Complex Congenital Heart Disease in Unaffected Relatives of Adults With 22q11.2 Deletion Syndrome

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Abstract

The 22q11.2 deletion syndrome (22q11DS) is a common genetic condition associated with 22q11.2 microdeletions and classically has included congenital heart disease (CHD) as a part of the variable expression. Some evidence has shown that relatives of those with 22q11DS might be at an increased risk of CHD in the absence of 22q11.2 deletions. We obtained a detailed family history of CHD in the first- to third-degree relatives (n = 2,639) of 104 adult probands with 22q11DS. We compared the prevalence of CHD in the relatives without 22q11.2 deletions to the published general population prevalence. We also investigated the effect of CHD in the probands on prevalence of CHD in the relatives. Of the 104 probands with 22q11DS, 14 (13.5%) had 17 relatives (17 of 2,639, 0.6%) with CHD. Of 66 probands with CHD, 15 (0.9%) of their 1,663 relatives had CHD, a significantly greater prevalence than that for the relatives of probands without CHD (0.2%, 2 of 976, p = 0.041, odds ratio 4.43, 95% confidence interval 1.03 to 40.00). In relatives of probands with CHD, the prevalence of those with severe CHD (0.36%) was significantly elevated compared to population expectations (0.061%, p = 0.007, odds ratio 5.88, 95% confidence interval 2.16 to 12.85). In conclusion, these results support a heritable susceptibility to CHD in families of probands with 22q11DS, in addition to that imparted by microdeletion 22q11.2. The occurrence of CHD in relatives might be related to the expression of CHD in the proband with 22q11DS. These findings have potential implications for the genetic counseling of families of those with 22q11DS and support the notion that interacting genetic variants might contribute to the variable expression of 22q11DS.

The 22q11.2 deletion syndrome (22q11DS) is a common, multisystem disorder associated with microdeletion 22q11.2 that occurs at an estimated prevalence of 1/4,000 live births.¹ Congenital heart disease (CHD) is a classic feature of 22q11.2DS, found in about 40% of patients.^{2–5} Conotruncal anomalies such as tetralogy of Fallot (TOF), interrupted aortic arch, and truncus arteriosus have been most strongly associated.^{6,7} Multiple factors are

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thought to affect the expression of CHD in patients with 22q11DS. These include the hemizygosity of the 45 genes in the 22q11.2 deletion region and interaction of the effects of hemizygosity with genetic variants both in the intact chromosome 22 and elsewhere in the genome.^{8,9} In families of probands with 22q11.2 deletions, an elevated prevalence of CHD in relatives without 22q11.2 deletions would support this hypothesis of genetic interaction. Two previous pediatric studies have suggested such an elevated prevalence of CHD.^{10,11} However these studies involved in total just 6 first-degree relatives with CHD and did not report on the parental origin of the 22q11.2 deletion. In the present study, a well-characterized group of adults with 22q11DS was examined for a family history of CHD in their relatives without 22q11.2 deletions. We tested the hypothesis that a positive family history of CHD would be more common in the probands with CHD. We also predicted that CHD would segregate with the intact chromosome 22 in the families, consistent with the potential importance of variants in the 22q11.2 deletion region to CHD expression.^{8,9}

Methods

Patients monitored at our clinic for adults (>17 years) with 22q11DS (n = 131) were available for study. Those with 22q11.2 deletions who were adopted (n = 4), had an inadequate family history (n = 12), or were family members of probands (n = 11) were excluded. Most subjects were ascertained because of the presence of CHD or a psychiatric disorder.¹² The probands and their parents provided written informed consent. The research ethics boards of the University of Toronto, Centre for Addiction and Mental Health and University Health Network approved the study.

We evaluated 104 probands with the 22q11.2 deletion, all of whom had met the clinical criteria for 22q11DS¹³ and had lifetime clinical data available, including cardiac assessments.² All probands with 22q11DS had echocardiograms and/or cardiac catheterization findings available to evaluate their cardiac status. CHD was classified by structural complexity, as previously described.^{14,15} Among probands with 22q11DS in the present series, major CHD included TOF, pulmonary atresia, or an absent pulmonary valve. Simple CHD included ventricular septal defects, or atrial septal defects.¹⁴ The ethnicity of the sample was 90% white (n = 94), 4% Asian (n = 4), 2% black (n = 2), and 4% other (n = 4).

