Complete Transposition of the Great Arteries
Patterns of Congenital Heart Disease in Familial Precurrence

Maria Cristina Digilio, MD; Brett Casey, MD; Alessandra Toscano, MD; Raffaele Calabrò, MD; Giuseppe Pacileo, MD; Maurizio Marasini, MD; Elena Banaudi, MD; Aldo Giannotti, MD; Bruno Dallapiccola, MD; Bruno Marino, MD

Background—Transposition of the great arteries (TGA) is considered to be associated only rarely with genetic syndromes and to have a low risk of precurrence among relatives of affected patients. Because most family studies have involved a relatively small number of patients and evaluated all types of TGA as a single group, we performed a large, prospective study investigating the precurrence of congenital heart disease in families of children with complete, nonsyndromic TGA.

Methods and Results—From January 1997 through December 2000, 370 patients with nonsyndromic, complete TGA were consecutively evaluated and enrolled in the study. The occurrence of cardiac and noncardiac anomalies among relatives of the probands was investigated. Relatives with congenital heart disease were found in 37 of 370 families (10%), including 5 of 37 families (13.5%) with more than one affected relative. TGA itself was the most common precurrent malformation: complete TGA occurred in 6 families and congenitally corrected TGA occurred in 5 families. Precurrence risks for congenital heart disease were calculated at 1.8% (8 of 436) for siblings, 0.5% (4 of 740) for parents, 0.5% (16 of 3261) for first cousins, 0.2% (4 of 2101) for uncles/aunts, and 0.06% (1 of 1480) for grandparents.

Conclusions—The present study shows that TGA is not always sporadic in families. Precurrence of concordant cardiac defects within affected family members supports monogenic or oligogenic inheritance of TGA in certain kindreds. Moreover, the occurrence of complete TGA and congenitally corrected TGA among first-degree relatives in several different families strongly suggests an underlying pathogenetic link between these 2 malformations that has been previously unrecognized. (Circulation. 2001;104:2809-2814.)

Key Words: heart defects, congenital ■ transposition of great vessels ■ genetics

Transposition of the great arteries (TGA) accounts for 5% to 7% of all congenital heart defects (CHDs),1-3 with a prevalence rate of 0.2 per 1000 live births.4 TGA is the most frequent cyanotic CHD5 and the most frequent CHD diagnosed in the neonatal period.1

The genetic contribution to the pathogenesis of TGA is not considered to be strong given that very few familial cases have been described6,7 and that genetic syndromes or extra-cardiac malformations are uncommonly associated with TGA.1,8 Currently, the mean precurrence risk for CHD among siblings of patients affected with any type of TGA is considered to be 1.4%,7,9-17 and a recent large population study failed to identify any familial precurrence among 20 offspring of adult patients with TGA.16

Information about precurrence risks among different subgroups of TGA have been provided in only one study,17 which reported that patients with complete TGA (ie, situs solitus, D-loop ventricle, and TGA with or without a ventricular septal defect [VSD]) have the lowest precurrence rate of CHD among siblings (0.27%), whereas a precurrence risk of 2% has been calculated for siblings of patients with complex TGA (with or without a single ventricle, tricuspid atresia, or double outlet right ventricle) or with TGA with the asplenia syndrome/right isomerism form of heterotaxy. Correspondingly, the results of the Baltimore-Washington Infant Study8 showed that complete TGA also has a lower percentage of associated extracardiac defects in comparison with complex TGA.

Anecdotal clinical experience suggested that the occurrence of familial CHD among index cases of TGA might be higher than previously reported, particularly among the subgroup of patients with complete TGA. This study was
designed specifically to investigate this hypothesis and to
determine whether any particular CHD occurred more
commonly than others among relatives of index cases.

Considering that most previous familial studies have in-
volved a relatively small number of patients and evaluated all
types of TGA as a single group, we performed a prospective
investigation of familial precurrence of CHD in families of
children with complete TGA evaluated in 5 Italian depart-
ments of pediatric cardiology over 4 years. The study was
designed to verify if the familial analysis of a large series of
patients could help in the identification of pedigrees at high
risk for CHD and to study the types of CHD occurring in
relatives of patients with complete TGA.

