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CASE REPORT

Transposition of the great arteries - a phenotype associated with 16p11.2 duplications?

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Author contributions: Lauridsen MH conducted the primary research, selected the patients, obtained informed consent from the parents and children, retrieved the blood samples, and communicated the genetic results to the families; Vestergaard EM performed and interpreted the chromosomal microarray analyses; Karunanithi Z collected the patient information from medical records; Karunanithi Z, Vestergaard EM and Lauridsen MH collectively summarized the data and wrote the manuscript.

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Abstract

Genetic analyses of patients with transposition of the great arteries have identified rare copy number variations, suggesting that they may be significant to the aetiology of the disease. This paper reports the identification of a 16p11.2 microduplication, a variation that has yet to be reported in association with transposition of the great arteries. The 16p11.2 microduplication is associated with autism spectrum disorder and developmental delay, but with highly variable phenotypic effects. Autism and attention deficit disorders are observed more frequently in children with congenital heart disease than in the general population. Neonatal surgery is proposed as a risk factor, but as yet unidentified genetic abnormalities should also be taken into account. Thus, congenital heart abnormalities may constitute a part of the phenotypic spectrum associated with duplications at 16p11.2. We suggest chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

Key words: Transposition of the great arteries; Copy number variation; Genetics; 16p11.2; Microduplication

Core tip: Rare copy number variations may be of significance to the aetiology of transposition of the great arteries. This paper reports, for the first time, the finding of a 16p11.2 microduplication in a patient with transposition of the great arteries. Recognizing a possible genetic association to transposition of the great arteries will spur investigations into associated phenotypic effects such as developmental delays, thus allowing for earlier identification and treatment. We recommend that chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

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INTRODUCTION

Structural gene mutations are emerging as important causes of congenital heart diseases[1]. Transposition of the great arteries is a rare, life-threatening form of congenital heart disease. In contrast to some congenital heart defects, such as atrioventricular septal defects and tetralogy of Fallot, simple transposition of the great arteries is rarely associated with syndromes[2].

Although the aetiology of the disease of is currently unknown, rare copy number variations have recently been identified in patients with transposition of the great arteries[1,3-5] (Table 1). To investigate this further, we screened 13 patients with transposition of the great arteries for copy number variations using high-resolution chromosomal microarray analyses. Approximately half of the screened patients had additional congenital heart diseases.

CASE REPORT

Here, we present the case of a young patient with a genetic mutation that has yet to be reported in association with transposition of the great arteries.

Blood samples were collected from patients and their parents during planned visits. Informed consent to perform chromosomal microarray was obtained. Chromosomal microarray (Agilent Technologies Inc., Santa Clara, CA, United States; 180K CGH for nine patients or 400K CGN + SNP for four patients) was performed on DNA extracted from blood leucocytes as per the manufacturer's protocol.

In one patient, the chromosomal microarray revealed a 0.5 Mb duplication at chromosome 16p11.2 {arr(hg19) 16p11.2 [(29664529-30198600)] × 3 mat} covering the region involved in chromosome 16p11.2 duplication syndrome (OMIM 614671). This microduplication was subsequently detected in the patient's 35-year-old Caucasian mother, who was phenotypically unaffected. The mother was without any cardiac symptoms or murmurs and was not interested in further examinations of her heart.

The patient was born at gestational age 40 wk, weighing 3.06 kg and measuring 50 cm in length. The patient's Apgar score was 9 at one minute and 10 at five minutes. In addition to transposition of the great arteries, a pulmonary valve stenosis and ventricular and atrial septal defects were present. The patient had an arterial switch operation at birth and the Nikaidoh procedure at 7 years of age. Postoperatively, the patient achieved a relatively high level of activity and had no cardiac or respiratory discomfort. At 8 years of age, the patient was diagnosed with attention deficit hyperactive disorder. The patient was followed until the age of 9.5 years.

The 16p11.2 microduplication is associated with autism spectrum disorder and developmental delay, but with highly variable phenotypic effects. This duplication does not always result in severe impairment and may be inherited from a parent with minimal or no clinical features[6]. The 16p11.2 microduplication has not previously been associated with transposition of the great arteries. In the Decipher database, two cases of persistent arterial duct and one case of ventricular septal defect were seen among all patients with a 16p11.2 microduplication[7].

