



HAL
open science

Familial Recurrence Patterns in Congenitally Corrected Transposition of the Great Arteries: An International Study

Marine Tortigue, Lynne E. Nield, Matilde Karakachoff, Christopher J. Mcleod, Emre Belli, Sonya V. Babu-Narayan, Solene Prigent, Angele Boet, Miriam Conway, Robert W. Elder, et al.

► **To cite this version:**

Marine Tortigue, Lynne E. Nield, Matilde Karakachoff, Christopher J. Mcleod, Emre Belli, et al.. Familial Recurrence Patterns in Congenitally Corrected Transposition of the Great Arteries: An International Study. *Circulation: Genomic and Precision Medicine*, 2022, 15 (3), pp.e003464. <10.1161/CIRCGEN.121.003464>. <hal-03780375>

HAL Id: hal-03780375

<https://amu.hal.science/hal-03780375v1>

Submitted on 10 Nov 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Familial Recurrence Patterns in Congenitally Corrected Transposition of the Great Arteries: An International Study

Marine Tortigue, MD, Lynne E. Nield, MD, Matilde Karakachoff, PhD, Christopher J. McLeod, MD, PhD, Emre Belli, MD, Sonya V. Babu-Narayan, BSc, MBBS, PhD, Solène Prigent, MD, Angèle Boet, MD, PhD, Miriam Conway, MD, Robert W. Elder, MD, Magalie Ladouceur, MD, PhD, Paul Khairy, MD, PhD, Ewa Kowalik, MD, PhD, David M. Kalfa, MD, PhD, David J. Barron, MD, Shafi Mussa, MD, Anita Hiippala, MD, Joel Temple, MD, Sylvia Abadir, MD, Laurianne Le Gloan, MD, Matthias Lachaud, MD, Shubhayan Sanatani, MD, Jean-Benoit Thambo, MD, PhD, Céline Grunenwald Gronier, MD, Pascal Amedro, MD, PhD, Guy Vaksman, MD, Anne Charbonneau, MD, Linda Koutbi, MD, Caroline Ovaert, MD, PhD, Ali Houeijeh, MD, Nicolas Combes, MD, Philippe Maury, MD, Guillaume Duthoit, MD, Bérengère Hiel, MD, Christopher C. Erickson, MD, Caroline Bonnet, MD, George F. Van Hare, MD, Christian Dina, PhD, Clément Karsenty, MD, Emmanuelle Fournier, MD, Mathieu Le Bloa, MD, Robert H. Pass, MD, Leonardo Liberman, MD, Juha-Matti Happonen, MD, James C. Perry, MD, Bénédicte Romefort, MD, Nadir Benbrik, MD, Quentin Hauet, MD, Alain Fraisse, MD, PhD, Michael A. Gatzoulis, MD, PhD, Dominic J. Abrams, MD, Anne M. Dubin, MD, Siew Yen Ho, MD, PhD, Richard Redon, PhD, Emile A. Bacha, MD, Jean-Jacques Schott, PhD, and Alban-Elouen Baruteau, MD, PhD

BACKGROUND: Congenitally corrected transposition of the great arteries (ccTGA) is a rare disease of unknown cause. We aimed to better understand familial recurrence patterns.

METHODS: An international, multicentre, retrospective cohort study was conducted in 29 tertiary hospitals in 6 countries between 1990 and 2018, entailing investigation of 1043 unrelated ccTGA probands.

RESULTS: Laterality defects and atrioventricular block at diagnosis were observed in 29.9% and 9.3%, respectively. ccTGA was associated with primary ciliary dyskinesia in 11 patients. Parental consanguinity was noted in 3.4% cases. A congenital heart defect was diagnosed in 81 relatives from 69 families, 58% of them being first-degree relatives, including 28 siblings. The most prevalent defects in relatives were dextro-transposition of the great arteries (28.4%), laterality defects (13.6%), and ccTGA (11.1%); 36 new familial clusters were described, including 8 pedigrees with concordant familial aggregation of ccTGA, 19 pedigrees with familial co-segregation of ccTGA and dextro-transposition of the great arteries, and 9 familial co-segregation of ccTGA and laterality defects. In one family co-segregation of ccTGA, dextro-transposition of the great arteries and heterotaxy syndrome in 3 distinct relatives was found. In

another family, twins both displayed ccTGA and primary ciliary dyskinesia.

CONCLUSIONS: ccTGA is not always a sporadic congenital heart defect. Familial clusters as well as evidence of an association between ccTGA, dextro-transposition of the great arteries, laterality defects and in some cases primary ciliary dyskinesia, strongly suggest a common pathogenetic pathway involving laterality genes in the pathophysiology of ccTGA.

Key Words: aorta ■ arteries ■ heterotaxy syndrome ■ mitral valve ■ rare disease

Nonstandard Abbreviations and Acronyms

ccTGA	congenitally corrected transposition of the great arteries
CHD	congenital heart disease
d-TGA	dextro-transposition of the great arteries
PCD	primary ciliary dyskinesia
VSD	ventricular septal defect

Congenitally corrected transposition of the great arteries (ccTGA) is a rare and complex heart defect prevalent in nearly 0.05% of patients with congenital heart disease (CHD), with an estimated incidence of 1 per 33 000 live births.¹ It is characterized by the combination of discordant atrioventricular and ventriculoarterial connections.² The morphological right atrium is connected to the morphological left ventricle across the mitral valve, with the left ventricle then connected to the pulmonary trunk; the morphological left atrium is connected to the morphological right ventricle across the tricuspid valve, with the morphological right ventricle connected to the aorta. In usual atrial arrangement, the morphological left ventricle is positioned to the right and the aorta, arising from the right ventricle, is more commonly left-sided ([S,L,L] configuration; S, situs solitus of the atria; L, L-loop of the ventricles; L, levoposition of the aorta). In mirror-image atrial arrangement, the morphological left ventricle is left-sided, and the aorta is usually positioned to the right ([I,D,D] configuration; I, situs inversus of the atria; D, D-loop of the ventricles; D, dextroposition of the aorta). Most patients have at least one associated cardiac malformation, with the most common being ventricular septal defect (VSD), subvalvar and valvar pulmonary stenosis and Ebstein-like abnormalities of the systemic tricuspid atrioventricular valve with accessory atrioventricular pathways.^{2,3} Atrioventricular block is frequent in the setting of a displaced atrioventricular node with an elongated and fragile course of the proximal, infra-nodal conduction system.⁴

On the basis of exceptional forms of familial recurrence of CHD in subjects with ccTGA, a genetic background has been evoked,⁵ along with an association with environmental factors such as air pollutants.⁶ Nevertheless, the cause of ccTGA remains unknown.^{2,3}

This international, multicentre retrospective study examined the familial recurrence of CHD and laterality defects in a large cohort of ccTGA probands.

METHODS

In accordance with the Transparency and Openness Promotion Guidelines, the data that

support the findings of this study are available from the corresponding author on reasonable request. Institutional review board approval was obtained from all participating institutions with waiver of informed consent. The research study complies with the Declaration of Helsinki.

RESULTS

A total of 1131 patients fulfilled the inclusion criteria. However, 88 (7.8%) patients were excluded from the analysis due to unknown family history, yielding a study population of 1043 patients.