Methods

From January 1997 to December 2000, 370 consecutive patients with
nonsyndromic, complete TGA were evaluated and enrolled in this
Italian multicenter study, which was coordinated by the Bambino
Gesù Hospital in Rome. Five pediatric cardiology institutions par-
ticipated to this study: the Bambino Gesù Hospital in Rome (179
patients), the Gaslini Hospital in Genova (87 patients), the Monaldi
Hospital in Naples (67 patients), the Regina Margherita Hospital in
Torino (23 patients), and the La Sapienza University in Rome (14
patients). There were 260 male (70.3%) and 110 female (29.7%)
patients. Mean age was 5.95 ± 2.62 years (range, newborn to 17.7
years). The majority of the patients (347 of 370, 93.8%) were
enrolled at the time of a routine postoperative appointment. The
remaining patients (23 of 370, 6.2%) were enrolled at the time of
initial presentation. In all patients, the cardiac diagnosis was con-
firmed by one or more of the following: echocardiography, cardiac
catheterization, surgical intervention, and/or autopsy. The study
was restricted to patients with TGA and discordant ventriculoarterial
connections (patent semilunar valves), with or without a VSD and/or
outflow tract obstructions. All had situs solitus of the atria, levocar-
dia, β-loop of the ventricle, and concordant atrioventricular connec-
tions (patent atrioventricular valves). Patients with any type of single
ventricle and/or classic findings of heterotaxy (41 patients) were
excluded.

Clinical and phenotypical evaluations were performed in all
patients by a geneticist to detect extracardiac anomalies. The
definition of nonsyndromic was based on an examination at the time
of enrollment in the study. Standard karyotype on peripheral
lymphocytes and fluorescent in situ hybridization with Sc11.1 probe
for 22q11.2 microdeletion were performed in all cases. Patients with
major extracardiac malformations and/or with facial dysmorphisms
in the setting of chromosome anomalies, mendelian syndromes, or
associations (28 patients) and one patient with a 22q11.2 microde-
letion were excluded.

Information about family history was obtained by an interview
with the parents of the index cases. The precurrence of cardiac and
noncardiac congenital anomalies in relatives of the probands was
investigated. Family pedigrees were constructed to include siblings,
parents, grandparents, aunts/uncles, and first cousins. Information
about more distant relatives was volunteered by some families. The
study was approved by our ethics committee. All living first-degree
relatives underwent clinical and electrocardiographic examination.
In families in which CHD occurred in more than one member, a
complete echocardiographic study was performed on all living first-
and second-degree relatives.

Results

TGA with intact ventricular septum (IVS) was diagnosed in
246 of 370 cases (66.5%), and TGA with a VSD was
diagnosed in 124 of the 370 cases (33.5%). Of the 246
patients with TGA and IVS, 184 (74.8%) were male and 62
(25.2%) were female; in the 124 patients with TGA and VSD,
there were 76 (61.3%) males and 48 (38.7%) females. The
difference in sex distribution between the 2 groups (TGA
with IVS and TGA with VSD), using χ² analysis (with
P < 0.05 accepted as significant), is statistically significant
(P = 0.01).

One or more relatives with CHD were found in 37 of the
370 families (10%). In particular, familial precurrence of
CHD was detected in 22 of 246 families (8.9%) of probands
with TGA and IVS and in 15 of 124 families (12.1%) of
probands with TGA and VSD (P = 0.441). The affected
relatives had complete TGA in 6 families (Figure 1) and
congenitally corrected TGA (situs solitus, β-loop ventricle
disorder discordant atrioventricular connections, and TGA with
discordant ventriculoarterial connections) in 5 families (Fig-
ure 2). Different types of CHD were also found among
relatives of 2 of the families included in Figure 1. In the
remaining 26 families, the affected relatives had CHDs
different from TGA (Table 1). Some pedigrees with familial
aggregation of TGA included in the present study were also
previously reported.18,19 Precurrence risks for CHD among
relatives in our series of patients with TGA are shown in
Table 2. Considering the occurrence of CHD in first-degree
relatives of our probands, the heritability of TGA can be
estimated as ≈10%.

Noncardiac anomalies in relatives of the probands were
identified in 36 families. The type of noncardiac anomaly is
shown in Table 3. The risk rates for noncardiac anomalies in
relatives of our probands were 0.7% (3 of 436) for siblings,
0.5% (4 of 740) for parents, 0.8% (26 of 3261) for first
cousins, and 0.3% (7 of 2101) for uncles/aunts.

