000 live births (Balasubramanian et al., 2021); the risk is further increased 6–9-fold for monochorionic twin pregnancies (Bahtiyar et al., 2007; Gijtenbeek et al., 2019). Despite a shared genetic code, mono-di twins frequently present with discordant phenotypes, with fewer than 20% showing concordant congenital anomalies (Imany-Shakibai et al., 2021). Recent evidence has supported previously unrecognized genomic differences in monozygotic twins due to early developmental mutations (Jonsson et al., 2021). It is possible that these gene changes can lead to discordant presentations in mono-di twins. However, other studies have emphasized the relative impact of other mechanisms on discordant cardiac phenotypes, including epigenetic (Grunert et al., 2020; Lyu et al., 2018; Repetti et al., 2021) and hemodynamic differences (AlRais et al., 2011). We consider these various factors here in the context of the microduplication seen in our case study patients.

On the SNP array, both twins were found to have a ~345 kb interstitial duplication in 15q26.3 (Figure 1), a location that overlaps with the previously described 15q overgrowth syndrome (Cannarella et al., 2017; Faivre et al., 2002; Tatton-Brown et al., 2009). Distal 15q duplications have now been reported in at least 96 patients (Cannarella et al., 2017). Patients with these duplications present with a common phenotype of pre- and postnatal overgrowth, developmental delay, learning disabilities, and facial abnormalities (long triangular face, downslanting palpebral fissures, prominent nose, micrognathia, and low-set ears) (Cannarella et al., 2017; Faivre et al., 2002; Tatton-Brown et al., 2009). Patients have also presented variably with cardiac and renal anomalies, genital abnormalities and cryptorchidism, craniosynostosis, and hand abnormalities (including arachnodactyly, syndactyly, and clinodactyly) (Cannarella et al., 2017; Faivre et al., 2002; Tatton-Brown et al., 2009). A range of duplicated regions have been reported, including from 15q23.1-qter to 15q26.1-qter (Tatton-Brown et al., 2009). This variation likely explains the differences in observed phenotypes. However, the overgrowth phenotype has been most consistently seen for distal terminal duplications ranging from 15q25.1-qter to 15q26.1-qter (Luo et al., 2015). Per previous literature (Leffler et al., 2016) as well as cases available on the DECIPHER database (Firth et al., 2009), most previously reported distal 15q duplications associated with pathology are relatively large (>3 Mb in size). Thus, the duplication observed in our twins is particularly small.

The described duplication partially overlapped the *IGF1R* gene, which is thought to be responsible for the overgrowth phenotype of distal 15q duplication. IGF1R is a transmembrane receptor tyrosine kinase that mediates the effects of IGF1 and IGF2, leading to the activation of pathways relevant to cell growth and proliferation (Chitnis et al., 2008; Iams & Lovly, 2015). Several studies have made the link between *IGF1R* dosage and patient phenotypes. Trisomy of *IGF1R* has been associated with overgrowth while haploinsufficiency has been associated with IUGR and postnatal growth failure (Nagai et al., 2002; Ocaranza et al., 2017; Okubo et al., 2003; Tatton-Brown et al., 2009). It should be noted that several case reports of a distal 15q26.3 duplication-related overgrowth presentation have been described that do not involve *IGF1R*, suggesting that other genes in this region may also play a role in the syndromic features (De Schepper et al., 2017; Leffler et al., 2016). Moreover, others have described patients with 15q26.3 duplication involving *IGF1R* presenting with IUGR, failure to thrive, and short stature rather than overgrowth (Burada et al., 2021; Cannarella et al., 2017; Roggenbuck et al., 2004). This is particularly relevant to our case study. Here, while our twins presented with facies and limb differences consistent with the previously described 15q overgrowth syndrome (microretrognathia, sloping forehead, clinodactyly), neither presented with overgrowth. Instead, Twin A presented with sIUGR and a relatively smaller size compared with Twin B. One possible explanation for variable phenotypes produced by 15q26.3 duplication is variations in the specific breakpoint on chromosome 15. As discussed by Roggenbuck et al., different breakpoints may lead to the juxtaposition of *IGF1R* near an active promoter or to alteration of normal regulatory

sequences of the gene (Roggenbuck et al., 2004). Similarly, it is possible that the specific partial duplication in our patients led to disruption of gene function, producing IUGR rather than the classic overgrowth phenomena. Further studies, including measuring *IGF1R* gene dosages, may help further clarify the genotype–phenotype relationship.