Characteristics of ccTGA Probands

A cohort of 1043 unrelated ccTGA probands was compiled, with a male/female sex ratio of 0.9. Median age at diagnosis was 20 years (interquartile range, 31). Isolated ccTGA was diagnosed in 284 (27.2%) patients. Cardiac phenotype and type of atrial situs of the 1043 ccTGA probands are presented in [Table 1](#). At the time of diagnosis, 97/1043 (9.3%) ccTGA probands had impaired cardiac conduction, consisting in permanent first-degree atrioventricular block in 53, second-degree atrioventricular block in 7 and complete atrioventricular block in 37. A laterality defect was observed in 312 (29.9%) ccTGA probands, with dextrocardia in 207 (19.8%) patients, mesocardia in 60 (5.7%), mirror-image atrial arrangement in 94 (9.0%), heterotaxy syndrome in 95 (9.1%; right atrial isomerism in 80 [7.7%], left atrial isomerism in 15 [1.4%]).

Table 1. Main Associated Cardiac Defects in Probands With Congenitally Corrected Transposition of the Great Arteries (N=1043) ([Table view](#))

Associated cardiac defects in ccTGA probands	% of the whole cohort of ccTGA patients, N=1043	Usual atrial arrangement (situs solitus), N=854	Mirror-image atrial arrangement (situs inversus), N=94	Heterotaxy syndrome (situs ambiguus), N=95
Isolated ccTGA, n (%)	284 (27.2)	279 (32.7)	5 (5.3)	0 (0.0)
VSD without PS, n (%)	254 (24.3)	233 (27.3)	9 (9.6)	12 (12.6)
PS without VSD, n (%)	33 (3.2)	26 (3.0)	2 (2.1)	5 (5.3)
VSD and PS, n (%)	334 (32.0)	245 (28.7)	18 (19.1)	71 (74.7)
Atrioventricular block of any type*, n (%)	97 (9.3)	95 (11.1)	0 (0.0)	2 (2.1)
Secundum atrial septal defect, n (%)	238 (22.8)	184 (21.5)	14 (14.9)	40 (42.1)
Patent ductus arteriosus, n (%)	109 (10.4)	92 (10.8)	2 (2.1)	15 (15.8)
Ebstein-like's anomaly of the tricuspid valve, n (%)	95 (9.1)	89 (10.4)	3 (3.2)	3 (3.2)
Coarctation of the aorta, n (%)	56 (5.4)	52 (6.1)	2 (2.1)	2 (2.1)

ccTGA indicates congenitally corrected transposition of the great arteries; PS, pulmonary stenosis; and VSD, ventricular septal defect.

* Transient catheterization-induced and postoperative atrioventricular blocks are not included.

Genetic analyses had been performed in 30 (2.9%) ccTGA probands but no relative from familial cases. Thirty patients had a normal karyotype. Of the 23 patients who were tested for

22q11.2 deletion syndrome, diagnosis was genetically confirmed in a 8-year old boy with a sporadic form of ccTGA (S,L,L), VSD, pulmonary stenosis. A 30 genetic heart disease-susceptibility genes panel screening was negative in a proband with dextrocardia, ccTGA (I,D,D), ASD, VSD, pulmonary stenosis, features of right atrial isomerism and family history of dextro-transposition of the great arteries (d-TGA) in his sibling.

Co-occurrence of ccTGA and PCD

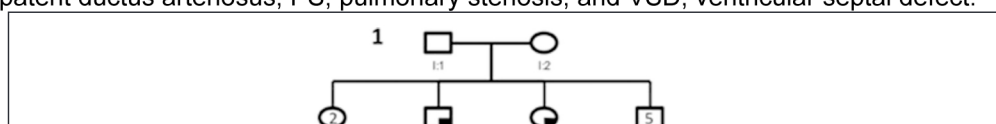
Primary ciliary dyskinesia (PCD) was diagnosed in 11/739 (1.5%) ccTGA patients, 2 of whom displayed features of right atrial isomerism. Two patients with ccTGA and PCD had a sibling diagnosed with ccTGA as well (pedigree_5 and pedigree_6 in Figure 1), including a set of identical twins displaying both ccTGA and PCD (Table 2). In these 11 patients, PCD was clinically diagnosed and documented using nasal nitric oxide measurement. PCD diagnosis was ascertained by ciliary light microscopy in 2 patients, but all patients declined genetic screening. None of these 11 patients with PCD and ccTGA had parental consanguinity.

Table 2. Characteristics of Patients With Co-Occurrence of Congenitally Corrected Transposition of the Great Arteries and Primary Ciliary Dyskinesia (N=11) (Table view)

	Heart position	Atrial arrangement	Heterotaxy syndrome?	Cardiac phenotype	AV conduction	Familial cluster
Patient_1	Levocardia	Usual	No	ccTGA (S,L,L), PS, secundum ASD	Normal	Pedigree_5
Patient_2	Dextrocardia	Usual	No	ccTGA (S,L,L), secundum ASD	Normal	Pedigree_5
Patient_3	Dextrocardia	Usual	No	ccTGA (S,L,L), secundum ASD	Native, first-degree AVB	Pedigree_6
Patient_4	Levocardia	Usual	Right atrial isomerism	ccTGA (S,L,L), VSD, PS, secundum ASD, PDA	Postoperative complete AVB	No
Patient_5	Levocardia	Usual	No	ccTGA (S,L,L)	Native, complete AVB	No
Patient_6	Dextrocardia	Usual	No	ccTGA (S,L,L), VSD	Normal	No
Patient_7	Levocardia	Usual	No	ccTGA (S,L,L), VSD, secundum ASD	Normal	No
Patient_8	Dextrocardia	Usual	No	ccTGA (S,L,L), VSD, PS	Postoperative complete AVB	No
Patient_9	Levocardia	Usual	No	ccTGA (S,L,L)	Normal	No
Patient_10	Levocardia	Usual	No	ccTGA (S,L,L), VSD, PS	Native, complete AVB	No
Patient_11	Dextrocardia	Mirror image	Right atrial isomerism	ccTGA (I,D,D), VSD, PS	Native, first-degree AVB	No

Pedigree_5 denotes patient_1 and patient_2 are twins; both patients display ccTGA and PCD; and pedigree_6, patient_3 had a brother with isolated ccTGA (see Figure 1).

ASD indicates atrial septal defect; AVB, atrioventricular block; ccTGA, congenitally corrected transposition of the great arteries; PDA, patent ductus arteriosus; PS, pulmonary stenosis; and VSD, ventricular septal defect.



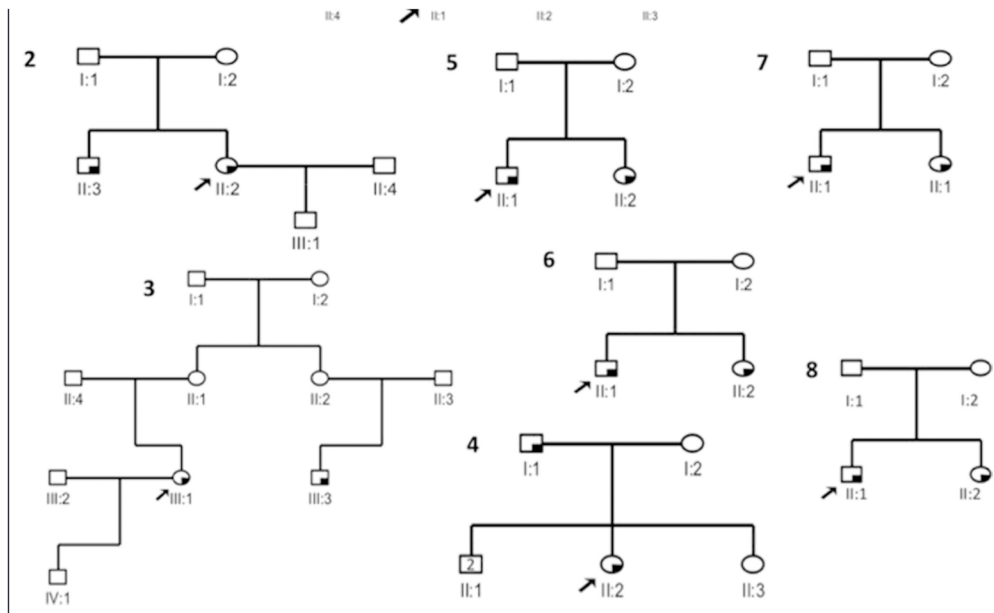


Figure 1. Concordant familial aggregation of congenitally corrected transposition of the great arteries (ccTGA) cases. Concordant familial aggregation of ccTGA was identified in 8 families. All ccTGA were in usual atrial arrangement.

