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

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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

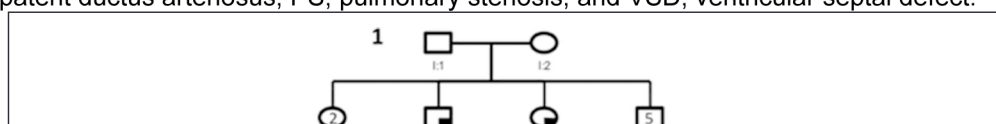
Primary ciliary dyskinesia (PCD) was diagnosed in 11/739 (1.5%) ccTGA patients, 2 of whom displayed features of right atrial isomerism. Two patients with ccTGA and PCD had a sibling diagnosed with ccTGA as well (pedigree_5 and pedigree_6 in Figure 1), including a set of identical twins displaying both 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.



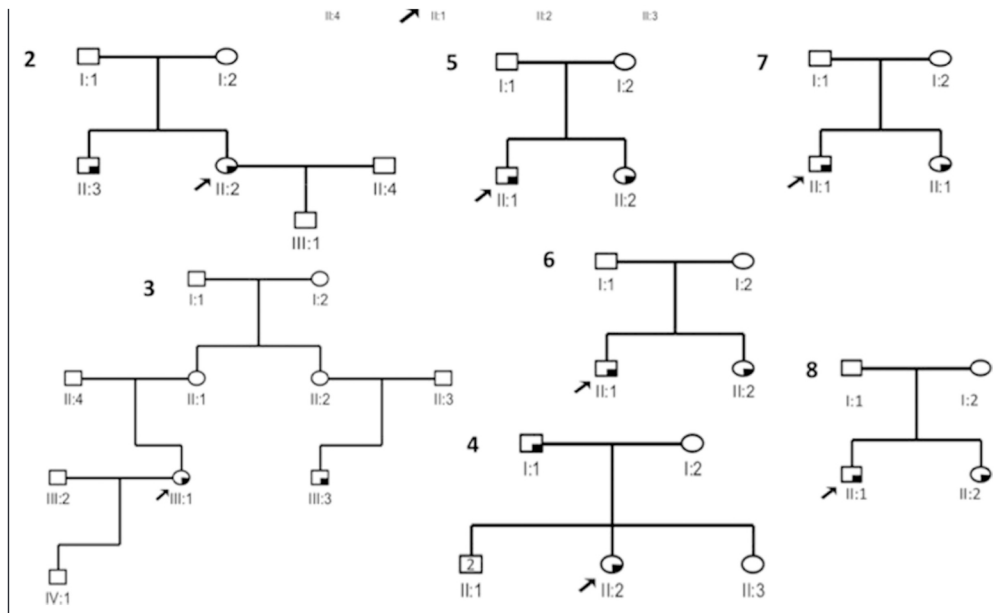


Figure 1. Concordant familial aggregation of congenitally corrected transposition of the great arteries (ccTGA) cases. Concordant familial aggregation of ccTGA was identified in 8 families. All ccTGA were in usual atrial arrangement.

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 %.

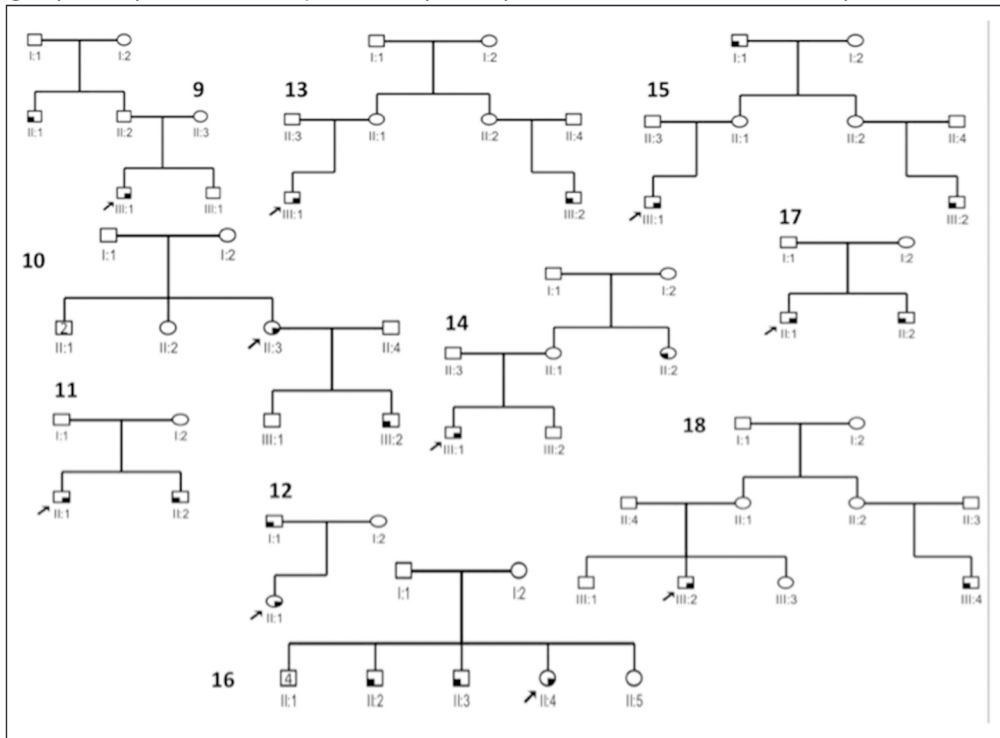
† Exact 95%CI were estimated assuming a binomial distribution.