A comprehensive family history was obtained from multiple interviews with all families, and pedigrees were constructed to include the first- to third-degree relatives. A history of CHD in the relatives was confirmed by medical record review where possible. To avoid a falsely elevated recurrence rate of CHD, a history of heart murmurs or cardiac conditions that were detected later in life were not considered CHD. All available parents of probands underwent assessment for the clinical features suggestive of 22q11DS.¹² Potential syndromal features in other relatives with CHD were determined by history or direct clinical assessment, as possible. The relatives with CHD who were confirmed (n = 8; 6 children, 1 mother, and 1 sibling) to have microdeletion 22q11.2 or were suspected (n = 6; 5 siblings and 1 uncle) to have microdeletion 22q11.2, according to the presence of syndromal features or when the 22q11.2 deletion status of one or both parents was unavailable, were excluded.

Genetic testing for syndromes other than for 22q11DS and for karyotypic anomalies was not performed.

The 22q11.2 microdeletion was confirmed in all probands by standard fluorescence in situ hybridization techniques using a TUPLE 1 (Vysis, Inc., Abbott Park, Illinois) or N25 (Oncor, Inc., Gaithersburg, Maryland) probe.¹⁶ Once the 22q11.2 deletion was confirmed in the proband, testing was offered to all available parents. For a study of the copy number variation in 22q11DS, DNA samples from 99 subjects (probands) with 22q11DS and 122 unaffected parents were genotyped for approximately 250,000 single nucleotide polymorphisms with the Affymetrix Gene CHIP Human mapping 250K NspI Array (Affymetrix Inc., Santa Clara, California), as previously described.¹² These data were used to determine the mode of 22q11.2 deletion and the parental origin of the de novo deletions, as well as the copy number variant (CNV) content. The mode of the 22q11.2 deletion within the cohort was confirmed to be de novo in 70 probands and transmitted in 5 probands. In cases in which parental DNA was unavailable for genotypic study, we assigned a “probable de novo” (n = 14) or “probable transmitted” (n = 2) deletion status according to the clinical features.¹² We had 13 probands for whom the origin of the 22q11.2 deletion could not be determined.¹² Among the probands with confirmed or probable de novo 22q11.2 deletions, the parental origin of the 22q11.2 deletion was determined for 74 probands, of whom 42 were of maternal origin. In the confirmed or probable transmitted group (n = 7), parental origin was maternal in 4 cases.¹²

All statistical analyses were performed using Statistical Package for Social Sciences, version 11.5 (SPSS, Chicago, Illinois) and Statistical Analysis Systems, version 9.13 (SAS Institute, Cary, North Carolina). The chi-square or 2-tailed Fisher exact test was used to compare the categorical variables. The comparisons with the general population prevalence of any CHD (0.58%) or severe CHD (0.061%) used the data derived from combined numbers for adults and children in a large Canadian study.¹⁷

Results

Of the 104 probands with 22q11DS in the present study (48 men and 56 women, mean age 33.3 ± 10.3 years), 66 (63.5%) had CHD (23 with simple CHD and 43 with major CHD). The presence of CHD in the proband was not significantly associated with the parental origin of the 22q11.2 deletion for either the de novo (maternal 29 of 42 [69%] vs paternal 17 of 32 [53%], $p = 0.16$) or transmitted (maternal 2 of 4 [50%] vs paternal 3 of 3 [100%], $p = 0.43$) groups. In addition, the probands with CHD did not exhibit de novo CNVs or any excess of novel inherited CNVs outside the 22q11.2 region (data not shown).¹²

A total of 2,639 relatives were included in the present study, with a median of 23 relatives per proband (range 10 to 64 relatives). A total of 14 probands (13.5%), 9 with confirmed and 5 with probable de novo 22q11.2 deletions, had a positive family history of CHD of various types in a total of 17 relatives (0.64%; Table 1).

The overall prevalence of CHD in the relatives of 22q11DS probands (0.64%) was similar to that of the general population for any CHD (0.58%, $p = 0.8$).¹⁷ However, probands with

22q11DS who themselves had CHD were more likely to have relatives with any CHD than were probands with no CHD (15 of 1,663 [0.9%] vs 2 of 976 [0.2%], $p = 0.041$, odds ratio [OR] 4.43, 95% confidence interval [CI] 1.03 to 40.00). In addition, 6 (40%) of the 15 relatives of the 22q11DS probands with CHD had severe and/or cyanotic CHD, significantly greater than the general population prevalence¹⁷ (0.36% [6 of 1,663] vs 0.061%, OR 5.88, 95% CI 2.16 to 12.85, $p = 0.007$). Of 11 second- and third-degree relatives with CHD, 8 (73%) were maternal relatives (Table 1). In contrast to our prediction, no apparent relation was seen between the familial side (maternal or paternal) of the affected relative and that of the intact chromosome 22 (Table 1).