DISCUSSION

Transposition of the great arteries is one of the more severe congenital cardiac defects, but only few studies have investigated the possible aetiology of this defect[1,2]. Two clinical reports have documented a variety of genetic variations associated with transposition of the great arteries[4,5]. On a review of the literature, Unolt *et al*[3] identified frequent syndromes, such as Turner and Noonan, that were rarely associated with transposition of the great arteries; however, a sporadic association with several other genetic variations is possible (Table 1). Costain *et al*[2] studied a cohort of patients with transposition of the great arteries (n = 101) and identified 11 different rare copy number variations, none of which were found in the control group (n = 10528)[2]. Osoegawa *et al*[8] searched for candidate gene loci and sex chromosome aneuploidy among patients with conotruncal cardiac anomalies, of which 194 patients had transposition of the great arteries. They identified a 22q11.22 microdeletion in one patient, an 8p23.2 micro duplication in another patient, and sex chromosome abnormalities (47XYY and

Table 1 Known genetic associations with transposition of the great arteries

		Cytoband	Ref.
Non-syndromic	ZIC3	Xq26.3	Bamford *et al*[12]
	Nodal	10q22.1	Nomura *et al*[13]
	CFC1	2q21.1	Bamford *et al*[12]
	Smad2	18q21.1	Nomura *et al*[13]
		1p31.1	Costain *et al*[2]
		3q25.33-q25.32	Costain *et al*[2]
		4q28.3-4q28.2	Costain *et al*[2]
		7q21.11	Costain *et al*[2]
		8p22	Costain *et al*[2]
		12q24.33	Costain *et al*[2]
		13q13.1-13q13.2	Costain *et al*[2]
		16p12.3-16p13.11	Costain *et al*[2]
		16p12.2	Costain *et al*[2]
		Xp22.12	Costain *et al*[2]
		16p11.2	Current paper
Syndromic	CHARGE		Unolt *et al*[3]
	Deletion 11q		Jacobsen *et al*[14]
	Deletion 18p		Digilio *et al*[15]
	DiGeorge/deletion 22q11		Van Mierop *et al*[16]
	Heterotaxy (right isomerism)		Marino *et al*[17]
	Marfan syndrome		Unolt *et al*[3]
	Noonan syndrome		Unolt *et al*[3]
	Trisomy 18		Unolt *et al*[3]
	Trisomy 8		Unolt *et al*[3]
	Tuberous sclerosis		Jiang *et al*[18]
	Turner syndrome		Unolt *et al*[3]
	VACTERL		Unolt *et al*[3]
	Williams syndrome		Unolt *et al*[3]

47XXY) in two patients with transposition of the great arteries.

We are the first to document the presence of a 16p 11.2 microduplication in a patient with transposition of the great arteries. Deletions and duplications of the recurrent 600 base pair region on chromosome 16p11.2 are frequent findings in patients with autism spectrum disorders and the concomitant finding of congenital heart disease may be an incidental finding not caused by the microduplication[9]. It is, however, well known that congenital abnormalities can occur in the context of recurrent duplications associated with susceptibility to intellectual disability.

Autism and attention deficit disorders are observed more frequently in children with congenital heart disease than in the general population[10]. Neonatal surgery is proposed as a risk factor[11], but as yet unidentified genetic abnormalities should also be taken into account.

Thus, congenital heart abnormalities may constitute a part of the phenotypic spectrum associated with duplications at 16p11.2. We suggest chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

In conclusion, rare copy number variations may be of significance to the aetiology of transposition of the great arteries. This paper reports, for the first time, the finding of a 16p11.2 microduplication in a patient with transposition of the great arteries. Recognizing a possible genetic association to transposition of the great arteries will spur investigations into associated phenotypic effects such as developmental delays, thus allowing for earlier identification and treatment. We therefore recommend that chromosomal microarray be considered part of the diagnostic work-up in patients with transposition of the great arteries.

ARTICLE HIGHLIGHTS

Case characteristics

Young patient diagnosed with transposition of the great arteries and a 16p11.2 microduplication.

Clinical diagnosis

The child deteriorated after birth, when the arterial duct closed. Echocardiography revealed transposition of the great arteries, pulmonary valve stenosis and ventricular and atrial septal defects. Around school age the child was diagnosed with attention deficit disorder.

Differential diagnosis

Regarding deterioration after birth, differential diagnoses are: Neonatal sepsis, metabolic disease, and other cyanotic heart defects. Neonatal surgery is a risk factor for attention deficit disorder.

Laboratory diagnosis

Chromosomal microarray revealed the 0.5 Mb chromosomal duplication at chromosome 16p11.2.

Imaging diagnosis

The congenital heart diseases were diagnosed using echocardiography.

Treatment
The transposition of the great arteries was treated with an arterial switch operation at birth and the Nikaidoh procedure at the age of 7 years.

Related reports
Transposition of the great arteries is rarely associated with genetic variations. Transposition of the great arteries have once before been associated with a 16p13.11 duplication (Ref. [19]). The authors are the first to report the 16p11.2 microduplication in association with transposition of the great arteries.

Term explanation
Copy number variation: A structural variation in the DNA that results in the cell having an abnormal number of copies of one or more sections of the DNA.

Experiences and lessons
The case document that copy number variations may be of significance in transposition of the great arteries and chromosomal microarray should be considered part of the diagnostic work-up in these patients.

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