Aortopathy in the 7q11.23 microduplication syndrome

Ashley Parrott[1], Jeanne James[1], Paula Goldenberg[1], Robert B. Hinton[1], Erin Miller[1], Amy Shikany[1], Arthur S. Aylsworth[2,3], Kathleen Kaiser-Rogers[2,3,4], Sunita J. Ferns[2], Seema R. Lalani[5], and Stephanie M. Ware[6]

[1]Cincinnati Children's Hospital Medical Center, Department of Pediatrics, Heart Institute, Cincinnati, Ohio

[2]University of North Carolina, Department of Pediatrics, Chapel Hill, North Carolina

[3]University of North Carolina, Department of Genetics, Chapel Hill, North Carolina

[4]University of North Carolina, Department of Pathology and Laboratory Medicine, Chapel Hill, North Carolina

[5]Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, Texas

[6]Indiana University School of Medicine, Department of Pediatrics and Medical and Molecular Genetics, Indianapolis, IN

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Running Head Author: Parrott et al.

Corresponding Author:
Ashley Parrott
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue MLC 7020
Cincinnati, Ohio 45229
Telephone – (513) 803-3318
Fax – (513) 803-1748
Email – Ashley.parrott@cchmc.org

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ABSTRACT

The 7q11.23 microduplication syndrome, caused by the reciprocal duplication of the Williams-Beuren syndrome (WBS) deletion region, is a genomic disorder with an emerging clinical phenotype. Dysmorphic features, congenital anomalies, hypotonia, developmental delay highlighted by variable speech delay, and autistic features are characteristic findings. Congenital heart defects, most commonly patent ductus arteriosus, have been reported in a minority of cases. Included in the duplicated region is elastin (*ELN*), implicated as the cause of supravalvar aortic stenosis in WBS. Here we present a series of eight pediatric patients and one adult with 7q11.23 microduplication syndrome, all of whom have aortic dilation, the opposite vascular phenotype of the typical supravalvar aortic stenosis found in WBS. The ascending aorta was most commonly involved, while dilation was less frequently identified at the aortic root and sinotubular junction. The findings in these patients support a recommendation for cardiovascular surveillance in patients with 7q11.23 microduplication syndrome.

Key words: 7q11.23 microduplication, Williams-Beuren, thoracic aortic aneurysm, elastin, pediatrics

INTRODUCTION

The 7q11.23 microduplication syndrome is caused by the reciprocal duplication of the Williams-Beuren syndrome (WBS) deletion region. Deletions and duplications in this region arise due to non-allelic homologous recombination between low copy number repeat sequences. Williams syndrome has a prevalence of approximately 1/7,500-1/10,000 births [Stromme et al., 2002], whereas the prevalence of the 7q11.23 microduplication has been estimated to be 1/13,000-1/20,000 [Van der Aa et al., 2009].

The 7q11.23 microduplication syndrome was first reported in 2005 [Somerville et al., 2005]. Since that time, several case reports have been published including two recent larger case series [Dixit et al., 2013; Van der Aa et al., 2009]. The clinical phenotype continues to emerge and includes dysmorphic features, developmental delay with variable speech delay (most commonly expressive language delay), autistic features, hypotonia and various congenital anomalies including cryptorchidism. The aforementioned case series describe dysmorphic features that may outline a characteristic and recognizable facial phenotype including straight and neatly placed eyebrows, broad forehead, high broad nose, short philtrum, thin upper lip, and various ear abnormalities. Abnormal brain MRI findings as well as seizures have been reported. Additionally, neurobehavioral concerns including self-mutilating behavior, agitation, and aggressive behavior have been described in adults [Van der Aa et al., 2009]. The microduplication has also been identified in a large schizophrenia cohort. These individuals were noted to have a history of social anxiety and language delay predating their schizophrenia diagnosis [Mulle et al., 2013]. Congenital heart disease has been reported previously. In one series of 14 individuals, three were found to have a patent ductus arteriosus, and one further

patient had an atrial septal defect [Van der Aa et al., 2009]. One patient has been reported to have supravalvar aortic stenosis (SVAS) with post-stenotic dilation [Orellana et al., 2008].