Table 2 lists the recurrence risk for CHD in the first- to third-degree relatives of 104 22q11DS probands in our cohort and comparable data from another study of 108 probands with 22q11DS that reported nonsyndromic CHD in the first-degree relatives.¹⁰ The recurrence risks for first-degree relatives using the combined data for 22q11DS ($n = 212$ probands) and for relatives of a pediatric sample of 97 nonsyndromic patients with TOF with no 22q11.2 deletions¹⁸ are also included for comparison purposes (Table 2). Our data suggested a greater prevalence of CHD in the aunts and uncles of 66 probands with 22q11DS and CHD than in the comparable relatives of probands with nonsyndromic forms of TOF (8 of 439 [1.82%] vs 1 of 572 [0.17%], OR 10.60, 95% CI 1.41 to 471.01, $p = 0.013$). Comparing only probands with TOF, we still found a greater prevalence of CHD among aunts and uncles of the 43 probands in our sample than in the comparable relatives of those with non-syndromic TOF (6 of 258 [2.33%] vs 1 of 572 [0.17%], OR 13.60, 95% CI 1.63 to 626.30, $p = 0.004$).

Discussion

The present study investigated the presence of CHD in families of adult probands with 22q11DS. We found that the relatives of those with 22q11DS, who did not themselves have microdeletion 22q11.2, appeared to have an increased risk of CHD if the proband with 22q11DS also had CHD. As with CHD in 22q11DS^{6,10} and consistent with the data from a previous family study,¹⁰ the recurrent CHD in relatives tended to involve severe or complex defects. The prevalence of these major CHD lesions in relatives was significantly elevated compared to the population estimates for severe CHD.¹⁷ Collectively, these results support a heritable susceptibility to CHD in these families, in addition to the susceptibility imparted by the microdeletion 22q11.2.

The specific origins of this increased susceptibility remain unclear, but our results suggest they might be related to the factors that contribute to the expression of CHD in the proband with the 22q11.2 deletion. The genes on the intact chromosome 22q11.2, such as *TBX1*, have been shown to play a role in the expression of CHD in animal models and humans.^{9,19–21} Our findings, however, suggest that factors outside of the 22q11.2 region could also be involved in risk of CHD. Four of the relatives with CHD were not from the known side (paternal or maternal) of the intact chromosome 22 in the probands and four had, at most, a 50% chance of sharing the same chromosome 22 (Table 1). Using the results from our previous study of genome-wide CNVs in this cohort of patients with 22q11DS,¹² in which CNVs of about 30 kb could be detected, we did not identify any novel CNVs in the

probands that could explain the observed familial CHD susceptibility. However, the possibility exists that newer technologies with improved resolution could identify such CNVs. The results from adequately powered genome-wide studies might identify modifier variants that increase the risk of CHD expression in the presence of a 22q11.2 deletion.

The greater prevalence of CHD in the second-degree compared to the first-degree relatives in our CHD subgroup was an interesting finding. Compared to recurrence data for nonsyndromic TOF, which is thought to have a multifactorial etiology,²² the level of elevated risk of CHD in our cohort was considerably greater than has previously been reported for second-degree relatives.^{18,23} This might in part be explained by the ability to ascertain additional relatives (nieces and nephews), conferred by examining an adult sample. However, the results for comparable numbers of aunts and uncles showed a significantly greater risk for the 22q11DS group. Consistent with the published data implicating a somewhat greater role for maternal than paternal inheritance of a susceptibility to CHD,^{18,23,24} we found that most affected second- and third-degree relatives in our series were maternal. These findings might have been related to a better knowledge of maternal than paternal relatives but could also suggest a potential role for genes on the X chromosome. Although the finding of no parents with CHD could be explained by a survival disadvantage of older parents in our sample, the relatively low recurrence in the siblings of those with 22q11DS was more difficult to account for. It is possible that the exclusion of 5 siblings with CHD but with an unknown 22q11.2 deletion status was overly conservative. Alternatively, this pattern of results might suggest that additive genetic effects are more likely than dominant Mendelian inheritance, with reduced penetrance in the expression of CHD in these families. Also, there were relatively low numbers of siblings in the comparison studies used.^{10,18}

Among the children of probands with 22q11DS, the recurrence risk of CHD appeared to be greatly elevated, even without the transmission of deletion 22q11.2. The numbers were small; however, assortative mating is an important consideration. For example, the child of proband 1 in our sample with confirmed absence of the 22q11.2 deletion but with CHD and developmental delay could represent such an effect (Table 1).