Congenital cardiac anomalies have been previously identified in approximately 50% of patients with distal 15q duplications (Cannarella et al., 2017). These have included a range of pathologies, including patent ductus arteriosus, mitral valve stenosis, septal defect, atrioventricular canal, aortic coarctation, hypoplastic left heart, Ebstein anomaly, and others (Burada et al., 2021; Cannarella et al., 2017; Thorsson et al., 2013). Interestingly, Thorsson et al. identified a primary critical region in 15q26.3 that appears to be involved in cardiac pathogenesis (Thorsson et al., 2013). This region includes *MEF2A*, a known regulator of cardiac development and function (Iida et al., 1999). Notably, *IGF1R* appears to fall outside this critical region. Moreover, patients carrying *IGF1R* mutations as well as knockout mice lacking *IGF1R* typically do not display cardiac anomalies (Benbouchta et al., 2021). Thus, it is unlikely that the microduplication in our patients contributed to the observed cardiac pathology through a direct gene effect.

Another mechanism by which *IGF1R* microduplication may have caused cardiac pathology in our patients is through an impact on hemodynamics. Twin–twin transfusion, sIUGR, and single umbilical artery have all been associated with cardiac abnormalities in mono-di twin pregnancies (Balasubramanian et al., 2021; Cohen et al., 2016; de Haseth et al., 2012; Gijtenbeek et al., 2019; Mitchell et al., 2015; Negis et al., 1994). Notably, hemodynamic mechanisms have been implicated in the development of discordant cardiac pathologies in twins (AlRais et al., 2011). Coarctation of the aorta, valvular disease (particularly aortic stenosis), and septal defects are associated with mono-di twin pregnancies and have a likely hemodynamic etiology (Gijtenbeek et al., 2019; Herskind et al., 2013). This corresponds well to our affected patient Twin A, who presented with aortic arch and isthmus hypoplasia, aortic valve disease, and VSD. A plausible explanation is that *IGF1R* microduplication promoted altered hemodynamics that was exacerbated in the context of mono-di twin pregnancy, leading to sIUGR and the development of discordant cardiac abnormalities. In this sense, gene- and environmental-level effects contributed to the presentation.

Other potential mechanisms for producing discordant cardiac pathology in this case study should also be considered. It should be noted that 15q26.3 falls outside the imprinting region of chromosome 15 (Butler & Duis, 2020), and *IGF1R* is not imprinted (Tatton-Brown et al., 2009). However, other modes of regulation may also be relevant. For example, two recent studies showed the contribution of differential DNA methylation to discordant cardiac phenotypes in mono-di twins (Grunert et al., 2020; Lyu et al., 2018). Additionally, we focused our attention on *IGF1R* as the primary gene appearing in the duplication region. However, this region also encodes for other RNAs, including the microRNA *MIR4714* and the long noncoding RNAs *SNRPA1-DT* and *LUNAR1* (Figure 1). Deregulated microRNA levels have been found in twins with discordant cardiac defects (Abu-Halima et al., 2019). Thus, further investigation of epigenetic modification and noncoding regions in our observed duplication may contribute to the observed differences in phenotypic expression.

In addition to cardiac anomalies, the 15q duplication syndrome has previously been associated with renal malformations, including horseshoe kidney, renal agenesis, hydronephrosis, and others (Cannarella et al., 2017; Tatton-Brown et al., 2009). This was noteworthy given the history of renal agenesis on both the maternal and the paternal sides of the family of our patients. However, both twins presented with bilateral kidneys with no noted abnormalities to ultrasound. Further follow-up, including genetic testing for the extended family, may provide further elucidation of the genetics underlying this family's renal disease and help clarify the role of the identified microduplication in this pathology.

4 | CONCLUSION

We report here the case of two mono-di twins with a maternally inherited 15q26.3 duplication and discordant cardiac phenotype. In contrast with the typically described overgrowth syndrome, the affected infant presented prenatally with sIUGR and a single umbilical artery. This difference from previously reported cases may be due to a unique breakpoint within 15q26.3, leading to dysregulation of *IGF1R*, though further functional studies will be required to validate this. This dysregulation may have in turn produced hemodynamic perturbations between the twins, leading to the discordant cardiac pathology. It is currently unclear to what degree we expect the patients to exhibit other traits previously associated with distal 15q duplications, such as developmental delay or intellectual disability, but the mother's typical cognitive function is reassuring. Further follow-up will be important to characterize the full phenotypic effects of this microdeletion and to compare these twins to the clinical course of previously described patients with 15q overgrowth syndrome.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

All authors were responsible for gathering relevant patient data. The initial draft was prepared by Suraj Kannan and edited by Joann N. Bodurtha, Ada Hamosh, and Christopher Jordan. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics approval was not required for this case report.

CONSENT FOR PUBLICATION

Written consent was obtained from the legal guardian of the patients. These consent forms are available on request.

DATA AVAILABILITY STATEMENT

This study makes use of data generated by the DECIPHER community. A full list of centres who contributed to the generation of the data is available from https://deciphergenomics.org/about/stats and via email from contact@deciphergenomics.org. Funding for the DECIPHER project was provided by Wellcome.

ORCID

Suraj Kannan https://orcid.org/0000-0002-7820-7381

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