Included in the region of the duplication is elastin (*ELN*). Elastin (derived from tropoelastin) is an essential component of elastic fibers, which are highly organized extracellular matrix proteins present in tissues that require elasticity, or the ability to deform and recoil, such as arteries [Baldwin et al., 2013; Rosenbloom et al., 1993]. Decreased dosage of *ELN* is implicated as the cause of SVAS in WBS, and both *ELN* deletions and mutations have been identified in individuals without WBS who have SVAS [Ewart et al., 1994; Li et al., 1997; Metcalfe et al., 2000]. Furthermore, *ELN* mutations have also been identified in patients with autosomal dominant cutis laxa and thoracic aortic aneurysm and dissection [Szabo et al., 2006]. These findings demonstrate the deleterious effects of decreased *ELN* dosage or abnormal gene function on the aorta. The effect of increased *ELN* dosage on the aorta has not been reported.

METHODS

Seven patients in three families were identified through standard clinical practice at two institutions. Two additional patients were identified through Medical Genetics Laboratory (MGL) at Baylor College of Medicine. Patients included in this report had echocardiographic data available.

A microduplication of 1.42 Mb and 1.45 Mb of 7q11.23 was identified by single nucleotide polymorphism (SNP) Microarray (Illumina HD Human610-quad BeadChip platform) in the probands in Families A and B, respectively (Patient's 1 and 3). In Family A, the duplication was identified in the proband's maternal half-sibling (Patient 2) through fluorescence in situ hybridization (FISH) using the Vysis Williams Probe. The mother in Family A has been confirmed to have the microduplication but has not been evaluated clinically, and thus is not

included in this series. In Family B, the duplication was also identified through FISH using the Vysis Williams Probe in a full sibling and a maternal half-sibling (Patients 4 and 5). The mother in Family B (Patient 6) is a presumed carrier of the microduplication due to the presence of consistent features including dysmorphic features and learning disability, and the transmission of the duplication to children with different fathers. However confirmatory genetic testing has not been completed so the possibility of germline mosaicism cannot be formally excluded.

Patient 7 with ~1.1 Mb duplication and patient 8 with ~1.5 Mb *de novo* duplication were screened using custom-designed exon-targeted array-CGH oligonucleotide microarrays (patient 7 V7.4 OLIGO, 105K; patient 8 V8.1 OLIGO, 180K) designed by MGL at BCM (http://www.bcm.edu/geneticlabs) and manufactured by Agilent Technology (Santa Clara, CA), as previously described [Boone et al., 2010]. The parents of Patient 7 have not had parental testing for the duplication, and Patient 8 has a *de novo* duplication.

The 7q11.23 microduplication in patient 9 was also identified using a SNP microarray platform (Affymetrix CytoScan HD) and confirmed by both metaphase and interphase fluorescence in situ hybridization (FISH) using Empire Genomics' RP11-19F19 probe. . The duplication involved 1,564 markers and approximately 1.4 Mb of genetic material. Although no paternal sample has been received for follow-up testing, maternal FISH testing was normal.

CLINICAL REPORTS

Patient 1, the proband in Family A (Figure 1), is an African American male and was found to have the 7q11.23 duplication at age 4 on a SNP microarray performed due to a history of hypotonia, developmental delay, dysmorphic features, dysphagia and lung disease. The patient had right orchidopexy and inguinal hernia repair at age 5 and at age 6, was noted to have mild intellectual disability, mixed receptive and expressive language disorder, and difficulty with

attention regulation (Table I). He originally presented with aortic dilation in infancy identified on echocardiographic evaluation of a murmur. His cardiac evaluations have continued to demonstrate dilation of the aortic root, sinotubular junction, and ascending aorta, as well as a patent ductus arteriosus. Beta-blocker therapy was initiated at age 5.

Patient 2, the proband's maternal half-sister, was subsequently found to have the 7q11.23 duplication through FISH at age 10. She has a history of learning difficulty and severely deficient receptive language skills, as well as dysmorphic features. She is noted to make fair grades in a traditional education setting with supports from an individualized education plan. Her cardiac evaluation revealed dilation of the ascending aorta and a small patent foramen ovale. An unaffected maternal half-sibling had a normal echocardiogram with the exception of a small patent foramen ovale. The affected mother has not had a formal evaluation and thus was not included in this report. She is reported to have an unspecified mental health diagnosis.