The results combining our sample with that from Digilio et al¹⁰ indicated that overall the risk of familial recurrence of CHD among unaffected relatives of those with 22q11DS appears similar to the recurrence among relatives of subjects with TOF but without a 22q11.2 deletion¹⁸ (Table 2). This finding has important implications for the genetic counseling of patients with 22q11DS. Beyond the 50% risk of transmitting the 22q11.2 deletion and the elevated risk of CHD associated with the deletion, the relatives who do not have deletion 22q11.2 might still have an increased risk of CHD compared to the general population expectations, especially for severe disease. The potential for an elevated risk of complex cardiac disease in relatives without deletion 22q11.2 warrants additional investigation.

The present study is the first to investigate CHD not associated with 22q11.2 deletions in the second- and third-degree relatives of 22q11DS probands and the first to report a significant finding of elevated recurrence risk of severe CHD. The data available for the parental origin

of the 22q11.2 deletion¹² allowed us to consider whether the intact chromosome 22q11.2 appeared to be a factor with respect to the presence of CHD in the relatives. The study was adequately powered to detect significant differences in familial recurrence between the 22q11DS probands with and without CHD, although the large CIs indicated the need for caution in the interpretation. Our sample size was also sufficient to show significant results for severe CHD compared to the data from a large population study.¹⁷ The consistency with the results from other studies supports the overall findings.^{10,18}

The information on the family history of CHD was obtained in multiple personal interviews with the families and substantiated where possible by a review of the clinical data. Nonetheless, we were unable to determine a definitive CHD diagnosis in every reported case of recurrence. Ideally, neonatal echocardiographic data would have been available for all 2,639 relatives. Subclinical CHD is unlikely to be detected by the family history. Also, the recall bias in family history taking would be more likely to result in underreporting than in overreporting. Collectively, these factors suggest the true prevalence of CHD in relatives is likely greater than we have reported. The effects of these limitations would have been minimized, however, for severe CHD. In contrast, for children of probands with 22q11DS, the small numbers and possible effects of assortative mating between the proband and coparent might have magnified the recurrence risk of CHD. The cohort effects must also be considered. The contemporary general population prevalence study used for comparison¹⁷ included only living subjects and would have reflected improved survival compared to previous generations. Our study reported on both living and deceased relatives. Arguably, 4 of the 5 deceased relatives with severe CHD in our study (3 children and 1 adult born in the 1940s to 1950s) might have survived if born in more recent decades. Also, genetic testing for the 22q11.2 deletion was not available for all relatives with CHD. This could have contributed to a lower recurrence risk, because we excluded the affected relatives with CHD who had syndromal features but an unknown deletion status.

A difference from other family studies that warrants consideration was that the probands with CHD and 22q11DS represented a sample with enhanced genetic homogeneity. The samples of other probands with CHD were etiologically heterogeneous, with discoveries of major causal factors emerging.^{25–27} Future studies promise to identify the interacting variants that contribute to the variable expression of 22q11.2 deletions and other high penetrance mutations that affect cardiac development.

Acknowledgments

The authors thank the patients and their families for their participation, Chantal Morel, MD for medical genetics input, Cristina Digilio, MD for unpublished data, and the staff and students at our Clinical Genetics Research Program and staff at the Toronto Congenital Cardiac Centre for Adults for their assistance.

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Details of congenital heart disease (CHD) in 17 relatives of 14 adult 22q11.2 deletion syndrome (22q11DS) probands with confirmed or probable de novo 22q11.2 deletions

Table 1

Proband				Relative(s)							
Pt. No.	22q11.2 Deletion			CHD in Proband	Relative	Degree of Relation	CHD in Relative	Severe CHD	Syndromal Features	Absence of 22q11.2 Deletion*	Relative on Same Family Side as Intact Chromosome 22
Length (Mb)	Confirmed or Probable De Novo	Parental Origin									
1	3	Probable	—	0	Child	First	CHD unspecified	—	Developmental delay	Confirmed	—
2	3	Confirmed	Maternal	0	Sibling	First	PDA	0	0	Presumed	—
3	3	Confirmed	—	TA	Sibling	First	VSD	0	0	Confirmed	—
4	3	Probable	—	VSD	Nephew	Second	CHD unspecified	—	0	Confirmed	—
5	3	Probable	—	TOF	Niece	Second	VSD not requiring surgery	0	0	Presumed	—
6	3	Confirmed	Paternal	TOF	Nephew	Second	D-TGA	—	0	Confirmed	—
6					Maternal aunt	Second	CHD unspecified "blue baby," died at 1 y	—	0	Presumed	+ [†]
7	3	Confirmed	Maternal	PA/VSD	Maternal aunt	Second	PDA, repaired at 8 y	0	0	Presumed	0
8	3	Confirmed	Maternal	TOF	Maternal aunt	Second	TOF, died at 18 mo without repair	+	0	Presumed	0
9	1.5	Confirmed	Maternal	TOF	Maternal aunt	Second	"Hole in heart," detected in pregnancy	0	0	Presumed	0
10	3	Confirmed	Paternal	VSD, ASD	Maternal uncle	Second	2 "holes in heart," repaired at 12 y	0	0	Presumed	+ [†]
11	3	Confirmed	Maternal	TOF	Paternal uncle	Second	"Hole in heart" not requiring surgery	0	0	Presumed	+ [†]
12	3	Probable	—	TOF	Maternal aunt	Second	CHD unspecified "blue baby," infant death	+	0	Presumed	—
12					Maternal uncle	Second	CHD unspecified cyanotic, died at 38 y	+	0	Presumed	—