Consanguinity was identified in the parents of 5 probands
(second cousins in 4 cases and first cousins in one). Eight
probands with TGA (6 with TGA and IVS and 2 with TGA
and VSD, P = 0.89) had an unaffected twin sibling (dizy\nogic in 5 cases, monozygotic in 3). The ethnicity of the families
was Italian in 369 of the 370 families; the ethnicity of the
remaining family (pedigree 2 in Figure 1) was Slavic gypsy.

Discussion

We analyzed familial precurrence of CHD in a large series of
patients with complete TGA from an Italian multicenter
study. The results obtained from the investigation of 370
families show a precurrence risk for CHD in siblings of 1.8%
(Table 2). Six families with precurrence of discordant TGA
(Figure 1) were identified and, surprisingly, in 5 other
families, congenitally corrected T- TGA was identified in
relatives of index cases (Figure 2).

According to previous literature reports, the mean precurrence
rate in siblings of patients with TGA is considered to be
1.4%,7,9–17 which is just lower than that in our results. In this
regard, it is important to consider that most of the studies
investigating familial TGA are referring to all types of TGA
as a single group. The only exception is the article by Becker
et al,17 which showed that the study group of complete TGA
(168 patients) had a precurrence rate of only 0.27%. The
recent population study published by Burn et al,16 which
investigated vertical transmission of TGA, found no cases of
CHD among 20 offspring of 104 probands with TGA. In the
same study, the precurrence of CHD in siblings of patients with TGA was 0.97% (one case among 103 siblings).

The variety of recurrence risk rates found among different studies may reflect different genetic and geographic backgrounds in populations. The finding of more families with precurrent TGA than previously expected could mean that a study of large numbers of patients may identify pedigrees at high risk for CHD. A combination of chance, decreased penetrance, and nondominant transmission may account for the absence of vertical transmission of CHD found in the study performed by Burn et al.16 Ascertainment bias may also affect the study results, because different anatomic types of TGA allowing survival to adulthood could have a possible different genetic impact in comparison with more severe TGA.

The rate of consanguinity in our series is 1.4% (5 of 370 families). Only few data are available from the literature, but first-cousin matings among parents of patients with TGA have been occasionally reported.20

The higher proportion of male patients affected by TGA reported in previous series1,21,22 was confirmed in our experience. In addition, a statistically significant male preponderance in patients with TGA and IVS in comparison with those with TGA and VSD was also found in our study, similar to the observations reported in the Baltimore-Washington Infant Study.21 The segregation of an X-linked gene could be suspected in families with precurrent TGA in males (Figures 1 and 2), but this type of transmission can be excluded in most of our families because of apparent male-to-male segregation of a putative disease gene (Figures 1 and 2).

Kindreds with familial TGA show that both TGA with VSD and TGA with IVS can occur in the same family. No significant difference was found in precurrence risk rates in families of patients with TGA and IVS in comparison with those with TGA and VSD. Discordant CHDs precurring more often in our pedigrees include tetralogy of Fallot and VSD (Table 1); a multifactorial mode of inheritance of predisposition to familial CHD can be hypothesized in these cases.

Some patterns of familial precurrence observed in our study suggest that the recent pathogenetic classification of CHD is not completely adequate to account for all cases of TGA. In fact, according to the pathogenetic classification proposed by Clark,23,24 complete TGA is grouped among

Figure 1. Pedigree of 6 families with concordant TGA in affected members. TF indicates tetralogy of Fallot; ASD, atrial septal defect. Arrow indicates propositus; ■, male affected; □, male unaffected; ●, female affected; ○, female unaffected; slashes, deceased.

Figure 2. Pedigree of 5 families of probands with TGA and additional family member with congenitally corrected L-TGA. CCTGA indicates congenitally corrected transposition of the great arteries. For symbols, see Figure 1.
conotruncal heart defects due to abnormalities of ectomesenchymal tissue migration, which are frequently associated with chromosomal deletion 22q11.2 in the setting of DiGeorge/velocardiofacial syndrome. Actually, only a few cases of TGA and deletion 22q11.2 have been reported, suggesting that in only a small percentage of cases can TGA be definitively explained on the basis of a defect in neural crest cell migration. An interesting observation in our series is the occurrence of tetralogy of Fallot related to deletion 22q11.2 in a sister of a male proband with TGA without chromosomal abnormalities (Table 1). The occurrence of CHD in siblings with discordant karyotypes supports the existence of additional genetic predisposing factors, which could play a role in the pathogenesis of familial aggregation of CHDs.