The proband in Family B (Figure 1), Patient 3, is a biracial Caucasian and African American female and was found to have the 7q11.23 duplication at age 3 on a SNP microarray performed due to a history of developmental delay and dysmorphic features. In addition to the 7q duplication, the proband was also found to have a 1.68Mb deletion of 15q13.2-15q13.3, which was paternally inherited but absent in her other siblings. This deletion overlaps with the recurrent 15q13.3 microdeletion region, which has been proposed to be associated with developmental delay, dysmorphic features, epilepsy, and behavioral abnormalities, but also identified in apparently normal individuals [Masurel-Paulet et al., 2010]. The proband's initial cardiac evaluation performed at age 3 due to a family history of cardiomyopathy identified aortic root and sinotubular junction dimensions at the upper limits of normal and minor left ventricular apical trabeculations. Subsequent imaging revealed mild dilation of the aortic root, sinotubular

junction, and ascending aorta at age 4 which normalized by age 7. At age 7 she was noted to have learning difficulty, communication disorder, attention deficit and gross and fine motor delay. She was receiving special education services.

The proband's brother (Patient 4) and maternal half-sister (Patient 5), both also biracial, were subsequently found to have the duplication through FISH analysis. Their mother (Patient 6) has not had genetic testing and thus the possibility of germline mosaicism cannot be excluded. At age 5, Patient 4 has a history of mild speech delay with speech therapy received at age 4 but ceasing in kindergarten at age 5. His initial cardiac evaluation was performed at age 2 due to the family history of cardiomyopathy, and he was found to have aortic root dimensions at the upper limits of normal. Subsequent evaluations at ages 5 and 6 revealed aortic findings in the borderline to mildly dilated range. He is also noted to have prominent left ventricular free wall trabeculations.

Patient 5, also a biracial female, was diagnosed with dilated cardiomyopathy (DCM) in infancy and required initial hospitalization for approximately a month after her diagnosis. She was later also noted to have left ventricular noncompaction cardiomyopathy (LVNC). After her hospitalization she reportedly had failure to thrive with feeding difficulty and NG tube requirement for six months. At age 14 she was noted to have normal growth and development but did have dysmorphic features. She was found to have the 7q11.23 duplication at age 15. Patient 5 had been followed by Cardiology with many echocardiograms performed since infancy due to her diagnosis of cardiomyopathy. She had negative genetic testing for DCM through a gene panel including 19 genes. The patient was admitted to a cardiac intensive care unit at age 15 with a suspected bacterial infection and had severe cardiac decompensation. She died during that admission subsequent to heart failure associated with her diagnosis of cardiomyopathy.

Review of aortic findings from her cardiac imaging showed mild aortic root dilation between the ages of 6 and 8 before normalization of aortic dimensions.

Patient 6 in Family B, a Caucasian female, reported a history of learning disability and auditory discrimination problems. She was noted to have mild dysmorphic features which were not further specified. An echocardiogram performed at age 34 revealed mild dilation of the ascending aorta.

Patient 7 presented with intractable seizures around the age of 5 years. Brain MRI revealed cortical thickening extending from the medial left parietal lobe to the anterior left temporal lobe, consistent with cortical dysplasia. Her intellectual functioning was assessed using the WISC – IV at the age of 11 years and was found to have a Full Scale IQ of 42. Echocardiogram showed a mildly dilated ascending aorta. On physical exam, her growth parameters were appropriate for age. No facial dysmorphic features were noted. Her neurological exam was normal. The patient had one healthy sibling, with no family history of aortopathy.

Patient 8 was ascertained at 3 months of age with seizures. EEG showed focal epileptic discharges in the right fronto-parietal region, which normalized by 6 years of age. Brain MRI indicated dysmorphic prominent supratentorial ventricular system. Echocardiogram at 2 years of age showed mildly dilated ascending aorta, with normal aortic root and sinotubular junction. At 5 years, the echocardiogram continued to show a mildly dilated ascending aorta.The aortic root and sinotubular junction measured within normal limits for body surface area. His overall development was delayed, with severe language deficits. On physical exam, his stature was 105.9 cm (Z=-2.11), and his weight was 14.6kg (Z=-3.09). No dysmorphic features were noted

on exam. Both parents were reportedly healthy. The duplication was found to be *de novo* in this patient.