Congenital Heart Defects in Relatives

One or more relatives with CHD were found in 69 (6.6%) families, with a median of 1 (range: 1–3) affected relatives per family (Table 3). Twelve families had at least 3 affected relatives. Of the 81 relatives with CHD, 47 (58.0%) were first-degree relatives including 28 siblings (6 twin-sibs including 2 identical twins). The most prevalent CHD phenotypes diagnosed in relatives were d-TGA (28.4%), laterality disorders (13.6%; dextrocardia, atrial situs inversus and heterotaxy syndrome diagnosed in 8, 1 and 5 relatives, respectively), ccTGA (11.1%), isolated VSD (11.1%), and complete atrioventricular septal defect (8.6%; Table 4). D-TGA and ccTGA were more prevalent in siblings of ccTGA probands than in the general population (Table 5).⁷ Two probands with ccTGA had an affected identical twin sibling presenting with ccTGA. No relative was diagnosed with PCD. Although data was missing in 255 (24.5%) patients, parental consanguinity was identified in 27/788 (3.4%) ccTGA patients. Empirical recurrence risk for ccTGA, dTGA, and any type of CHD is presented in Table 4.

Table 3. Characteristics of Familial Cases of ccTGA (N=69) (Table view)

	Familial clusters*	Number of relatives with CHD	Number of relatives who underwent echocardiographic screening in the family	CHD (relationship) in affected relatives
Family_1	Pedigree_1	1	10	ccTGA (sibling)
Family_2	Pedigree_2	1	5	ccTGA (sibling)
Family_3	Pedigree_3	1	9	ccTGA (cousin)
Patient_4	Pedigree_4	1	5	ccTGA (father)
Patient_5	Pedigree_5	1	3	ccTGA (twin sib)
Patient_6	Pedigree_6	1	3	ccTGA (sibling)
Family_7	Pedigree_7	1	3	ccTGA (sibling)
Family_8	Pedigree_8	1	3	ccTGA (sibling)
Family_9	Pedigree_9	1	6	d-TGA (paternal uncle)
Patient_10	Pedigree_10	1	8	d-TGA (child)
Patient_11	Pedigree_11	1	3	d-TGA (sibling)

	Familial clusters*	Number of relatives with CHD	Number of relatives who underwent echocardiographic screening in the family	CHD (relationship) in affected relatives
Patient 12	Pedigree 12	1	2	d-TGA (father)
Family 13	Pedigree 13	1	7	d-TGA (cousin)
Family 14	Pedigree 14	1	6	d-TGA (maternal aunt)
Family_15	Pedigree_15	2	7	d-TGA (father), d-TGA (cousin)
Patient_16	Pedigree_16	2	9	d-TGA (sibling), d-TGA (sibling)
Patient 17	Pedigree 17	1	3	d-TGA (sibling)
Patient 18	Pedigree 18	1	9	d-TGA (cousin)
Patient 19	Pedigree 19	1	6	d-TGA (paternal uncle)
Patient 20	Pedigree 20	1	9	d-TGA (cousin)
Patient 21	Pedigree 21	1	2	d-TGA (father)
Patient_22	Pedigree_22	2	10	d-TGA (father), d-TGA (cousin)
Family 23	Pedigree 23	1	7	d-TGA (cousin)
Family 24	Pedigree 24	1	4	d-TGA (child)
Family 25	Pedigree 25	1	9	d-TGA (cousin)
Patient 26	Pedigree 26	1	3	d-TGA (sibling)
Patient 27	Pedigree 27	1	3	d-TGA (sibling)
Patient_28	Pedigree_28	3	10	Dextrocardia (sibling), dextrocardia (cousin), dextrocardia (cousin)
Patient_29	Pedigree_29	1	4	HS, polysplenia, HLHS (sibling)
Patient_30	Pedigree_30	3	12	ccTGA (cousin), d-TGA (cousin), HS (cousin)
Family_31	Pedigree_31	2	7	HS, single ventricle, dextrocardia (uncle) HS, single ventricle, dextrocardia (uncle)
Family_32	Pedigree_32	2	4	Dextrocardia (father), dextrocardia (paternal grandfather)
Family_33	Pedigree_33	1	8	HS, univentricular heart (cousin)
Patient_34	Pedigree_34	1	3	HS, common atrium, VSD (sibling)
Patient 35	Pedigree 35	1	4	Dextrocardia (child)
Patient_36	Pedigree_36	2	5	Situs inversus (sibling), VSD (paternal grandfather)
Family 37	n/a	1	6	Complete AVSD (cousin)
Family 38	n/a	1	4	Tetralogy of Fallot (cousin)
Family 39	n/a	1	5	SECUNDUM ASD (sibling)
Patient 40	n/a	1	5	complete AVSD (sibling)
Patient 41	n/a	1	6	HLHS (sibling)
Patient 42	n/a	1	3	CoA (sibling)
Patient 43	n/a	1	5	PA-IVS (cousin)
Patient 44	n/a	1	6	VSD (cousin)

	Familial clusters*	Number of relatives with CHD	Number of relatives who underwent echocardiographic screening in the family	CHD (relationship) in affected relatives
Patient_45	n/a	1	5	Mitral valve prolapse (father)
Patient_46	n/a	1	6	CoA, secundum ASD (cousin)
Family_47	n/a	1	5	HLHS (sibling)
Family_48	n/a	1	3	pulmonary valve stenosis (child)
Family_49	n/a	1	5	HLHS (cousin)
Patient_50	n/a	1	3	Tetralogy of Fallot (mother)
Patient_51	n/a	1	3	Complete AVSD (sibling)
Patient_52	n/a	1	4	Tetralogy of Fallot (uncle)
Patient_53	n/a	1	7	Complete AVSD (sibling)
Patient_54	n/a	1	3	Complete AVSD (cousin)
Patient_55	n/a	1	3	Complete AVSD (cousin)
Patient_56	n/a	1	3	PDA (child)
Patient_57	n/a	1	3	Ventricular rhabdomyoma (sibling)
Family_58	n/a	1	5	IAA-VSD (mother)
Family_59	n/a	1	4	IAA-VSD (sibling)
Family_60	n/a	1	3	VSD (cousin)
Patient_61	n/a	1	5	Complete AVSD (cousin)
Patient_62	n/a	1	5	VSD (cousin)
Patient_63	n/a	1	3	Mitral valve prolapse (cousin)
Patient_64	n/a	1	5	ALCAPA (sibling)
Patient_65	n/a	1	2	Mitral valve prolapse (mother)
Patient_66	n/a	2	4	Tetralogy of Fallot (maternal aunt)
				Tetralogy of Fallot (cousin)
Patient_67	n/a	2	5	Secundum ASD, VSD (sibling)
				VSD (cousin)
Patient_68	n/a	1	1	VSD (child)
Patient_69	n/a	1	3	DORV (sibling)

*Familial clusters refer to [Figures 1 through 4](#).

