Patterns of Recurrence of Congenital Heart Disease
An Analysis of 6,640 Consecutive Pregnancies Evaluated by Detailed Fetal Echocardiography
Harinder K. Gill, MSc, MRCP,* Miranda Splitt, MD, MRCP,* Gurleen K. Sharland, MD, FRCP,† John M. Simpson, MD, MRCP†

OBJECTIVES
We sought to investigate the pattern of recurrence of congenital heart disease (CHD) where there is one or more affected first-degree relative.

BACKGROUND
There are little data on patterns of recurrence of different types of CHD. Analysis of a fetal series allows a high ascertainment of affected cases.

METHODS
We performed an analysis of referrals for detailed fetal echocardiography to a tertiary fetal cardiology unit, where there was a first-degree family history of CHD from 1990 to the end of 1999. Data were entered prospectively on a computerized database. Recurrences were exactly concordant if CHD was identical to the index case, and concordant for the group if belonging to a similar group of CHD.

RESULTS
A recurrence of CHD was seen in 178 (2.7%) of 6,640 pregnancies. The referral numbers for sibling, maternal, or paternal CHD cases were 5,151, 1,119, and 370, respectively. Exact concordance was seen in 37% of cases (range 0% to 80%), and group concordance was seen in 44%. In families where there were two or more recurrences, the exact concordance rate was 55%. Exact concordance rates were particularly high for isolated atrioventricular septal defects (4 of 5 [80%]) and laterality defects (7 of 11 [64%]).

CONCLUSIONS
The concordance rates of different types of CHD vary widely. Accurate diagnosis of the index case is essential for reliable counseling on patterns of recurrence. Minor CHD in the index case does not exclude more severe disease in recurrences. There appears to be significant under-referral for fetal echocardiography in paternal CHD.

Early studies of familial recurrence of CHD suggested either polygenic or multifactorial inheritance (2). The recurrence risk for first-degree relatives was found to be between 2% and 5%, which corresponds to the mathematical prediction expected from the polygenic threshold model. More recent studies report significantly higher recurrence risks than would be compatible with polygenic inheritance for specific cardiac lesions (3–5). Improved diagnostic and surgical techniques employed over the last 20 years have meant that children with CHD are now surviving to adulthood and parenthood. There are very little reliable data on the recurrence risk of CHD in offspring. In 1998, a U.K. multicenter, prospective study of adult survivors of CHD documented cardiac malformations in 15 (3.6%) of 393 live offspring (6). They suggested that recurrence risk was significantly higher if the affected parent was the mother. There are few large studies that look at the pattern of recurrent heart defects and the degree of concordance and discordance for different heart lesions within families.

The aim of this study was to document the pattern of recurrence of CHD in a large, prospective cohort of fetuses who had a first-degree relative with CHD. Examination of a fetal series ensures a high ascertainment of recurrences, by including pregnancies ending in termination or intrauterine death.

METHODS
Subjects. Study patients were drawn from mothers presenting for fetal echocardiography at a tertiary fetal cardiology center. We selected a 10-year period from January 1, 1990, to December 31, 1999. Relevant data on referral indication, family history, and pregnancy outcome were...
prospectively entered on a computerized data base (Filemaker Pro, V 2–4, Claris Corp., Santa Clara, California) throughout the study period. The database was used to select pregnancies at increased risk of CHD due to a family history of CHD. Pregnant women who had a first-degree relative with CHD were selected. Further information on pregnancies was obtained by examining the relevant case notes, postmortem records, and postnatal investigations. Even after a normal fetal echocardiogram, families were sent a follow-up questionnaire, returned at the age of six to eight weeks postnatally, which was obtained in over 95% of cases. The index case was defined as the affected individual who had prompted the referral. This was either the woman herself, the father, or a sibling of her current pregnancy. Any future affected pregnancy recorded for each mother was documented as being the first, second, or third recurrent case for each index case. Any affected relatives more distant than first-degree were not included in the detailed analysis.