Patient 9 is a Caucasian female who presented at age 37 months for evaluation of developmental delays, dysmorphic features, and a seizure disorder. Details of her delays are unknown. Early milestone history from parents seemed normal but she received play, physical and speech therapies from age 8 months to almost 3 years. Records describe symptoms of anxiety, sad expression without reason to be sad, and withdrawn behaviors. An evaluation at 2yr 4mo showed normal speech development. The seizure history included a febrile seizure at age 14 months and subsequent "staring spells" of unclear significance. On physical exam, she is overweight and has macrocephaly (+3SD> the mean), a prominent forehead, the appearance of closely spaced eyes and short palpebral fissures (interpupillary and palpebral fissure measurements were 3rd-25th centile for chronologic age and << 3rd for her head circumference age of 12 years), a narrow nasal tip with prominent grooves between tip and alae, and a shy affect with poor eye contact and no communication. Her echocardiogram showed a normal aortic valve annulus size and function and a moderately dilated ascending aorta. The family history is very complex with neurodevelopmental problems on both sides.

Genetic testing for these patients was performed on a clinical basis. No patients were found to have features of Marfan syndrome, Loeys Dietz syndrome, or another connective tissue disorder which prompted investigation of other genetic causes of aortopathy.

Cardiac Phenotype

All individuals with the duplication in this series demonstrated aortic dilation ranging from mild to moderate (Table I). Dilation of the ascending aorta (AAo) (Figure 2, panel C) was identified in 8/9 patients; dilation of the aortic root (AoR) and/or sinotubular junction (STJ) were

also seen, but less frequently (4/9 and 2/9, respectively). Insufficient information is available on the lifetime risk for progressive aortic disease in these individuals, but dilation appears to be stable, at least over the first decade of life, based on a limited number of observations (Figure 1, panels A and B). Longitudinal data is available for a subset of patients. At this time, only single measurements are available for Patients 6, 7, and 9. One individual was found to have a silent patent ductus arteriosus, which has been previously reported in association with the 7q11.23 microduplication syndrome. Both affected individuals in Family A are on a beta-blocker for medical management of their aortopathy.

The duplication phenotype in Family B is complicated by the coexisting diagnosis of dilated cardiomyopathy (DCM) and left ventricular non-compaction (LVNC) in Patient 5 and prominent left ventricular trabeculations in two other relatives carrying the duplication (Patients 3 and 4). Patient 5 had dilation of the AoR present from approximately 6 to 8 years of age, with a normal AoR dimension documented at age 8. This patient died at age 14 due to heart failure secondary to cardiomyopathy. In this family, Patient 3 also demonstrated normalization of aortic dimensions from age 4 to age 7, and Patient 4 demonstrated a similar pattern with only borderline dilation of the aortic root at 6 years of age. Neither Patient 3 nor 4 have received medical therapy, but they continue to be followed with serial echocardiograms and clinical evaluations.

In both Family A and B, a half-sibling of the proband without the duplication has had an echocardiogram demonstrating normal aortic dimensions, consistent with segregation of aortopathy with the duplication (Figure 1). No additional affected relatives are available for evaluation in these families.

DISCUSSION

Here we characterize the cardiac findings and extracardiac features in 9 patients with the 7q11.23 microduplication syndrome. Aortic dilation was identified in all individuals, with no individuals demonstrating marked progression of their aortopathy over baseline and two individuals demonstrating normalization of their aortic dimensions over time. Consistent with previous reports, we identified one individual with a patent ductus arteriosus. While congenital heart disease has been identified in patients previously, aortic dilation has not been described in those individuals. However, the ages at which previously described patients had an echocardiogram which identified the heart defect, or if serial surveillance was performed, is unknown. It is also unclear whether previously reported individuals who were not described as having congenital heart disease ever had cardiac imaging. Therefore, we cannot comment on the presence or absence of aortopathy in these previously described patients.

Extracardiac features previously reported as common to the duplication were observed in this series including language delay and dysmorphic features. Only one individual in this series was not found to have a history of developmental delay, learning disability, need for developmental therapy, or behavioral concerns. In light of identification of the 7q11.23 microduplication in individuals with schizophrenia and other behavioral concerns, we note concern for a mental health disorder in an adult relative known to have the duplication, but not included in this series as she has not had a cardiac evaluation.

