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Cardiovascular findings in duplication 17p11.2 syndrome

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Purpose: Cardiovascular abnormalities are newly recognized features of duplication 17p11.2 syndrome. In a single-center study, we evaluated subjects with duplication 17p11.2 syndrome for cardiovascular abnormalities.

Methods: Twenty-five subjects with 17p11.2 duplication identified by chromosome analysis and/or array-based comparative genomic hybridization were enrolled in a multidisciplinary protocol. In our clinical evaluation of these subjects, we performed physical examinations, echocardiography, and electrocardiography. Three of these subjects were followed up longitudinally at our institution.

Results: Cardiovascular anomalies, including structural and conduction abnormalities, were identified in 10 of 25 (40%) of subjects with duplication 17p11.2 syndrome. The most frequent abnormality was dilated aortic root (20% of total cohort). Bicommissural aortic valve (2/25), atrial (3/25) and ventricular (2/25) septal defects, and patent foramen ovale (4/25) were also observed.

Conclusion: Duplication 17p11.2 syndrome is associated with structural heart disease, aortopathy, and electrocardiographic abnormalities. Individuals with duplication 17p11.2 syndrome should be evaluated by electrocardiography and echocardiography at the time of diagnosis and monitored for cardiovascular disease over time. Further clinical investigation including longitudinal analysis would likely determine the age of onset and characterize the progression (if any) of vasculopathy in subjects with duplication 17p11.2 syndrome, so that specific guidelines can be established for cardiovascular management.

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Key Words: chromosome 17p duplication; congenital heart defects; dilated aortic root; Potocki-Lupski syndrome; PTLS; vasculopathy

INTRODUCTION

Duplication 17p11.2 syndrome (Potocki-Lupski syndrome: OMIM# 610883) was the first predicted reciprocal microduplication syndrome described.[1,2] Most individuals with duplication 17p11.2 syndrome (approximately 65%) harbor a common 3.7 Mb duplication within 17p11.2, which is the homologous recombination reciprocal of the Smith-Magenis syndrome (SMS: OMIM# 182290) microdeletion.[1,3] The common Potocki-Lupski syndrome duplication and common SMS deletion are caused by nonallelic homologous recombination between the flanking distal and proximal low-copy repeats called SMS-REPs.[4] Nonallelic homologous recombination can also use other low-copy repeats within this region and result in the so-called uncommon recurrent duplications.[3] Furthermore, DNA replication-based mechanisms or nonhomologous end-joining are responsible for the majority of the nonrecurrent duplications.[3,5]

The clinical features of duplication 17p11.2 syndrome include hypotonia, failure to thrive, developmental delay, intellectual disability, sleep-disordered breathing, and structural cardiovascular abnormalities.[1,2,6–8] The behavioral phenotype of duplication 17p11.2 syndrome includes autistic spectrum disorder, anxiety, and inattention.[9] Although several cases of 17p11.2 duplication were reported before its molecular mechanism was known, cardiovascular disease was not recognized as a feature of duplication 17p11.2 syndrome until individuals were systematically evaluated through a protocol-driven, multidisciplinary clinical study.[1] Herein, we detail the cardiovascular findings in 25 subjects with duplication 17p11.2 syndrome, including 11 subjects who were described previously.[1,10] Three of these subjects (527, 1106, and 2362) had more than one echocardiogram at our institution.

MATERIALS AND METHODS

The study was approved by the Baylor College of Medicine Institutional Review Board (Houston, TX). Individuals with 17p11.2 duplications identified by chromosome analysis, fluorescence in situ hybridization (FISH), and/or array-based comparative genomic hybridization (array CGH) were referred to our institution and enrolled in a multidisciplinary clinical protocol in the General Clinical Research Center at Texas Children's Hospital. Informed consent was obtained from the subjects' parent or legal guardian. Molecular characterization of almost all the subjects (except subject 3028) was described previously (Table, **Supplementary Data** online).[1,3,5,10]

Medical and family histories were recorded, and physical examination was performed on all subjects on enrollment into the study. Two-dimensional transthoracic echocardiography