Cardiac diagnoses. Echocardiographic studies were performed using Hewlett-Packard Ultrasound Systems, model Sonos 1000-5500 (Agilent Technologies, Andover, Massachusetts), or Toshiba, model Sonolayer SSA-270A (Toshiba, Zoetermeyer, The Netherlands). Studies were routinely recorded onto videotape throughout the study period. All studies were performed or reviewed by an attending fetal cardiologist.

Defects were broadly classified using the sequential segmental classification described by Tynan et al. (7). To facilitate analysis, this was abbreviated into the following 16 categories: hypoplastic left heart (HLH); coarctation of the aorta (CoA); aortic stenosis; pulmonary stenosis (PS); pulmonary atresia with intact ventricular septum (PA/IVS); tricuspid atresia; atrial septal defect; atroventricular septal defect (AVSD); ventricular septal defect (VSD); tetralogy of Fallot (TOF); pulmonary atresia with VSD (PA/VSD); common arterial trunk (CAT); transposition of the great arteries (TGA); laterality defect; total anomalous pulmonary venous drainage; complex structural defects i.e., structural defects that do not easily fit into the aforementioned classification; and “others” for miscellaneous CHD not fitting into any of these categories.

Defects in the index case and the first affected pregnancy were analyzed for concordance and discordance. The defect in the first affected pregnancy was described as exactly concordant if it was identical to that seen in the index case, and discordant for the group if the defect belonged to the same spectrum of CHD as seen in the index case. The major groups used were left heart lesions, right heart obstructive lesions, septal defects, outflow tract abnormalities, and laterality defects.

Genetics follow-up. As part of this study, we were granted ethical approval to contact families in which there had been a recurrence of CHD. The family general practitioner was contacted seeking consent to contact all families in which there had been a recurrence. Sixty-seven families agreed to participate and were reviewed by a clinical geneticist.

Exclusions. Affected cases due to chromosomal disorders, including fetal trisomies, were not included, because the heart defect was assumed to be secondary to the chromosomal abnormality. Some families were referred because of known genetic disorders (e.g., tuberous sclerosis) and were excluded. Cases were not excluded if a 22q11 deletion was detected in the pregnancy without such a family history before referral, and these are detailed in the Results section. In some fetuses, there was a suspicion of more minor CHD, particularly VSD on the fetal echocardiogram, which was not confirmed postnatally. For the purposes of our analysis, such “affected” cases were excluded, despite the fact that it might be argued that some of these fetuses had such defects in utero, which closed spontaneously.

RESULTS

During the study period, a total of 14,116 pregnancies were assessed by fetal echocardiography. In 7,933 (56%), the referral indication was a family history of CHD. After exclusion of second-degree or more distant relatives, the study group was restricted to 6,640 pregnancies where a first-degree relative was known to have CHD. Within this group, the index case was the mother in 1,119 cases (17%), the father in 370 (6%), and a sibling in 5,151 (77%). The median gestational age at referral was 20 weeks (range 14 to 36 weeks). In our cohort, CHD was diagnosed in 178 (2.7%) of 6,640 pregnancies. These 178 affected pregnancies were in 147 mothers (Table 1). One hundred twenty mothers had one affected pregnancy, 23 mothers had two affected pregnancies, and four mothers had three affected pregnancies. In 115 cases, the index and first recurrences were in sibling pairs, and in 32 cases, they were parent/child pairs. The incidence of CHD in pregnancies referred
because of sibling CHD was 138 (2.7%) of 5,151 (95% confidence interval [CI] 2.2% to 3.1%), 32 (2.9%) of 1,119 (95% CI 2.0% to 4.0%) for maternal CHD, and 8 (2.2%) of 370 (95% CI 0.9% to 4.2%) for paternal CHD.

**Maternal factors.** Six of 147 mothers with at least one recurrence had insulin-dependent diabetes mellitus and another three mothers developed gestational diabetes during the pregnancy. No other maternal illness or potentially teratogenic drugs were identified.

**Pregnancy outcome.** The pregnancy outcome until the end of the neonatal period was analyzed for all 178 affected pregnancies. A total of 58 (33%) of 178 pregnancies were lost in this period. Thirty-nine pregnancies were terminated, 6 resulted in intrauterine death, and 13 resulted in neonatal death.