Previous references have been made to the apparent opposite phenotypes caused by the 7q11.23 deletion and duplication, including opposing dysmorphic features and the relative strength/weakness in expressive language [Dixit et al., 2013]. Additional reciprocal deletions/duplications display similar evidence including opposing effect on growth associated

with the 1q21.1 locus as well as the 5q35 locus containing *NSD1* [Brunetti-Pierri et al., 2008; Rosenfeld et al., 2013]. Here we demonstrate an interesting example of contrasting phenotypes involving the 7q11.23 locus, with SVAS commonly observed in WBS and aortic dilation identified in these individuals with the 7q11.23 microduplication syndrome. While the SVAS in WBS has been attributed to *ELN* deletion, we postulate that a gene dosage effect of *ELN* may be the underlying cause for the aortopathy in these patients with the microduplication. However at this time, the exact cause of aortic dilation in these patients is not known. While the frequency of the observed aortopathy in the individuals presented here appears unlikely to have occurred by chance, we cannot rule out the possibility of another gene within the region of duplication being responsible for the aortic findings.

The findings in this series support a recommendation for cardiovascular surveillance in all individuals with the 7q11.23 microduplication. This series indicates a high penetrance of aortopathy occurring in childhood. Aortopathy is typically a silent disease until late stage disease, at which time morbidity and mortality are high. Early identification of aortic dilation provides the opportunity for medical intervention, thus periodic surveillance is indicated. While aortic disease in this series appeared to be stable, and to date there have been no reports of aortic dissection or rupture, two of the patients are on beta blocker therapy since their ascending aortic dimension z-scores are well over +3.0. The 2010 Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease includes syndrome specific recommendations and risk stratification [Hiratzka et al., 2010]. This highlights the need to understand the genetic etiology in patients with thoracic aortic aneurysm and to fully delineate the natural history of genetic syndromes in which aortopathy is a feature. This series adds 7q11.23 microduplication syndrome to that list. Longitudinal studies are needed to determine the lifetime risk of

progressive aortopathy and sudden cardiac death, so that evidence-based recommendations may be made regarding frequency of surveillance and the timing and impact of medical intervention.

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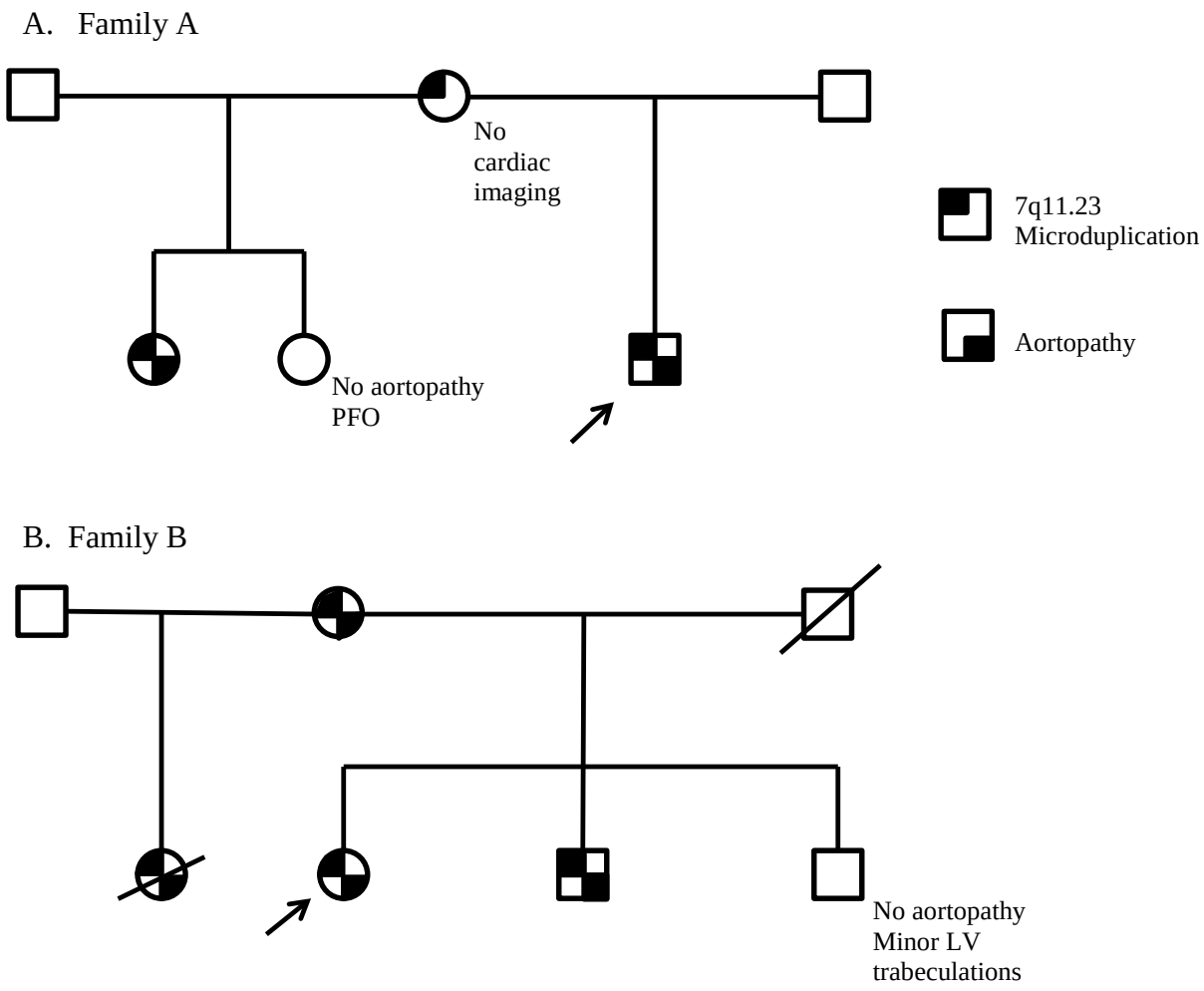