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and Doppler imaging were performed according to institutional guidelines. Aortic root dimensions were measured according to guidelines of the American Society of Echocardiography.[11] Intracardiac structure and dimensions of the great vessels were measured. Using widely accepted criteria,[12] *Z* scores (standard deviation units) were calculated and compared with those of normal individuals with matched body surface area, gender, and age. A standard 15-lead electrocardiogram (ECG) was obtained at rest. Images and measurements were reviewed independently by a pediatric echocardiologist who was unaware of the underlying diagnosis (R.H.P.). Subjects 527, 1006, and 2362 were followed longitudinally to age 16 years, 27 years, and 3 years 10 months, respectively. Abnormal findings of Subjects 527 and 2362 are detailed within the "Results" section and in **Table 1**. Subject 1006 had normal cardiovascular evaluations.

RESULTS

Twenty-five subjects with 17p11.2 duplication (10 males, 15 females; age range at time of most recent cardiac evaluation from 2 years 1 month to 27 years) were included. Of the 25 subjects, 10 (40%) showed cardiovascular involvement. No individual had a family history of congenital heart defects (CHDs) or was exposed to teratogenic agents or maternal diabetes. Abnormal cardiovascular findings are summarized in **Table 1**. A summary of all subjects is provided in the Table (**Supplementary Data** online).

Clinical details of subjects with abnormal cardiovascular finding

Subject 527 was diagnosed with duplication 17p11.2p12 soon after birth by chromosome analysis that was performed because of hypotonia, poor feeding, and CHDs. He had a large (10–12 mm) membranous ventricular septal defect (VSD) that extended into the conoventricular septum, with low-velocity bidirectional shunting through the defect. In addition, the right coronary cusp of the aortic valve prolapsed into the VSD during systole. At 2 months of age, he was noted to have increased pulmonary blood flow and congestive heart failure by chest radiograph and underwent pulmonary artery banding that resulted in compensation of heart failure symptoms. He had routine echocardiograms performed at 1–2-year intervals; however, not all echocardiograms provided optimal visualization of the great vessels. The first echocardiogram to reveal an abnormality of the aorta was performed at the age of 6 years and 4 months and showed a mildly dilated aortic annulus of 1.7 cm (*Z* score: 3.63) and an aortic root of 1.76 cm (*Z* score: 0.37). An echocardiogram performed at age 11 years 9 months revealed an aortic annulus *Z* score of 4.45, and aortic root *Z* score of 5.43, and a sinotubular junction *Z* score of 3.37. Echocardiogram at age 13 years 5 months revealed an aortic annulus *Z* score of 3.52, and aortic root *Z* score of 4.73, and sinotubular junction *Z* score of 2.98. At the age of 12 years, he was noted to have atrial ectopic tachycardia and was started on an antiarrhythmic therapy (Sotalol, 50 mg twice a day); since that time, he has not had episodes of tachycardia. The most recent follow-up echocardiogram at age 16 years that was performed to evaluate cardiac anatomy and function revealed a large nonrestrictive perimembranous VSD with bidirectional shunting, mild tricuspid regurgitation with a peak velocity approximately 4.0 m/second by echo Doppler, and moderate right ventricular hypertrophy with a moderately dilated right atrium and right ventricle. There was a mildly dilated aortic annulus (*Z* score: 3.95), moderately dilated aortic root (*Z* score: 5.35), and a sinotubular junction with a *Z* score of 4.57. The pulmonary artery band appeared to be in good position with a peak Doppler velocity of approximately 4.3 m/second.