ALCAPA indicates anomalous left coronary artery from the pulmonary artery; ASD, atrial septal defect; AVB, atrioventricular block; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected transposition of the great arteries; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; HS, heterotaxy syndrome; IAA, interrupted aortic arch; PA-IVS, pulmonary atresia with intact ventricular septum; PDA, patent ductus arteriosus; PS, pulmonary stenosis; and VSD, ventricular septal defect.

Table 4. Cardiac Phenotype in Relatives (N=81) ([Table view](#))

Congenital heart defects diagnosed in relatives	N (%)	First-degree relatives (N=47)	Second-degree relatives (N=34)
d-TGA	23 (28.4)	12	11

Congenital heart defects diagnosed in relatives	N (%)	First-degree relatives (N=47)	Second-degree relatives (N=34)
Laterality disorders	11 (13.6)*	6	5
Congenitally corrected transposition of the great arteries	9 (11.1)	7	2
Isolated ventricular septal defect	9 (11.1)	4	5
Complete atrioventricular septal defect	7 (8.6)	3	4
Tetralogy of Fallot	4 (4.9)	1	3
Mitral valve prolapse	4 (4.9)	3	1
Hypoplastic left heart syndrome	3 (3.7)	2	1
Interrupted aortic arch, ventricular septal defect	2 (2.5)	2	0
Coarctation of the aorta	2 (2.5)	1	1
Double outlet right ventricle	1 (1.2)	1	0
Pulmonary atresia with intact ventricular septum	1 (1.2)	0	1
Pulmonary valve stenosis	1 (1.2)	1	0
Patent ductus arteriosus	1 (1.2)	1	0
Secundum atrial septal defect	1 (1.2)	1	0
ALCAPA	1 (1.2)	1	0
Ventricular rhabdomyoma	1 (1.2)	1	0

ALCAPA indicates abnormal left coronary artery from pulmonary artery; and dTGA-IVS, dextro transposition of the great arteries with intact ventricular septum.

* Including 5 relatives with heterotaxy syndrome.

Table 5. Recurrence Risk of Congenital Heart Defects in First-Degree Relatives ([Table view](#))

CHD diagnosed in relatives		Any CHD		ccTGA + d-TGA	
		Affected	Recurrence risk %* [95%CI]†	Affected	Recurrence risk %* [95%CI]†
Prevalence in general population (per 1000)		6.12/1000 ⁷		0.1/1000 ⁷	
Siblings‡	N=652	29	4,4 [3–6,3]	13	2 [1,1–3,4]
Parents	N=994	12	1,2 [0,6–2,1]	5	0,5 [0,2–1,2]
Children	N=244	6	2,5 [0,9–5,3]	2	0,8 [0,1–2,9]
First-degree relatives	N=1890	47	2,5 [1,8–3,3]	20	1,1 [0,6-1,6]

Prevalence in general population is expressed per 1000 individuals. CHD indicates congenital heart defect; ccTGA, congenitally corrected transposition of the great arteries; and d-TGA, dextro transposition of the great arteries.

* Recurrence risk is the proportion of probands' affected relatives among all probands' relatives in %.

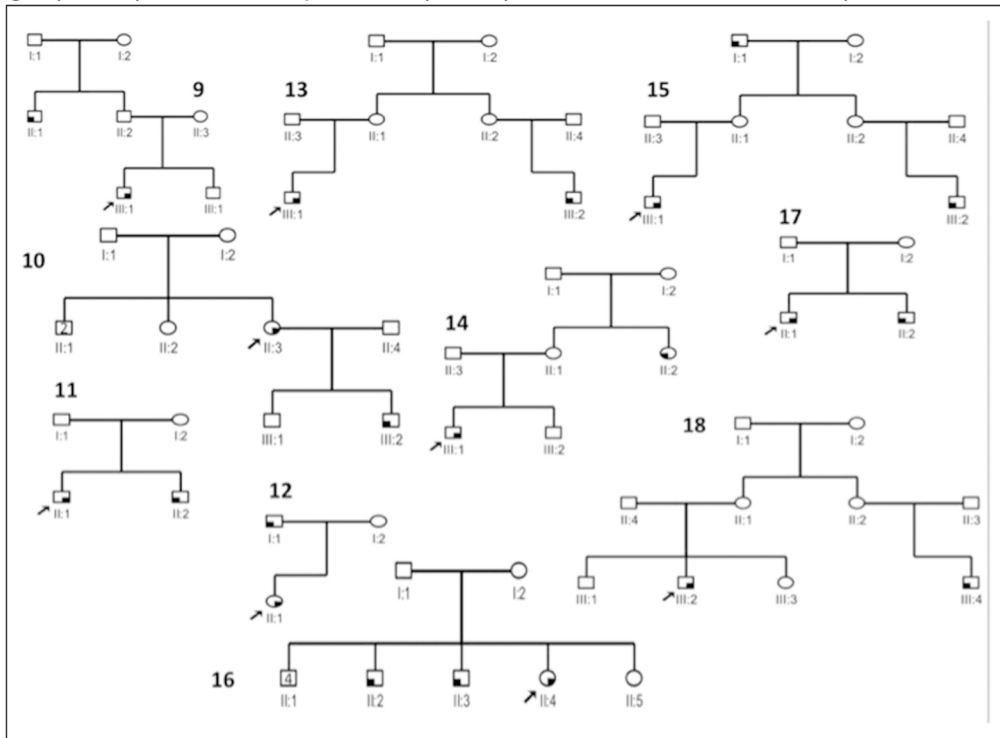
† Exact 95%CI were estimated assuming a binomial distribution.

‡ Twins are included.

Familial Clusters

Concordant familial aggregation of ccTGA was identified in 8 families ([Figure 1](#)) whereas familial aggregation of both ccTGA and dTGA was noted in 19 families ([Figures 2 and 3](#)). We also observed familial aggregation of ccTGA and laterality disorders in 9 families ([Figure 4](#)) including a unique familial pedigree associating ccTGA (the proband and a cousin), dTGA (a cousin), and heterotaxy syndrome (a cousin). Familial clusters were due to another CHD in

29/652 siblings (4.4%), in 12/994 parents (1.2%), and in 6/244 children (2.5%; [Table 5](#)).



Figures 2. Occurrence of dextro-transposition of the great arteries (d-TGA) in relatives of congenitally corrected transposition of the great arteries (ccTGA) probands. Familial occurrence of d-TGA in first- or second-degree relatives of ccTGA probands was found in 19 families.