Figure 1. Pedigrees. A. The proband and one maternal half-sister have both been confirmed to have the microduplication and aortopathy. A half-sister without the duplication had an echocardiogram at age 7 documenting normal aortic dimensions. The mother with the duplication has not had cardiac imaging. B. The proband and the affected parent and siblings have had cardiac imaging exhibiting aortopathy. The sole unaffected sibling has had several echocardiograms (due to the family history of cardiomyopathy) with normal aortic dimensions, most recently at age 4. No additional relatives from either family have had cardiac imaging.

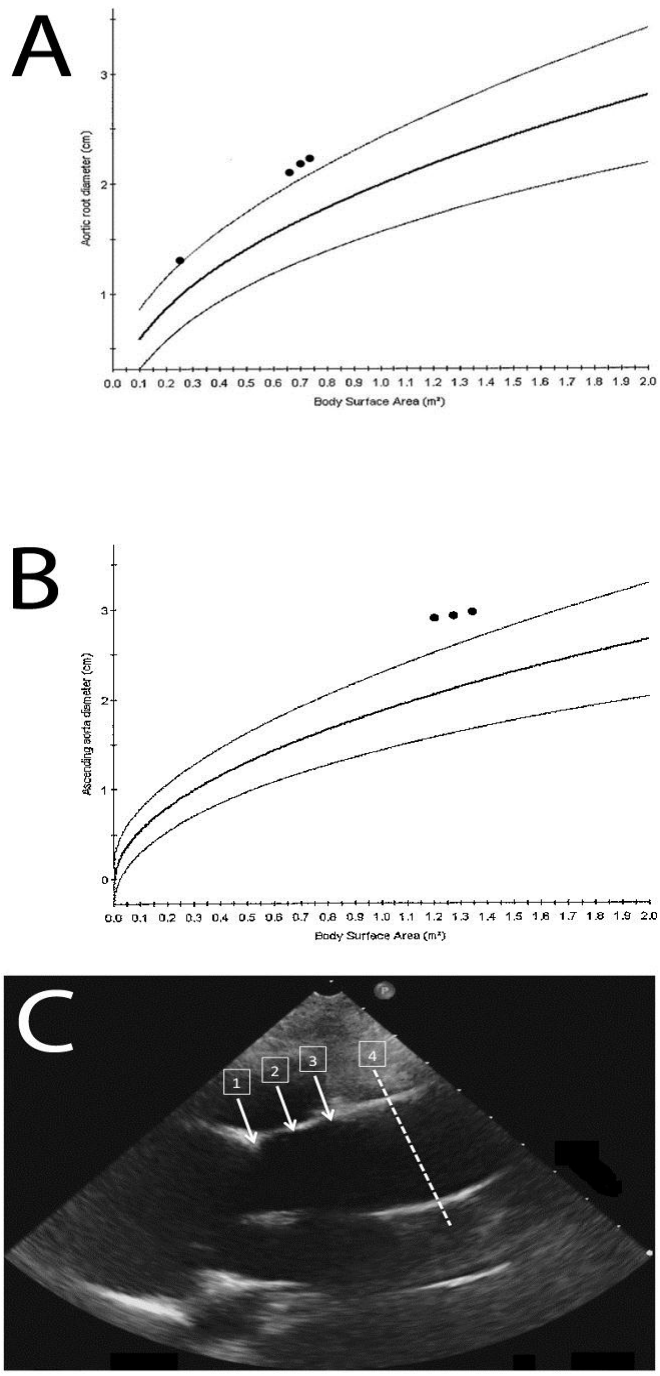

Figure 2. Dilation of the aorta in patients with 7q11.23 microduplication syndrome. A, Serial measurements of the aortic root in Patient 1, according to standard protocol . B, Serial measurements of the ascending aorta in Patient 2. C, Echocardiographic parasternal long axis image of Patient 2. Sites 1, 2 and 3 indicate location of the aortic valve annulus, aortic root and sinotubular junction, respectively. Site 4 is the ascending aorta, with the dashed line delineating the dimension of the ascending aorta.

Table I Cardiac and Extracardiac Phenotypic Features

Patient ID	Gender	Age at echocardiogram	Site of aortic dilation*	z-score	Other Cardiac Features	Extracardiac Clinic History	Dysmorphic Features
Family A							
1	Male	6 months 6 years 6 months 7 years 6 months	Root STJ AAo Root STJ AAo Root STJ AAo	2.2 2.3 5.2 2.8 2.1 3.5 2.1 2.6 5.1	Patent Ductus Arteriosus	Mild intellectual disability, mixed receptive and expressive language disorder, hypotonia, cryptorchidism	Broad forehead, broad and flat nasal bridge, mild epicanthus inversus, small low-set ears with mildly thickened helices