<table>
<thead>
<tr>
<th>Cardiac Defect</th>
<th>Relationship</th>
<th>No. of relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete TGA</td>
<td>Sister</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Uncle</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Second cousin</td>
<td>3</td>
</tr>
<tr>
<td>Congenitally corrected L-TGA</td>
<td>Sister</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Brother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>Sister (with deletion 22q11.2)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Aunt</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Second cousin</td>
<td>5</td>
</tr>
<tr>
<td>VSD</td>
<td>Aunt</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Second cousin</td>
<td>3</td>
</tr>
<tr>
<td>Aortic stenosis (valvular)</td>
<td>Brother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Father</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Second cousin</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary stenosis (valvular)</td>
<td>Brother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Father</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Second cousin</td>
<td>1</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>First cousin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Uncle</td>
<td>1</td>
</tr>
<tr>
<td>Atrial septal defect (os)</td>
<td>Mother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Grandfather</td>
<td>1</td>
</tr>
<tr>
<td>Single ventricle</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Partial anomalous pulmonary venous return</td>
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<td>1</td>
</tr>
<tr>
<td>Persistent left superior vena cava</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricle noncompaction</td>
<td>Brother</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relationship</th>
<th>No. of Family Members With Complete TGA (Risk)</th>
<th>No. of Family Members With Congenitally Corrected L-TGA (Risk)</th>
<th>No. of Family Members With CHD (Risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siblings</td>
<td>1/436 (0.2%)</td>
<td>3/436 (0.7%)</td>
<td>8/436 (1.8%)</td>
</tr>
<tr>
<td>Parents</td>
<td>0/740 (0)</td>
<td>1/740 (0.1%)</td>
<td>4/740 (0.5%)</td>
</tr>
<tr>
<td>First cousins</td>
<td>1/3261 (0.03%)</td>
<td>1/3261 (0.03%)</td>
<td>16/3261 (0.5%)</td>
</tr>
<tr>
<td>Uncles/aunts</td>
<td>1/2101 (0.05%)</td>
<td>0/2101 (0)</td>
<td>4/2101 (0.2%)</td>
</tr>
<tr>
<td>Grandparents</td>
<td>0/1480 (0)</td>
<td>0/1480 (0)</td>
<td>1/1480 (0.06%)</td>
</tr>
</tbody>
</table>
TABLE 3. Noncardiac Anomalies in Relatives of Patients With Complete TGA

<table>
<thead>
<tr>
<th>Type of Noncardiac Anomaly</th>
<th>Relationship</th>
<th>No. of Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>First cousin</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Aunt</td>
<td>2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Uncle</td>
<td>1</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Sensorineural deafness</td>
<td>First cousin</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Aunt</td>
<td>1</td>
</tr>
<tr>
<td>Chromosomal anomalies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>47,XXY</td>
<td>Father</td>
<td>1</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>First cousin</td>
<td>4</td>
</tr>
<tr>
<td>Blood disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia, factor X</td>
<td>Mother</td>
<td>1</td>
</tr>
<tr>
<td>Urogenital anomalies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vesicoureteral reflux</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>Second cousin</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal malformations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal atresia</td>
<td>Second cousin</td>
<td>1</td>
</tr>
<tr>
<td>Intestinal malformation</td>
<td>Brother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Aunt</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Skeletal defects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip defects</td>
<td>Uncle</td>
<td>1</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Cutaneous disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermolysis bullosa</td>
<td>Sister</td>
<td>1</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleft lip/palate</td>
<td>First cousin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Aunt</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Mother</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sister</td>
<td>1</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>First cousin</td>
<td>1</td>
</tr>
<tr>
<td>X-linked combined immunodeficiency</td>
<td>Second cousin</td>
<td>1</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>First cousin</td>
<td>1</td>
</tr>
</tbody>
</table>

Ferencz et al.,21 however, classified TGA with the group of conotruncal anomalies, but separated this malformation from those with “normally related great arteries,” ie, tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch. In fact, TGA seems to differ from the other types of conotruncal defects: it presents with a lower percentage of associated extracardiac anomalies,1,8 a lower risk of familial preincidence of CHD,6,7 and a lower prevalence of deletion 22q11.2.25-27