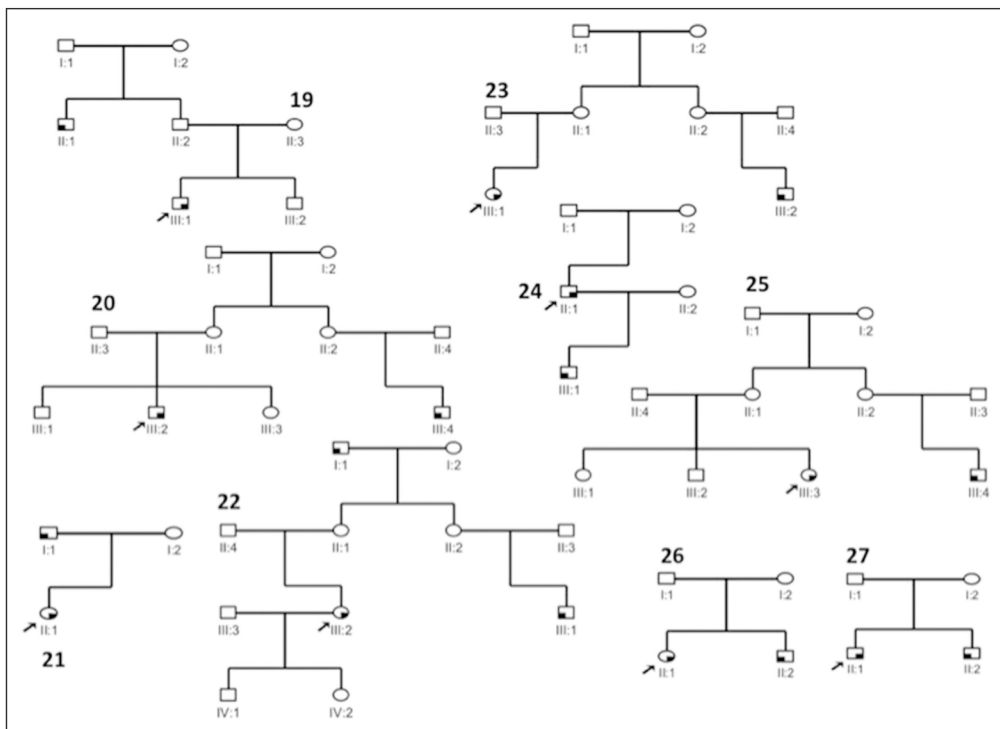
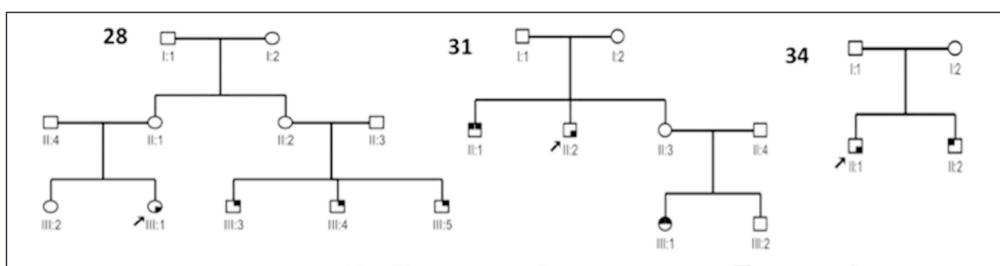


Figure 3. Occurrence of dextro-transposition of the great arteries (d-TGA) in relatives of congenitally corrected transposition of the great arteries (ccTGA) probands. Familial occurrence of d-TGA in first- or second-degree relatives of ccTGA probands was found in 19 families.



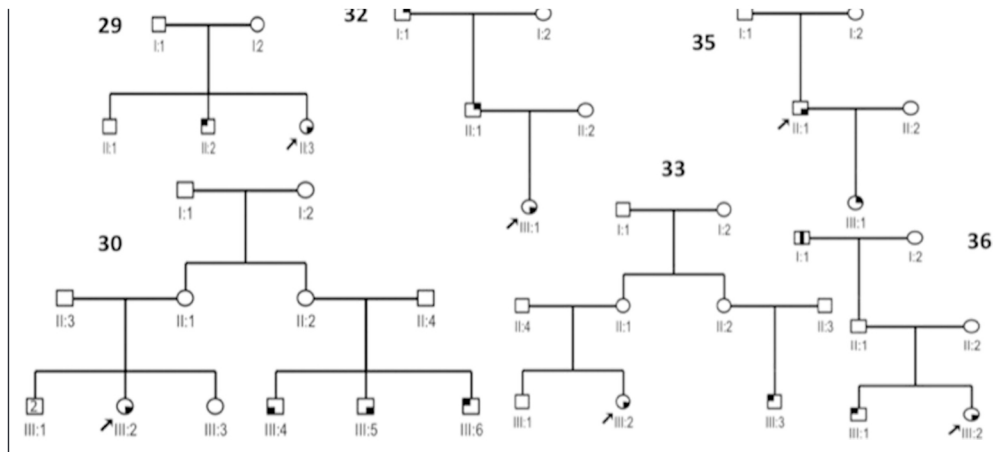


Figure 4. Occurrence of laterality disorders in relatives of congenitally corrected transposition of the great arteries (ccTGA) probands. In our series, 9 ccTGA probands had first- or second-degree relatives displaying laterality disorders, including a unique familial pedigree associating ccTGA (the proband and a cousin), dextro-transposition of the great arteries (d-TGA; a cousin) and heterotaxy syndrome (a cousin).

DISCUSSION

This international study investigates the largest cohort of ccTGA patients reported to date. In 1043 patients with ccTGA, we found familial recurrence of ccTGA, d-TGA, or laterality defects in 8, 19, and 9 cases, respectively, as well as co-occurrence of ccTGA and PCD in 11 patients.

A Pathogenetic Link Between ccTGA, d-TGA, and Laterality Defects

This series details recurrence of ccTGA and co-occurrence with d-TGA in 8 and 19 families, respectively, confirming that ccTGA is not always sporadic. Most probands from these 27 families had isolated ccTGA, with no associated laterality defect. Our 4.4% sibling recurrence risk of any CHD is in keeping with previous reports.^{8,9}

Familial cases of d-TGA are exceptional. Although chromosomal microarray analysis has an added value in the detection of pathogenic chromosomal abnormalities compared with conventional karyotype,¹⁰ especially in the investigation of prenatally diagnosed conotruncal defects,¹¹ this yield is influenced by the type of CHD and by the presence of extracardiac anomalies; previous studies have shown that its clinical value is limited when applied to isolated d-TGA,^{10,11} which strengthens the importance of our report of familial clustering including this phenotype in 19 new families, outside of an identified genetic condition.

Our study is the first report of concordant familial aggregation of ccTGA. Familial aggregation of ccTGA and d-TGA had been exceptionally reported so far, with only 6 family pedigrees published in 2001.^{5,12} Based on these limited data, authors postulated that these 2 distinct entities may share a common genetic background, a hypothesis that has remained controversial.^{13,14} Our study lends credence to this notion by documenting co-occurrence of isolated ccTGA, isolated d-TGA and laterality defects in some families. This evidence suggests the potential for mutations in genes affecting the left-right patterning process to underlie these 2 distinct cardiac phenotypes. It also raises the possibility that at least some isolated apparently sporadic cases of d-TGA should actually be considered to be laterality defects due to abnormal left-right patterning, instead of a conotruncal abnormality due to ectomesenchymal tissue migration.^{15,16} The pathogenetic link between d-TGA and laterality defects is not only

supported by familial forms but also by molecular studies. Some cases of d-TGA have been associated with mutations in laterality genes in mice and humans.^{17–19}

Of our 1043 ccTGA probands, 25.6% exhibited mesocardia/dextrocardia and 18.1% had either mirror-image atrial arrangement or heterotaxy syndrome. This high proportion of laterality defects in our cohort is concordant with a recent report of 58 ccTGA patients, in whom mesocardia/dextrocardia and mirror image atrial arrangement were found in 33% and 12%, respectively.²⁰ The occurrence rates of laterality defects were significantly higher in the setting of ccTGA than d-TGA, suggesting that ccTGA cases may have experienced more severe disruption in left-right patterning pathways during development.²⁰

A Pathogenetic Link Between ccTGA and Ciliary Function

Of the 81 relatives with CHD from our series, 28.4% had d-TGA, 11.1% ccTGA, and 8.6% complete AVSD. Our data are in keeping with growing evidence suggesting that some isolated forms of CHD, especially d-TGA and AVSD, which are commonly found in heterotaxy, may be considered in the pathogenetic field of laterality defects, even in the setting of a usual atrial arrangement pattern.²¹ Abnormal cilia function has also been associated with the occurrence of isolated CHD,^{22,23} including left-sided lesions²⁴; a recent exome-based case-control analysis on 249 TGA patients including 58 with ccTGA reported rare, potentially damaging variants in 19 ciliary genes.²⁰ This supports the role of dysfunctional cilia in the pathogenesis of d-TGA and ccTGA.