Subject 1913 was diagnosed at age 12 years by chromosome analysis and FISH that was performed because of dysmorphic features, poor growth, and developmental delay. Chromosome analyses at

Table 1 Cardiovascular findings in duplication 17p11.2 syndrome

					Echocardiogram								
Subject	**PE**	**PFO**	**VSD**	**ASD**	**Bi Ao V**	**R A dil**	**LMCA**	**AoA[a]**	**AoR[a]**	**STJ[a]**	**AsAo[a]**	**P[a]**	**ECG**
527	+[b]	N	+	nl	nl	+	nl	**3.95**	**5.35**	**4.57**	nl	nl	+[c]
1913	+[b]	N	nl	+	nl	+	nl	nl	2.52	nl	nl	nl	+[d]
2167	—	N	nl	+	nl	nl	nl	nl	nl	nl	nl	nl	nl
2211	—	**Y**[e]	+	nl	+	nl	nl	nl	**6.03**	**9.06**	**11.6**	**3.18**	nl
2306	—	**Y**[e]	nl	nl	+	nl	nl	nl	nl	nl	nl	nl	+[f]
2362	—	**Y**[e]	nl	nl	nl	nl	nl	nl	nl	nl	nl	**2.23**	nl
2578	—	N	nl	nl	nl	nl	nl	nl	nl	nl	nl	nl	+[g]
2695	—	N	nl	+	nl	nl	nl	**3.14**	**2.98**	**2.73**	**3.7**	nl	nl
2745	—	N	nl	nl	nl	nl	+	nl	nl	nl	nl	nl	+[h]
2998	—	**Y**[e]	nl	nl	nl	nl	nl	nl	**3.5**	nl	nl	nl	nl

Abnormal findings are in bold text.

AoA, aortic annulus; AoR, aortic root; AsAo, ascending aorta; ASD, atrial septal defect; Bi Ao V, bicuspid aortic valve; ECG, electrocardiogram; LMCA, low mitral chordal attachments; N, no; nl, normal; P, left pulmonary artery in 2211 and pulmonary valve annulus in 2362; PE, physical examination; PFO, patent foramen ovale; RA dil, right atrial dilatation; STJ, sinotubular junction; VSD, ventricular septal defect; Y, yes.

[a]Measurements in *Z* score. [b]Grade 2/6 systolic murmur. [c]Atrial tachycardia. [d]Pattern of right ventricular hypertrophy. [e]Patent foramen ovale with left-to-right shunting. [f]Prolonged QT interval. [g]Occasional premature atrial contractions. [h]Sinus arrhythmia with premature ventricular complexes and fusion complexes.

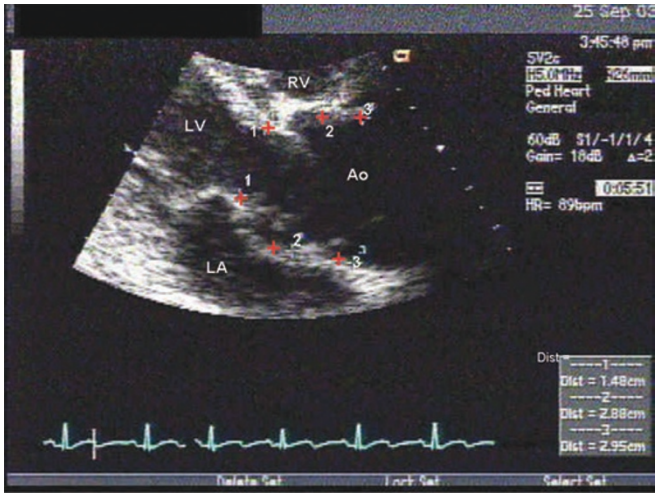

Figure 1 Subject 2211 in a parasternal long-axis view, the dilatation of the aorta is observed in different segments. The aortic annulus diameter is the distance between 1 and 1 (*Z* score: 3.27); the aortic root diameter is the distance between 2 and 2 (*Z* score: 6.03); and the sinotubular junction is the distance between 3 and 3 (*Z* score: 9.06). Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle.