**Recurrence pattern (Table 2).** This was analyzed for the index case and first affected case in 143 of the 147 cases; four index cases were excluded because no detail was available on the type of CHD in the index case. The overall exact concordance was 53 (37%) of 143, and group concordance was 67 (47%) of 143. The overall concordance was analyzed separately for families with one recurrence and those with more than one recurrence. Exact and group concordance rates for families with one recurrence were 33% and 43%, respectively. The concordance rates for families with two or more recurrences were 55% for exact concordance (p = 0.047) and 63% for group concordance.

**Left heart defects (Table 3).** Thirty-five index cases had a left heart defect. The exact concordance was 38% (3/8) for aortic stenosis, 33% (4/12) for HLH, and 13% (2/15) for CoA. Three of these 35 families had 10 affected cases (3 index cases, 7 recurrences) between them; all were left heart defects. One family had three affected siblings, all with HLH. The second family had three siblings, the first with HLH and the other two with recurrences had CoA. The third family had four affected pregnancies, three with HLH and one with CoA. Not surprisingly, all 12 of the HLH families consisted of sibling pairs, as HLH is a severe defect for which surgical palliation was unavailable in the past. Two of the 15 CoA families were parent/child pairs, and three of the aortic stenosis families were parent/child pairs, reflecting the milder nature of these defects as compared with HLH. Clustering of left heart defects in families has been seen in other studies (4,8). Maestri et al. (9,10) found that they could not rule out an autosomal recessive pattern of inheritance for this group of defects when testing mathematical models. Autosomal dominant transmission of left heart defects has also been described in some families (11).

**Septal defects (Table 4).** The exact concordance for this group was 80% (4/5) for AVSD, 55% (17/31) for VSD, and

### Table 2. Overall Concordance for Families With One, Two, or Three Recurrences

<table>
<thead>
<tr>
<th>No. of Recurrences</th>
<th>No. of Families</th>
<th>Total No. of Affected Pregnancies From Records</th>
<th>Group Concordance for Index and First Recurrence Case</th>
<th>Exact Concordance for Index and First Recurrence Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>116</td>
<td>116</td>
<td>50/116 (43%)</td>
<td>38/116 (33%)</td>
</tr>
<tr>
<td>Two or more</td>
<td>27</td>
<td>58</td>
<td>17/27 (63%)</td>
<td>15/27 (55%)</td>
</tr>
<tr>
<td>Total</td>
<td>143</td>
<td>174</td>
<td>67/143 (47%)</td>
<td>53/143 (37%)</td>
</tr>
</tbody>
</table>

### Table 3. Recurrence Type Seen Where the Index Case Has a Left Heart Defect

<table>
<thead>
<tr>
<th>Index Case</th>
<th>First Recurrence (n)</th>
<th>Second Recurrence (n)</th>
<th>Third Recurrence (n)</th>
<th>Total Recurrence Cases (n)</th>
<th>Group Concordance</th>
<th>Exact Concordance</th>
<th>Parent/Child Pairs-Sibling Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLH (n = 12)</td>
<td>HLH: 4 CoA: 2</td>
<td>VSD: 5 TAPVD: 1 CoA: 2</td>
<td>HLH: 1 Coa: 2</td>
<td>16</td>
<td>Left heart defects: 6/12</td>
<td>HLH: 4/12</td>
<td>0:12</td>
</tr>
<tr>
<td>AS (n = 8)</td>
<td>AS: 3</td>
<td>HLH: 2 PS: 1 TA: 1 Complex: 1</td>
<td>AS: 3</td>
<td>8</td>
<td>Left heart defects: 5/8</td>
<td>AS: 3/8</td>
<td>3:5</td>
</tr>
<tr>
<td>Total (n = 35)</td>
<td>35</td>
<td>3</td>
<td>1</td>
<td>39</td>
<td>16/35 (46%)</td>
<td>9/35 (26%)</td>
<td>5:28</td>
</tr>
</tbody>
</table>

*Concordance is calculated using first recurrence data.