Heterotaxy is a rare syndrome with an estimated prevalence at 1/10 000 individuals that is associated with complex and severe CHD in 90% of cases. Atrioventricular discordance and malposition/transposition of the great arteries may be part of the broad cardiac phenotypic spectrum, especially in the context of right atrial isomerism.^{25,26} In a familial form of heterotaxy syndrome linked to a *ZIC3* gene mutation, ccTGA was found with the usual arrangement of the inner organs (*situs solitus*), indicating that such cases of ccTGA may be considered as isolated phenotypic manifestations of heritable heterotaxy syndromes.²⁷ However, the known genes contributing to laterality defects account for only 15% to 20% of cases. They are mainly associated with NODAL/TGF β signaling (*NODAL*, *CFC1*, *ACVR2B*, *LEFTYB*, *GDF1*, *TGFBR2*, *FOXH1*), SHH signaling (*ZIC3*, *LZTFL1*), monocilia function (*NPHP2*, *NPHP3*, *NPHP4*, *PKD2*, *TTC8*), or early cardiac development (*NKX2-5*, *CRELD1*, *MMP21*, *KD1L1*).²⁸ The connection of laterality defects to ciliary function is further reinforced by the observation that \approx 50% of patients with PCD (prevalence: 1/20 000 individuals)²⁶ have mirror-image atrial arrangement and \approx 10% present with heterotaxy.²⁶ Interestingly, PCD was also diagnosed in a small subset of our ccTGA cases. This association is extremely rare, with only 4 cases reported so far, in a 18 year-old man with usual atrial arrangement,²⁹ a 40 year-old man with mirror-image atrial arrangement,³⁰ an 8 year-old girl with mirror-image atrial arrangement and dextrocardia,³¹ and a 17 year-old male with mirror-image atrial arrangement and dextrocardia.³² Herein, we describe 11 new cases of this unique association. Of note, 2 patients from our cohort presented with a previously unreported association of ccTGA, PCD and heterotaxy syndrome with right atrial isomerism, and 2 others had concordant familial aggregation of ccTGA in a sibling, including identical twin sibs displaying both ccTGA and PCD. In the other hand, Kartagener syndrome has been associated with d-TGA in patients with isomerism,¹⁹ and a heterozygous mutation of *DNAH1*, an inner dynein protein attached to the peripheral microtubule doublets in cilia that have been related to Kartagener syndrome, has been described in a *situs solitus*

d-TGA patient.³³ We believe that this altogether supports clinical evidence that ccTGA may be heritable, due to mutations in laterality genes and that cilia genes potentially play a central, mechanistic role in ccTGA pathogenesis.

Moreover, most of our familial forms include multiple affected siblings with unaffected parents, who are not consanguineous, as well as multiple CHD phenotypes within families. This altogether suggests that at least a portion of ccTGA cases have a complex genetic architecture with probably an oligogenic or polygenic inheritance model. Our results are in keeping with a recent exome-based case-control analysis showing that 33% of 249 TGA probands (66 family trios) had >1 candidate gene hit by putatively deleterious variants.¹⁷

Study Limitations

Data were collected over a 29-year period during which clinical practice evolved and considerable progress was made in imaging modalities for diagnosing CHD and laterality defects. Although systematic screening of first-degree relatives is not recommended for nonsyndromic CHD, except for some specific left-sided obstructive heart lesions, some investigators offered relatives to undergo a screening echocardiography. Variability of familial investigations among institutions, as well as absence of genetic testing of relatives in familial forms, are limitations of this work. For example, in some institutions, echocardiographic family screening was not deemed clinically or ethically justifiable owing to the low yield in identifying clinically relevant findings balanced against potential harmful effects that could arise from such screening (such as psychological stress, unforeseen diagnostic findings outside this context, health insurance refusal, or complaint). Our results further inform the debate regarding screening families of probands with ccTGA.

Conclusions

In this international study of the largest cohort of ccTGA probands thus far reported, nonsporadic cases were identified. Familial clusters were noted, as well as evidence of an association between ccTGA, d-TGA, laterality defects and, in some cases, PCD. These observations strongly suggest a common pathogenetic pathway involving laterality genes in the pathophysiology of ccTGA. Our data support the rationale for extensive familial screening in ccTGA patients and pave the way for further analysis of familial forms to elucidate the genetic background of ccTGA.

Correspondence

Correspondence to: Alban-Elouen Baruteau, MD, PhD, Département médico-chirurgical de cardiologie pédiatrique et congénital, Centre Hospitalier Universitaire de Nantes, 7 Quai Moncoussu, 44093 Nantes cedex 01, France. Email albanelouen.baruteau@chu-nantes.fr