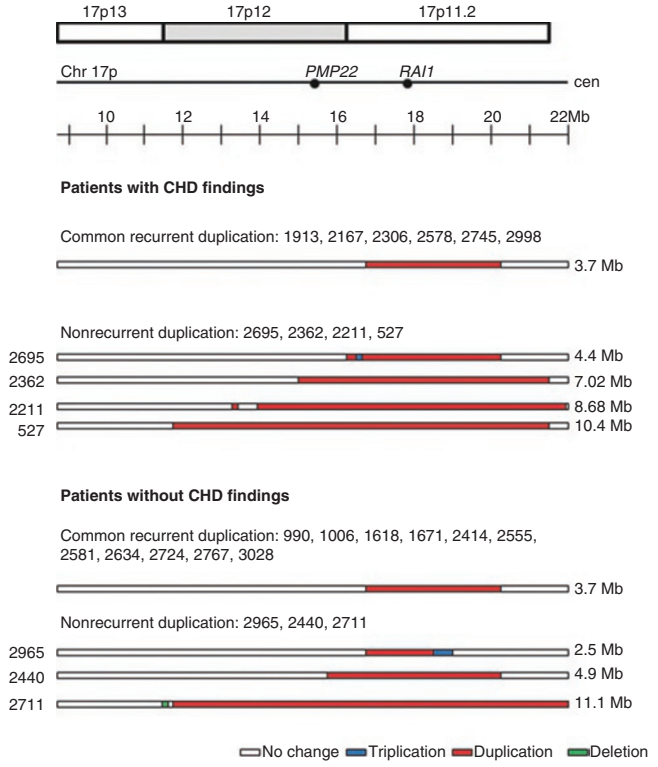

Figure 2 Summary of duplication sizes. The position and size of the genomic rearrangements (red (duplication), blue (triplication), and green (deletion) bars), as determined by array CGH are depicted for each subject. An ideogram of chromosome 17p, with a scale indicating the genomic coordinates (version hg18), and the locations of *PMP22* and *RAI1* genes are also included. Subject 2343 (mosaic marker) is not shown. Cardiac phenotype of each patient with CHD is briefly summarized in **Table 1** and detailed in the text. Modified with permission from Am J Hum Genet.[3] CGH, comparative genomic hybridization; CHD, congenital heart defect.

birth and earlier in childhood were normal. Cardiac evaluation at 12 years and 9 months revealed a grade 2/6 systolic murmur. An echocardiogram showed a large (19 mm) secundum atrial septal defect (ASD) with left-to-right shunting. The right atrium and right ventricle were moderately enlarged with preserved right ventricular systolic function. The aortic root was mildly dilated at 2.31 cm (*Z* score: 2.52). The subject's ECG revealed right ventricular hypertrophy based on an R wave in V1 and an S wave in V6 higher than the upper limits of normal range.

Subject 2167 was diagnosed at age 9 months by chromosome analysis and FISH that was performed because of hypotonia and poor feeding. At the age of 3 years 3 months, the patient's echocardiogram showed a small secundum ASD measuring 4–5 mm with left-to-right shunting. The right ventricle was normal in size and with systolic function. The remainder of the echocardiogram was normal.

Subject 2211 was diagnosed at age 3 years 6 months by chromosome analysis and FISH performed because of hypotonia, poor feeding, and developmental delay. An echocardiogram performed at the age of 4 years 8 months (**Figure 1**) revealed a bicuspid aortic valve with raphe present between the right and left coronary commissures and severe dilation of the aortic root (measuring 2.88 cm; *Z* score: 6.03), the sinotubular junction diameter (measuring 2.95 cm; *Z* score: 9.06), and the ascending aorta (measuring 3.38 cm; *Z* score: 11.60). A small patent foramen ovale (PFO) with left-to-right shunting was visualized, as well as a small, restrictive muscular VSD with left-to-right shunting. The mitral valve was abnormal with redundant anterior and posterior leaflets and mild prolapse of the anterior mitral leaflet with resultant trivial mitral regurgitation. The left pulmonary artery was dilated (measuring 1.33 cm; *Z* score: 3.18). He subsequently underwent surgical repair of the aorta at another institution, details of which are reported elsewhere.[13]

Subject 2306 was diagnosed at age 29 months by chromosome analysis and FISH that was performed because of hypotonia, failure to thrive, and developmental delay. An echocardiogram at the age of 2 years 7 months revealed a PFO with left-to-right shunting and bicommissural aortic valve with a partial fusion between the right and left commissures. The leaflets appeared mildly thickened without evidence of significant stenosis or regurgitation. The ECG revealed a prolonged QT interval of 488 milliseconds and a normal sinus rhythm.