AS = aortic stenosis; AVSD = atrioventricular septal defect; CoA = coarctation of the aorta; Complex = complex heart defect; HLH = hypoplastic left heart; PS = pulmonary stenosis; TA = tricuspid atresia; TAPVD = total anomalous pulmonary venous drainage; TGA = transposition of the great arteries; VSD = ventricular septal defect.
The concordance for AVSD is strikingly high, and this is in keeping with previous studies. Digilio et al. (12) found that the type of heart defect in first-degree relatives of individuals with AVSD was exactly concordant in 6 (75%) of 8. Isolated AVSD has been recognized in some families, conforming to an autosomal dominant pattern of inheritance with incomplete penetrance, and so far, one locus has been mapped (13–15). The discordant defects seen for VSD are highly variable in type and severity.

Outflow tract defects (Table 5). Exact concordance rates for this group were 60% (3 of 5) for CAT, 43% (3 of 7) for TOF, 25% (1 of 4) for TGA, and 0% (0 of 3) for PA/VSD. Two families with CAT consisted of three siblings each, all of whom had isolated CAT and normal karyotypes, consistent with an autosomal recessive mode of inheritance. A third family with a concordant sibling pair has been diagnosed as having the 22q11 microdeletion syndrome after the birth of the second affected child (discussed later). Digilio et al. (16) reported a consanguineous family in which two double first cousins had outflow tract defects and were not deleted for 22q11, supporting the likely monogenic inheritance of outflow tract abnormalities in some 22q11 deletion-negative families. The same group report an exact concordance of 8% (1 of 12) for simple TGA, similar to that seen in this study, although our numbers are low (17).

Right heart obstruction. Two families had a recurrence of CHD following a diagnosis of PA/IVS in the index case. The recurring lesions were PA/IVS (n = 1) and TOF (n = 1). Pulmonary valve stenosis was diagnosed in seven

Table 4. Recurrence Type Seen When the Index Case Has a Septal Defect

<table>
<thead>
<tr>
<th>Index Case</th>
<th>First Recurrence (n)</th>
<th>Second Recurrence (n)</th>
<th>Third Recurrence (n)</th>
<th>Total Recurrence Cases (n)</th>
<th>Group Concordance</th>
<th>Exact Concordance</th>
<th>Parent/Child Pairs:Sibling Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD (n = 31)</td>
<td>VSD: 17</td>
<td>HLA: 3</td>
<td>CoA: 3</td>
<td>PDA: 2</td>
<td>TOF: 1</td>
<td>ASD: 1</td>
<td>T: 1</td>
</tr>
<tr>
<td>ASD (n = 8)</td>
<td>VSD: 4</td>
<td>TOF: 1</td>
<td>Rhabdo: 1</td>
<td>Complex: 1</td>
<td>CoA: 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVSD (n = 5)</td>
<td>AVSD: 4</td>
<td>TOF: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>8</td>
<td>1</td>
<td>53</td>
<td>26/44 (60%)</td>
<td>21/44 (48%)</td>
<td>15:29</td>
</tr>
</tbody>
</table>

*Concordance is calculated using first recurrence data. †Indicates a recurrence case in whom a 22q11 deletion has been found.

ASD = atrial septal defect; PA/IVS = pulmonary atresia with intact ventricular septum; PDA = patent ductus arteriosus; Rhabdo = cardiac rhabdomyoma; TOF = tetralogy of Fallot; other abbreviations as in Table 3.

Table 5. Recurrence Type Seen When the Index Case Has an Outflow Tract Defect

<table>
<thead>
<tr>
<th>Index Case</th>
<th>First Recurrence (n)</th>
<th>Second Recurrence (n)</th>
<th>Third Recurrence (n)</th>
<th>Total Recurrence Cases (n)</th>
<th>Group Concordance</th>
<th>Exact Concordance</th>
<th>Parent/Child Pairs:Sibling Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF (n = 7)</td>
<td>TOF: 3</td>
<td>VSD: 1</td>
<td>PA/VSD: 1</td>
<td>ASD: 1</td>
<td>Complex: 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAT (n = 5)</td>
<td>CAT: 3†</td>
<td>TGA: 1</td>
<td>HLH: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGA (n = 4)</td>
<td>TGA: 1</td>
<td>VSD: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA/VSD (n = 3)</td>
<td>VSD: 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>5</td>
<td>0</td>
<td>24</td>
<td>9/19 (47%)</td>
<td>7/19 (37%)</td>
<td>2:17</td>
</tr>
</tbody>
</table>

*Concordance is calculated using first recurrence data. †Indicates a recurrence case where a 22q11 deletion has been found.