‡ 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.

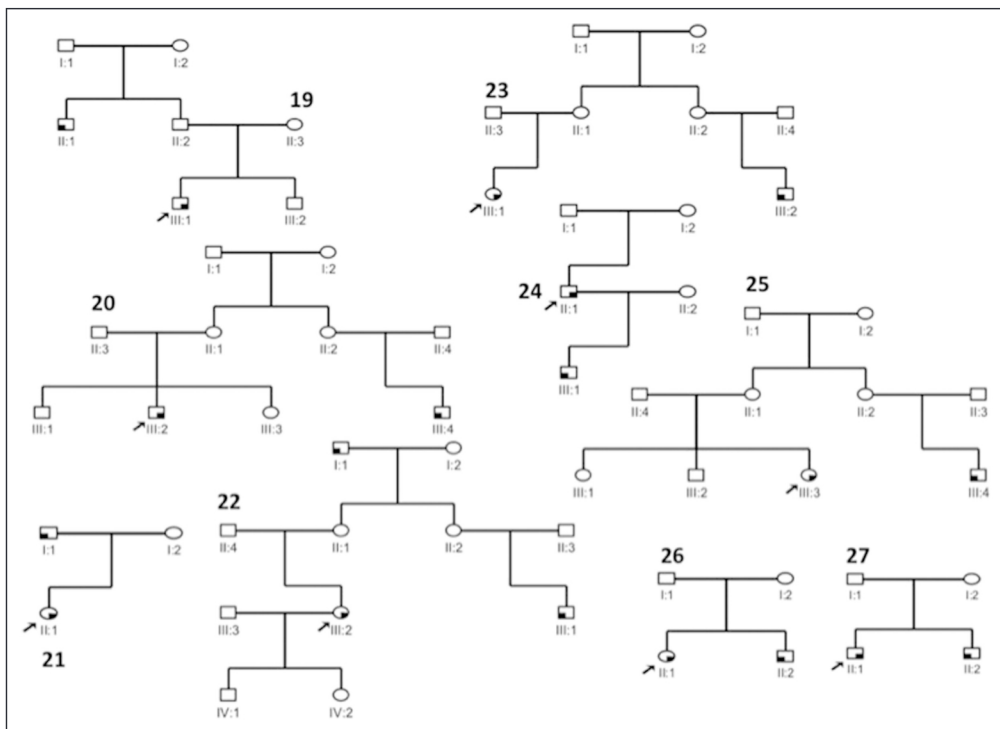
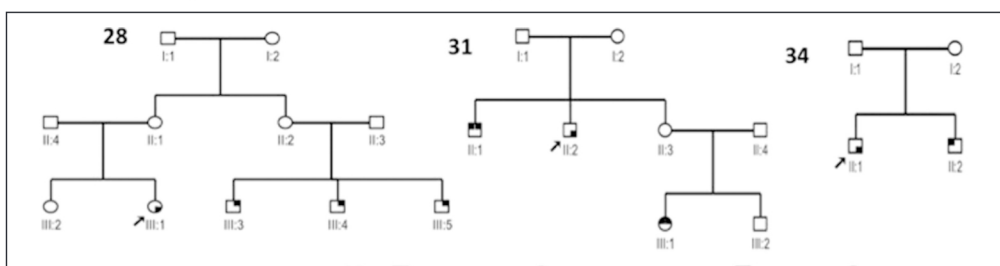


Figure 3. Occurrence of dextro-transposition of the great arteries (d-TGA) in relatives of congenitally corrected transposition of the great arteries (ccTGA) probands. Familial occurrence of d-TGA in first- or second-degree relatives of ccTGA probands was found in 19 families.



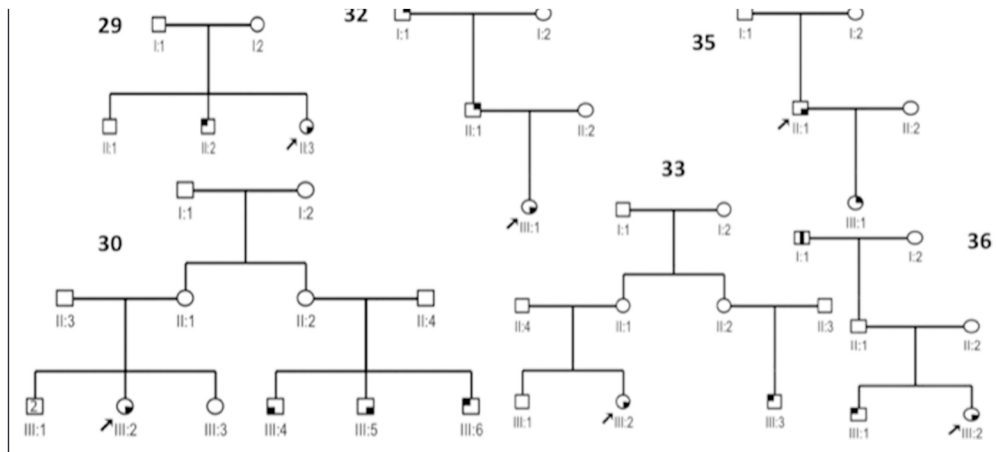


Figure 4. Occurrence of laterality disorders in relatives of congenitally corrected transposition of the great arteries (ccTGA) probands. In our series, 9 ccTGA probands had first- or second-degree relatives displaying laterality disorders, including a unique familial pedigree associating ccTGA (the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

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Disclosures

None.

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