Proband				Relative(s)						
Pt. No.	22q11.2 Deletion		CHD in Proband	Relative	Degree of Relation	CHD in Relative	Severe CHD	Syndromal Features	Absence of 22q11.2 Deletion*	Relative on Same Family Side as Intact Chromosome 22
	Length (Mb)	Confirmed or Probable De Novo								
13	3	Confirmed	Paternal	Paternal first cousin	Third	CHD unspecified, died at 9 y "Hole in heart"	+	0	Presumed	0
13				Maternal first cousin	Third		0	0	Presumed	+ [‡]
14	—	Probable	—	Paternal first cousin	Third	"Hole in heart," early childhood repair	0	0	Presumed	—

* Confirmed indicated direct testing using standard fluorescence in situ hybridization and 22q11.2 probe (n = 4); presumed indicated both parents of proband negative for 22q11.2 deletion (n = 9) and/or without features of 22q11DS (n = 4).

[‡] Even if the affected relative was on the same side as the origin of the intact chromosome 22 in the proband, the chance (in the case of an aunt/uncle) of sharing that intact chromosome 22 would be at most 50%.

ASD = atrial septal defect; PA = pulmonary atresia; TA = truncus arteriosus; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

Table 2

Recurrence risk figures for congenital heart disease (CHD) in relatives (no 22q11.2 deletion) of adult probands with 22q11.2 deletion syndrome (22q11DS) and in comparison studies

	22q11DS Family Studies									
	Present Study					Digilio et al ^{10*}				
	104 (total cohort)	66 (subgroup with CHD)	33 ± 10	32 ± 10	108	212	NA	NA	97	6.5
Probands (n)	104 (total cohort)	66 (subgroup with CHD)	33 ± 10	32 ± 10	108	212	NA	NA	97	6.5
Average proband age (years)	33 ± 10	32 ± 10	32 ± 10	32 ± 10	108	212	NA	NA	97	6.5
Relation of Relatives	CHD/Total (n)	Risk (%)	CHD/Total (n)	Risk (%)	CHD/Total (n)	Risk (%)	CHD/Total (n)	Risk (%)	CHD/Total (n)	Risk (%)
First degree	3/405	0.74	1/257	0.39	5/253	1.98	8/658 [‡]	1.22 [‡]	4/290	1.38
Parents	0/201	—	0/127	—	1/198 [§]	0.51	1/399	0.25	1/194	0.52
Siblings	2/192	1.04	1/122	0.82	3/54	5.56	5/246	2.03	3/96	3.13
Children	1/12	8.33	0/8	—	1/1 [‡]	—	2/13 [‡]	15.38 [‡]	—	—
Second degree	11/1276	0.86	11/806	1.36	NA	NA	—	—	2/960	0.21
Grandparents	0/416	—	0/264	—	—	—	—	—	1/388	0.26
Aunts/uncles	8/666	1.20	8/439	1.82	—	—	—	—	1/572	0.17
Nieces/nephews	3/145	2.07	3/85	3.53	—	—	—	—	—	—
Half siblings	0/49	—	0/18	—	—	—	—	—	—	—
First cousins	3/958	0.31	3/600	0.50	NA	NA	—	—	6/936	0.64

^{*} Study of nonsyndromic CHD in 253 first-degree relatives of 108 probands with deletion 22q11.2 (88 probands [81.5%] with CHD).¹⁰

[‡] Study of recurrence of CHD in relatives of 97 nonsyndromic probands with TOF without 22q11.2 deletion.¹⁸

[§] Eighteen parents with deletion 22q11.2 excluded.¹⁰

[§] In the study by Digilio et al.¹⁰ only 1 of the 253 first-degree relatives studied was a child of a proband (Cristina Digilio, MD, personal communication, 2010).

NA = not available.