Affiliations

Nantes Université, CHU Nantes, CNRS, INSERM, l'institut du thorax, France (M.T., L.L.G., C.D., R.R., J.-J.S., A.-E.B.). Nantes Université, CHU Nantes, Department of Pediatric Cardiology and Pediatric Cardiac Surgery, France (M.T., S.P., C.G.G., B.R., N.B., Q.H., A.-E.B.). Nantes Université, CHU Nantes, INSERM, CIC FEA 1413, France (M.T., S.P., C.G.G., A.-E.B.). Division of Pediatric Cardiology, Labatt Family Heart Centre, The Hospital for Sick Children, University of Toronto, Canada (L.E.N., D.J.B.). Clinique des Données, CHU Nantes, INSERM, CIC 1413, France (M.K.). Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN (C.J.M.). Department of Pediatric and Adult Congenital Heart Disease, M3C Marie Lannelongue Hospital, Groupe Hospitalier Saint Joseph, Paris, France (E.B., A.B., N.C., E.F.). National Heart and Lung Institute, Imperial College London, Royal Brompton and Harefield Hospitals, United Kingdom (S.V.B.-N., M.C., A.F., M.A.G., S.Y.H.). Department of Pediatrics, Yale University School of Medicine, New Haven, CT (R.W.E.). Department of Adult Congenital Heart Diseases, M3C Hôpital Européen Georges Pompidou, Paris, France (M.L.). Electrophysiology Service and Adult Congenital Heart Center, Montreal Heart Institute, University of Montreal, Quebec, Canada (P.K., S.A.). Department of Congenital Heart Diseases, National Institute of Cardiology, Warsaw, Poland (E.K.). Department of Pediatric and Congenital Cardiac Surgery, Morgan Stanley Children's Hospital – New York Presbyterian, Columbia University Medical Center, NY (D.M.K., L.L., E.A.B.). Department of Congenital Cardiac Surgery, University Hospitals Bristol NHS Foundation Trust, United Kingdom (S.M.). Department of Pediatric Cardiology, New Children's Hospital, Helsinki University Hospital, Finland (A.H., J.-M.H.). Department of Pediatrics, Nemours Cardiac Center, Alfred I. duPont Hospital for Children, Wilmington, DE (J.T.). Division of Cardiology, CHU Mère-Enfant Sainte-Justine, University of Montreal, Quebec, Canada (S.A.). Department of Cardiology, CHU Nantes, Nantes, France (L.L.G.). Department of Pediatric Cardiology, CHU Grenoble, France (M.L.). Division of Cardiology, British Columbia Children's Hospital, University of British Columbia, Vancouver, Canada (S.S.). Department of Cardiology, CHU Bordeaux, France (J.-B.T., P.A.). PhyMedExp, CNRS, INSERM, University of Montpellier, France (P.A.). Department of Pediatric Cardiology, Hôpital Privé de La Louvière, Lille, France (G.V.). Department of Pediatric and Congenital Cardiology, American Memorial Hospital, CHU Reims, France (A.C.). Department of Cardiology (L.K.), La Timone Hospital, CHU Marseille, France. Department of Pediatric Cardiology (C.O.), La Timone Hospital, CHU Marseille, France. Marseille Medical Genetics, Inserm UMR 1251, Aix-Marseille University, France (C.O.). Department of Pediatric Cardiology, CHRU Lille, France (A.H.). Department of Cardiology, Pasteur Clinic, Toulouse, France (N.C.). Department of Cardiology (P.M.), CHU Toulouse, France. Department of Pediatric and Congenital Cardiology, Children's Hospital (C.K.), CHU Toulouse, France. Department of Cardiology, Groupe Hospitalier Pitié Salpêtrière, Sorbonne Université, Paris, France (G.D.). Department of Pediatric Cardiology, CHU Amiens, France (B.H.). UDivision of Pediatric Cardiology, University of Nebraska Medical Center, Children's Hospital and Medical Center, Omaha, NE (C.C.E.). Department of Pediatric Cardiology, CHU Lyon, France (C.B.). Division of Pediatric Cardiology, St Louis Children's Hospital, Washington University School of Medicine (G.F.V.H.). Institut des Maladies Métaboliques et Cardiovasculaires, Inserm UMR 1048, Université de Toulouse, France (C.K.). Department of Cardiology, Lausanne University Hospital, University of Lausanne, Switzerland (M.L.B.). Department of Pediatric Cardiology, Mount Sinai Kravis Children's Hospital, NY (R.H.P.). Department of Pediatrics, Rady Children's Hospital, University of California San Diego (J.C.P.). Department of Cardiology, Boston Children's Hospital, Harvard Medical School, MA (D.J.A.). Division of Pediatric Cardiology, Stanford University, Palo Alto, CA (A.M.D.). European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart (R.R., J.-J.S., A.-E.B.).

Acknowledgments

We are grateful to Dr Sylvie Falcon-Eicher (CHU Dijon, France) for her kind help in data collection. We also gratefully acknowledge the Association for European Paediatric Cardiology, the Pediatric and Congenital Electrophysiology Society and the French Society of Cardiology for supporting this study. We also thank the European Reference Network on Rare and Complex Diseases of the Heart (ERN GUARD-HEART).

Sources of Funding

By a grant from the Polish Ministry of Science and Higher Education (to Dr Kowalik); by a research grant from the Association for European Paediatric Cardiology (to Dr Baruteau), a research grant from the Lefoulon-Delalande Foundation (to Dr Baruteau) and a research grant from the European Heart Rhythm Association (to Dr Baruteau).

Disclosures

None.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58:2241–2247. doi: 10.1016/j.jacc.2011.08.025
2. Wallis GA, Debich-Spicer D, Anderson RH. Congenitally corrected transposition. *Orphanet J Rare Dis*. 2011;6:22. doi: 10.1186/1750-1172-6-22
3. Warnes CA. Transposition of the great arteries. *Circulation*. 2006;114:2699–2709. doi: 10.1161/CIRCULATIONAHA.105.592352
4. Baruteau AE, Abrams DJ, Ho SY, Thambo JB, McLeod CJ, Shah MJ. Cardiac conduction system in congenitally corrected transposition of the great arteries and its clinical relevance. *J Am Heart Assoc*. 2017;6:e007759. doi: 10.1161/JAHA.117.007759
5. Piacentini G, Digilio MC, Capolino R, Zorzi AD, Toscano A, Sarkozy A, D'Agostino R, Marasini M, Russo MG, Dallapiccola B, et al. Familial recurrence of heart defects in subjects with congenitally corrected transposition of the great arteries. *Am J Med Genet A*. 2005;137:176–180. doi: 10.1002/ajmg.a.30859
6. Kuehl KS, Loffredo CA. Population-based study of l-transposition of the great arteries: possible associations with environmental factors. *Birth Defects Res A Clin Mol Teratol*. 2003;67:162–167. doi: 10.1002/bdra.10015
7. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation*. 2014;130:749–756. doi: 10.1161/CIRCULATIONAHA.113.008396
8. Brodwall K, Greve G, Leirgul E, Tell GS, Vollset SE, Øyen N. Recurrence of congenital heart defects among siblings—a nationwide study. *Am J Med Genet A*. 2017;173:1575–1585. doi: 10.1002/ajmg.a.38237
9. Peyvandi S, Ingall E, Woyciechowski S, Garbarini J, Mitchell LE, Goldmuntz E. Risk of congenital heart disease in relatives of probands with conotruncal cardiac defects: an evaluation of 1,620 families. *Am J Med Genet A*. 2014;164A:1490–1495. doi: 10.1002/ajmg.a.36500
10. Lee MY, Won HS, Han YJ, Ryu HM, Lee DE, Jeong BD. Clinical value of chromosomal microarray analysis in prenatally diagnosed dextro-transposition of the great arteries. *J Matern Fetal Neonatal Med*. 2020;33:1480–1485. doi: 10.1080/14767058.2018.1519800