According to general consent, congenitally corrected l-TGA is not included in the group of conotruncal defects, but is classified among the situs and looping abnormalities.21,23,24 The presence of congenitally corrected l-TGA in 5 first-degree relatives of our patients with TGA is quite surprising (Figure 2). Aggregation of complete TGA and l-TGA in the same family suggests a possible genetic and causative connection between the 2 defects. Considering the high prevalence of TGA in patients with heterotaxy29 and based on these cases of familial aggregation, the pathogenetic group of situs and loop abnormalities might include at least some cases of complete TGA.

In this regard, it is interesting to note that a relationship between complete TGA and laterality defects is corroborated by molecular studies investigating some new genes. In fact, mice trans-heterozygous for both SMAD2 and nodal mutations can have TGA, which is associated with right pulmonary isomerism in some cases.30 Mutations of the EGF-CFC gene, CRYPTIC, in humans have been found to be associated with heterotaxic phenotypes31 as well as with some cases of complete TGA.32

In addition, a mutation in the ZIC3 gene, an X-linked gene related to sporadic and familial situs abnormalities, has been detected in a family in which affected males have TGA and midline anomalies but no obvious left-right malformations.33 Familial segregation of both laterality defects and isolated TGA has been also recently observed in one family.34 All these data support the hypothesis that TGA could be included within the spectrum of laterality defects in some cases.

Data from animal studies support the suggestion that TGA and situs/looping abnormalities may be related pathogenetically. Although TGA is the most difficult cardiac malformation to reproduce experimentally, a consistent model of TGA was recently obtained by all-trans retinoic acid administration during mouse pregnancy.35,36 In this animal model, TGA could be found in the presence of both d- and l-loops of the ventricles (ie, complete TGA and congenitally corrected TGA),35 and treatment with retinoic acid in mouse embryos also could induce looping abnormalities with right isomerism.37 Moreover, complete TGA (ie, with situs solitus and d-loop ventricle) can be present among heart defects of homozygous iv/iv mice presenting with a high prevalence of visceral heterotaxy and lateralization anomalies.38 Animal models, therefore, support a common pathogenetic mechanism involved in causing some cases of complete TGA along with congenitally corrected TGA and other laterality defects. Complete TGA could be considered a less severe manifestation than typically encountered.

Noncardiac heritable disorders in relatives of patients with complete TGA include a great variety of conditions. Previous observations from the literature report a preferential occurrence of heritable blood disorders in parents of children with TGA,1,30 and this association was also noted in one of the families from our series (Table 3). The rarity of TGA and of hemophilia in the population suggests that the co-occurrence of these diseases in a family could be causally related. Also, in our series (Table 3) as in previous epidemiological studies,1 congenital hypothyroidism was found in relatives of patients with TGA.

In the present study, some limitations concerning the methods of ascertainment of the cases can be pointed out. In fact, our study is not a population-based analysis, considering that our series consists of patients with TGA enrolled at time of hospital admission. In addition, the great majority of the patients were collected when seen for a postoperative appointment. This could constitute a bias in data evaluation,
particularly considering that TGA has high preoperative and intraoperative mortality.\textsuperscript{20} An additional limitation could be due to the fact that imaging tests for CHD were performed routinely only in the first degree relatives of the probands, whereas the presence of CHD in more distant relatives was investigated by interview.

**Conclusions**

The present study shows that TGA is not always a sporadic occurrence in families. Familial concordance of concordant cardiac defects within affected family members supports monogenic or oligogenic inheritance of TGA in selected pedigrees. This observation has practical implications in genetic counseling for TGA. It is remarkable that TGA and congenitally corrected TGA can segregate in the same family due to a probable monogenic transmission supporting a pathogenetic link between some cases of complete TGA and the situs and looping abnormalities.

The complexity of these observations suggests a multigenic origin of TGA, probably with the involvement of multiple or even unrecognized causative and pathogenetic mechanisms. Large families with multiple members affected by CHD are fundamental for the identification of the genes related to the specific malformations using genetic techniques such as linkage analysis and positional cloning. The collection of pedigrees segregating the gene(s) of interest will provide an important aid for the delineation of the human gene map of CHDs.

**References**

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