CAT = common arterial trunk; PA/VSD = pulmonary atresia with ventricular septal defect; other abbreviations as in Tables 3 and 4.
index cases, and the recurrence lesions were pulmonary valve stenosis (n = 5) and VSD (n = 2). The high concordance rate of 71% (5 of 7) is partly accounted for by two sisters who have had three affected pregnancies each. Following subsequent clinical genetics assessment, both sisters have mild PS, which was previously undiagnosed. No syndromic diagnosis was apparent in the family after genetics assessment. Autosomal dominant families with PS have been previously reported (18), and mutations in the Alagille syndrome gene, Jagged 1, have been found in a child and her mother with isolated PS with no signs of Alagille syndrome (19). These individuals belonged to a family with a four-generation history of PS.

**Laterality defects.** For this study, a laterality defect is defined as any heart defect that has occurred with an abnormality in the normal positioning of the unpaired or paired asymmetric structures in the body (i.e., with heterotaxy or isomerism). There were 11 families with recurrences following a diagnosis of isomerism in the index case. Seven of the 11 recurrences seen in this group were laterality defects (64%), but the other recurrences were VSD (n = 2), TGA (n = 1), and congenitally corrected TGA (n = 1). Two families have had two recurrences of laterality defects. Four of these families were evaluated by a clinical geneticist, and in three of these families, evidence of a laterality disturbance was found in one parent, suggesting autosomal dominant inheritance with incomplete penetrance. Autosomal dominant, recessive, and gender–linked inheritance have been described in such families previously (20–22). Two loci for autosomal dominant families have been mapped (23,24).

**Complex structural heart defects and other groups.** There were 25 pregnancies with small numbers of affected index cases and recurrences. Dilated cardiomyopathy occurred in one of four families in which this was the index condition. In the remaining groups, the numbers of affected cases were low and therefore difficult to analyze.

**22q11 microdeletion syndrome.** Three of the first recurrence cases were found to have a 22q11 microdeletion that was thought to be responsible for the CHD and other extracardiac anomalies seen in these individuals. In one of these families, the affected case had VSD and learning difficulties.

**Further genetics assessment.** Sixty-seven of the families have had a clinical genetics assessment, including a detailed family tree, examination of affected family members, and any relevant investigations. Known syndromic causes of CHD have been excluded in all but one of these families, in which a newly diagnosed syndrome has been described (25).

In 15 (22%) of 67 of these families further affected first-, second-, or third-degree relatives of the index case have been diagnosed with CHD. These consisted of nine first-degree relatives, two second-degree relatives, and four third-degree relatives. Of the nine first-degree relatives, six were exactly concordant with the index case, concurring with the previous finding that the greater the number of affected relatives, the higher the degree of concordance (Table 2).

**DISCUSSION**

The observed incidence of CHD in pregnancies referred because of sibling CHD in our study (2.7%) is in line with that seen in a number of large population studies (2,4). There was a similar incidence of CHD for pregnancies referred because of maternal CHD (2.9%) or paternal CHD (2.2%). The observed incidence of CHD in pregnancies referred because of maternal CHD was lower than that seen in other studies (6), but ours was not a population-based study, and the incidences we present are not true recurrence risks. Our study population has been ascertained through referral to the fetal cardiology department and therefore will reflect biases in patterns of referral that vary between obstetricians and general practitioners. Where the parent is the index case, it is possible that the mother may not be referred for fetal cardiac assessment at all. Fewer pregnancies were referred where the father is the index case, compared with the mother as the index case. This is unlikely to be explained by better survival of females with CHD compared with males. It is more likely that the paternal history of CHD is simply not elicited in the assessment of the pregnancy. Four percent (6 of 147) of mothers who had at least one recurrence were insulin-dependent diabetics. The increased risk of CHD in the offspring of diabetic mothers is well recognized (26). Although the diabetic milieu is clearly a major contributory factor leading to fetal CHD, the underlying pathogenetic mechanism is not understood. It is likely that genetic factors also play a role in the increased susceptibility to CHD in these families.