11. Mustafa HJ, Jacobs KM, Tessier KM, Narasimhan SL, Tofte AN, McCarter AR, Cross SN. Chromosomal microarray analysis in the investigation of prenatally diagnosed congenital heart disease. *Am J Obstet Gynecol MFM*. 2020;2:100078. doi: 10.1016/j.ajogmf.2019.100078
12. Digilio MC, Casey B, Toscano A, Calabrò R, Pacileo G, Marasini M, Banaudi E, Giannotti A, Dallapiccola B, Marino B. Complete transposition of the great arteries: patterns of congenital heart disease in familial precurrence. *Circulation*. 2001;104:2809–2814. doi: 10.1161/hc4701.099786
13. Al-Zahrani RS, Alharbi SH, Tuwajri RMA, Alzomaili BT, Althubaiti A, Yelbuz TM. Transposition of the great arteries: a laterality defect in the group of heterotaxy syndromes or an outflow tract malformation? *Ann Pediatr Cardiol*. 2018;11:237–249. doi: 10.4103/apc.APC_24_18
14. Loomba RS, Anderson RH. Discordant ventriculo-arterial connections, or “transposition”, are not necessarily an essential part of isomerism. *Congenit Anom (Kyoto)*. 2017;57:66. doi: 10.1111/cga.12195
15. Unolt M, Putotto C, Silvestri LM, Marino D, Scarabotti A, Massaccesi Valerio, Caiaro A, Versacci P, Marino B. Transposition of great arteries: new insights into the pathogenesis. *Front Pediatr*. 2013;1:11. doi: 10.3389/fped.2013.00011
16. De Ita M, Cisneros B, Rosas-Vargas H. Genetics of transposition of great arteries: between laterality abnormality and outflow tract defect. *J Cardiovasc Transl Res*. 2021;14:390–399. doi: 10.1007/s12265-020-10064-x
17. Nomura M, Li E. Smad2 role in mesoderm formation, left-right patterning and craniofacial development. *Nature*. 1998;393:786–790. doi: 10.1038/31693
18. De Luca A, Sarkozy A, Consoli F, Ferese R, Guida V, Dentici ML, Mingarelli R, Bellacchio E, Tuo G, Limongelli G, et al. Familial transposition of the great arteries caused by multiple mutations in laterality genes. *Heart*. 2010;96:673–677. doi: 10.1136/hrt.2009.181685
19. D’Alessandro LC, Latney BC, Paluru PC, Goldmuntz E. The phenotypic spectrum of ZIC3 mutations includes isolated d-transposition of the great arteries and double outlet right ventricle. *Am J Med Genet A*. 2013;161A:792–802. doi: 10.1002/ajmg.a.35849
20. Liu X, Chen W, Li W, Priest JR, Fu Y, Pang K, Ma B, Han B, Liu X, Hu S, et al. Exome-based case-control analysis highlights the pathogenic role of ciliary genes in transposition of the great arteries. *Circ Res*. 2020;126:811–821. doi: 10.1161/CIRCRESAHA.119.315821
21. Versacci P, Pugnaroni F, Digilio MC, Putotto C, Unolt M, Calcagni G, Baban A, Marino B. Some isolated cardiac malformations can be related to laterality defects. *J Cardiovasc Dev Dis*. 2018;5:E24. doi: 10.3390/jcdd5020024
22. Li Y, Klena NT, Gabriel GC, Liu X, Kim AJ, Lemke K, Chen Y, Chatterjee B, Devine W, Damerla RR, et al. Global genetic analysis in mice unveils central role for cilia in congenital heart disease. *Nature*. 2015;521:520–524. doi: 10.1038/nature14269
23. Burnicka-Turek O, Steimle JD, Huang W, Felker L, Kamp A, Kweon J, Peterson M, Reeves RH, Maslen CL, Gruber PJ, et al. Cilia gene mutations cause atrioventricular septal defects by multiple mechanisms. *Hum Mol Genet*. 2016;25:3011–3028. doi: 10.1093/hmg/ddw155
24. Li AH, Hanchard NA, Furthner D, Fernbach S, Azamian M, Nicosia A, Rosenfeld J, Muzny D, D’Alessandro LCA, Morris S, et al. Whole exome sequencing in 342 congenital cardiac left sided lesion cases reveals extensive genetic heterogeneity and complex inheritance patterns. *Genome Med*. 2017;9:95. doi: 10.1186/s13073-017-0482-5
25. Shiraishi I, Ichikawa H. Human heterotaxy syndrome – from molecular genetics to clinical features, management, and prognosis –. *Circ J*. 2012;76:2066–2075. doi: 10.1253/circj.cj-12-0957

26. Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, McGuire AL, Mital S, Priest JR, Pu WT, Roberts A, et al; American Heart Association Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Genomic and Precision Medicine. Genetic basis for congenital heart disease: revisited: a scientific statement from the American Heart Association. *Circulation*. 2018;138:e653–e711. doi: 10.1161/CIR.0000000000000606
27. Gebbia M, Ferrero GB, Pilia G, Bassi MT, Aylsworth A, Penman-Splitt M, Bird LM, Bamforth JS, Burn J, Schlessinger D, et al. X-linked situs abnormalities result from mutations in ZIC3. *Nat Genet*. 1997;17:305–308. doi: 10.1038/ng1197-305
28. Li AH, Hanchard NA, Azamian M, D'Alessandro LCA, Coban-Akdemir Z, Lopez KN, Hall NJ, Dickerson H, Nicosia A, Fernbach S, et al. Genetic architecture of laterality defects revealed by whole exome sequencing. *Eur J Hum Genet*. 2019;27:563–573. doi: 10.1038/s41431-018-0307-z
29. Solomon MH, Winn KJ, White RD, Bulkley BH, Kelly DT, Gott VL, Hutchins GM. Kartagener's syndrome with corrected transposition. Conducting system studies and coronary arterial occlusion complicating valvular replacement. *Chest*. 1976;69:677–680. doi: 10.1378/chest.69.5.677
30. Conraads VM, Galdermans DI, Kockx MM, Jacob WA, Van Schaardenburg C, Coolen D. Ultrastructurally normal and motile spermatozoa in a fertile man with Kartagener's syndrome. *Chest*. 1992;102:1616–1618. doi: 10.1378/chest.102.5.1616
31. Bitar FF, Shbaro R, Mroueh S, Yunis K, Obeid M. Dextrocardia and corrected transposition of the great arteries (I,D,D) in a case of Kartagener's syndrome: a unique association. *Clin Cardiol*. 1998;21:298–299. doi: 10.1002/clc.4960210414
32. Tek I, Dinçer I, Gürlek A. Kartagener's syndrome with dextrocardia and corrected transposition of great arteries. *Int J Cardiol*. 2000;75:305–308. doi: 10.1016/s0167-5273(00)00341-7
33. Imtiaz F, Allam R, Ramzan K, Al-Sayed M. Variation in DNAH1 may contribute to primary ciliary dyskinesia. *BMC Med Genet*. 2015;16:14. doi: 10.1186/s12881-015-0162-5
34. Bellsham-Revell H, Masani N. Educational Series in Congenital Heart Disease: the sequential segmental approach to assessment. *Echo Res Pract*. 2019;6:R1–R8. doi: 10.1530/ERP-17-0039
35. Jacobs JP, Anderson RH, Weinberg PM, Walters HL, Tchervenkov CI, Del Duca D, Franklin RC, Aiello VD, Béland MJ, Colan SD, et al. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. *Cardiol Young*. 2007;17 Suppl 2:1–28. doi: 10.1017/S1047951107001138
36. Franklin RCG, Béland MJ, Colan SD, Walters HL, Aiello VD, Anderson RH, Bailliard F, Boris JR, Cohen MS, Gaynor JW, et al. Nomenclature for congenital and paediatric cardiac disease: the International Paediatric and Congenital Cardiac Code (IPCCC) and the Eleventh Iteration of the International Classification of Diseases (ICD-11). *Cardiol Young*. 2017;27:1872–1938. doi: 10.1017/S1047951117002244
37. Houyel L, Khoshnood B, Anderson RH, Lelong N, Thieulin AC, Goffinet F, Bonnet D; EPICARD Study group. Population-based evaluation of a suggested anatomic and clinical classification of congenital heart defects based on the International Paediatric and Congenital Cardiac Code. *Orphanet J Rare Dis*. 2011;6:64. doi: 10.1186/1750-1172-6-64
38. Olson JM, Cordell HJ. Ascertainment bias in the estimation of sibling genetic risk parameters. *Genet Epidemiol*. 2000;18:217–235. doi: 10.1002/(SICI)1098-2272(200003)18:3<217::AID-GEPI3>3.0.CO;2-8