Subject 2362 was diagnosed at age 8 months by chromosome analysis that was performed because of developmental delay. His initial echocardiogram at age 13 months revealed a PFO with left-to-right shunting and a dilated pulmonary valve annulus of 1.42 cm (*Z* score: 2.23). No other significant structural abnormalities were found. An echocardiogram performed at age 3 years 10 months was limited due to subject's hyperactivity and agitation.

Subject 2578 was diagnosed at age 18 months by chromosome analysis and FISH that was performed because of developmental delay, hypotonia, and failure to thrive. An echocardiogram at 4 years 4 months revealed no significant abnormalities. Two consecutive ECGs revealed premature atrial contractions that did not require medical intervention.

Subject 2695 was diagnosed at age 6 months by chromosome analysis and FISH that was performed because of hypotonia, failure to thrive, developmental delay, and congenital cardiovascular disease. Echocardiogram performed before diagnosis revealed a large (10 mm) ASD with left-to-right shunting. Follow-up echocardiogram at age 16 months revealed a smaller defect (by parental report). Echocardiogram performed at our institution, at age of 4 years 1 month revealed a small secundum ASD with left-to-right shunting. In addition, there was aortic involvement including dilation of the aortic annulus (1.69 cm; *Z* score: 3.14), the aortic root (1.96 cm; *Z* score: 2.98), the sinotubular junction (1.62 cm; *Z* score: 2.73), and the ascending aorta (1.79 cm; *Z* score: 3.7). A small echodensity of unknown etiology or clinical significance was noted at the tip of the mitral valve leaflet, without resultant stenosis or insufficiency.

Subject 2745 was diagnosed at age 2 years 9 months by array comparative genomic hybridization that was performed because of developmental delay and failure to thrive. An echocardiogram performed by the age of 3 years and 9 months revealed low mitral chordal attachments on the interventricular septum without evidence of obstruction. Trivial aortic insufficiency was also noted. The ECG revealed sinus arrhythmia with premature ventricular complexes and fusion complexes.

Subject 2998 was diagnosed at age 2 years 7 months by array comparative genomic hybridization that was performed because of hypotonia, failure to thrive, and developmental delay. At the age of 3 years 10 months, an echocardiogram revealed a PFO with left-to-right shunting. In addition, the aortic root was mildly dilated with a diameter of 1.46 cm (*Z* score: 3.5).

DISCUSSION

To our knowledge, this is the largest reported study to assess cardiovascular involvement in patients with duplication 17p11.2 syndrome. We identified cardiovascular abnormalities in 10 of 25 (40%) patients with duplication 17p11.2 syndrome. This ratio is higher than in the general population, even though ASD (0.66%),[14] VSD (0.4%),[15] and PFO (10–20%)[14] are relatively common CHDs. Nine of our 10 subjects had a structural abnormality; one had only an ECG abnormality. The most frequent abnormality was dilation of the aortic root with varying degrees of severity. Hypoplastic left heart was reported in two duplication 17p11.2 syndrome patients,[6,8] one of whom was evaluated at our institution after cardiac transplantation and was not included in this report because we did not perform his cardiac evaluation.[6]

Interestingly, only 6 of the 16 subjects (37.5%) with common duplications had a cardiovascular abnormality, although they all had the same 3.7 Mb genomic duplication (**Figure 2**). On the other hand, the individual with the largest duplication (2711) had a normal cardiac evaluation. These findings demonstrate incomplete penetrance of CHDs in patients with duplication 17p11.2 syndrome. Incomplete penetrance is observed for other phenotypic aspects of SMS deletion 17p11.2 syndrome[16,17] and other genomic disorders.[18] Intriguingly, CHD is observed in 57% (4/7) of all nonrecurrent duplication subjects and 66.7% (4/6) of the patients with nonrecurrent duplications larger than 3.7 Mb, whereas a lower observation ratio of 37.5% is observed in patients with the 3.7 Mb common duplication. This correlation indicates that there are potentially multiple genes or genetic factors in 17p11.2 that contribute to the cardiovascular phenotype in duplication 17p11.2 syndrome and that some of them may map outside of the 3.7 Mb common duplication interval.