2	Female	11 years 1 month 11 years 7 months 12 years 1 month	AAo AAo AAo	3.6 3.4 3.2	Small Patent foramen ovale	Learning difficulty, communication disorder, receptive language severely deficient	Small mouth, depressed nasal tip
Family B							
3	Female	4 years 4 months 6 years 7 years	Root STJ AAo Root Normal	2.3 2.3 2.9 2.1 -	Minor left ventricular apical trabeculations	15q13.2q13.3 deletion, developmental delay, mixed receptive and expressive language disorder	Short palpebral fissures, macrocephaly
4	Male	2 years 8 months 5 years	Root Root	2.0 2.5	Prominent left ventricular free wall trabeculations	Speech delay	Midface hypoplasia, mild hyperteolorism, straight eyebrows

		6 years	AAo Root	2.3 2.0			
5	Female	6 years 9 months 7 years 10 months 8 years 10 months	Root Root Normal	3.1 2.7 -	Dilated cardiomyopathy, Left ventricular noncompaction	-	Short upslanting palpebral fissures, bilateral epicanthal folds, bulbous nose, mildly posteriorly rotated ears
6	Female	34 years 1 month	AAo	2.8	-	Learning disability	Mild dysmorphic features, not further specified
Family C							
7	N/A	11 years	AAo	3.0	-	Cognitive delay, epilepsy, cortical dysplasia	No facial dysmorphism noted
Family D							
8	N/A	2 years 6 months 3 years 7 months 5 years 4months	AAo AAo AAo	2.4 3.1 2.7	-	Autism, short stature	Dysmorphic features, not further specified; microcephaly
Family E							
9	Female	3 years 5 months	AAo	3.5	-	Early milestones reportedly normal but received play, physical and speech therapy; behavior withdrawn and anxious; febrile seizure; current staring spells of unclear cause	Prominent forehead, narrow nasal tip, prominent grooves between tip and alae, BMI >97th centile, macrocephaly (maternal trait)

*Normal measurements are not listed unless a measurement was shown to normalize over time, in which case age at normalization is listed; Root – aortic root, STJ – sinotubular junction, AAo – ascending aorta
(-) indicates normal