We recognize that ASD, VSD, and PFO are relatively common congenital heart lesions. However, our findings of aortopathy are interesting and may be suggestive of connective tissue disease involvement. This could have clinical implications for patients with aortic and/or mitral valve disease, such as the one patient we identified with an abnormal mitral valve and prolapse of the anterior leaflet. Furthermore, aortic involvement was not confined to the root, suggesting that a more diffuse vasculopathy should be considered in these patients. This would have important diagnostic implications, as a more advanced imaging technique such as computed tomography angiography or magnetic resonance angiography may be indicated for comprehensive aortic assessment. In addition, evidence of aortopathy by noninvasive imaging analysis may necessitate appropriate medical therapy, and if severe dilation of the aorta was found (as in 2211), surgical intervention may be discussed secondary to the risk of possible dissection. Given the small number of patients in our cohort and limited clinical follow-up, the exact implications of aortic involvement, and medical and/or surgical interventions cannot be determined. Our study is meant to characterize the spectrum of disease, which includes vascular involvement. Because these clinical delineation studies represent the initial characterizations of a relatively newly defined condition, and our study is not longitudinal in nature, no clear clinical management inferences can be made regarding the potential severity of this finding. However, given the findings of aortopathy in multiple patients, future longitudinal studies are warranted.

Our study provides important insight into the long-term management of patients with duplication 17p11.2 syndrome. First, given the potential need for medical and surgical intervention, patients with duplication 17p11.2 syndrome should be referred to a qualified cardiovascular specialist. Given our findings of structural heart disease, a baseline echocardiogram and ECG should be obtained at the time of diagnosis. One subject had isolated premature atrial complexes with no evidence of structural heart disease. The authors recognize that the importance of these ECG findings is unknown, given the lack of follow-up and ambulatory monitoring. Findings of premature atrial complexes on ECG are common in the general healthy population, but the significance of these irregular beats in the duplication 17p11.2 population is unclear. However, in light of the important clinical manifestations of aortopathy documented herein, appropriate serial imaging studies are necessary to delineate the vascular structures. Because transthoracic echocardiography provides limited visualization of the proximal aorta, more advanced imaging techniques such as computed tomography angiography or

magnetic resonance angiography may be needed to further define the thoracic aorta, as well as the abdominal aorta and primary branch vessels.

There are limitations to our study. The patient population was small, and not all patients had follow-up echocardiograms to assess the progression of aortic or valvular disease. Limited data were available on the clinical course, including symptoms and medical therapies. Because no ambulatory electrocardiographic monitoring was performed in these patients, the occurrence of arrhythmia may have been underestimated.

In conclusion, duplication 17p11.2 syndrome is associated with structural heart disease, aortopathy, and electrocardiographic abnormalities. Patients should have thorough cardiac evaluation at diagnosis and should be monitored over time for the development of cardiovascular involvement. In addition, referral to a cardiologist for further management is indicated in patients with cardiovascular disease. Studies of the progression of cardiovascular disease in these patients may lead to the development of guidelines for patient care.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

J.R.L. is a consultant for Athena Diagnostics and Ion Torrent Systems, holds stock ownership of 23andMe, and is a coinventor on multiple United States and European patents for DNA diagnostics. P.L., W.G., J.R.L., and L.P. are currently based in the Department of Molecular and Human Genetics at Baylor College of Medicine (BCM), which derives revenue from molecular genetics testing provided by the Medical Genetics Laboratories; MGL, https://www.bcm.edu/geneticlabs. All other authors declare no conflict of interest.

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