When counseling a family who has had experience with a child or parent with CHD, one of the most frequently asked questions is the type of CHD that might recur. It is hoped that the data provided by this study may be helpful for counseling in this regard. Despite the overall exact concordance of 37% and the overall group concordance of 47%, it should be emphasized that some quite unexpected recurrences do occur and that the range for exact concordance is very wide (0% to 80%). Therefore, the precise subtype of defect is important when considering which types may recur. For example, isolated AVSD (with normal cardiac situs) has a concordance of 80% in our study and is also high in other studies (13,14). Atroventricular septal defects are often detected in the context of laterality disturbances, and confirmation of an abnormality of cardiac situs is essential. This is because of the high concordance of recurrences for laterality defects (64%), and the cardiac lesions associated with such defects are usually far more complex than an isolated AVSD, which affects the prognosis.

For the most common defect—VSD—exact concordance was 55%, but a very broad range of defects recurred, and the severity was highly variable. Thus, the finding of minor CHD in the index case does not exclude more severe disease in recurrences. Conversely, major CHD in the index case does not necessarily imply very severe CHD in recurring cases.
Previous studies have found slightly higher rates of exact concordance than ours. In a postnatal study, Corone et al. (27) reported exact concordance in 84 (47%) of 178 pairs of first-degree relatives. Interestingly, Corone et al. (27) saw an association between TOF, TGA, and VSD in their study before cytogenetic testing for 22q11 deletion syndrome was available. Families with this condition are therefore likely to account for this association in their data. We do not see such an association, as we excluded all families known to have this deletion before the birth of the recurrence case, leaving three families in which a 22q11 deletion was identified in the recurrence. Davison (28) looked at a small sample of 10 affected sibling pairs with a range of CHD: three were exactly concordant, three were concordant for the group of defect, and four pairs were discordant.

In our study, 23 mothers had two further recurrences and four mothers had three recurrences during the study period. Thus, 27 (18%) of 147 mothers had more than one recurrence. The finding of CHD in three or more first-degree relatives strongly suggests monogenic inheritance in these cases. The concordance for the index case and first recurrence in these mothers is higher than in the group that had only one further affected child (exact concordance 55% vs. 33%; group concordance 63% vs. 43%). However, even in these families in which there is strong evidence for monogenic inheritance, the type of heart defect is not always predictable; over 40% of index and first affected pregnancy cases were discordant.

In recent years, characterization of mutations affecting cardiovascular development in animal models has identified many key signaling molecules and transcriptional regulators of heart formation (29). At least one of these, the transcriptional regulator of cardiac gene expression, Nkx2.5, has been found to be mutated in patients with a diverse spectrum of nonsyndromic CHD (30,31). Genetic disorders have traditionally been divided into mendelian and multifactorial traits. In classic mendelian inheritance, the phenotype arises as a consequence of mutations in one (dominant) or both (recessive) copies of a gene. In contrast, multifactorial disorders are caused by a combination of multiple genetic polymorphisms and environmental factors. It is becoming increasingly apparent that many disorders exhibit complex inheritance, which falls into a category between these two (32). Within our cohort, there are families with multiple concordant heart lesions who exhibit classic autosomal dominant inheritance (e.g., 2 sisters with PS who had a total of 6 affected children between them) and classic autosomal recessive inheritance (2 families with 3 affected siblings with CAT). In the majority of cases, the genetics are likely to be more complex. A good example of this is laterality defects, for which there was a high but not complete degree of concordance. This high proportion may partly reflect ascertainment bias, as laterality defects are known to have a strong genetic basis; therefore, mothers are more likely to be referred for fetal echocardiography. The available evidence does not support straightforward mendelian inheritance in this condition. A significantly increased incidence of parental consanguinity suggests that at least some are the result of an autosomal recessive gene defect. However, segregation analysis in a highly inbred population showed a much lower than expected number of affected individuals (33). In addition, families showing apparent dominant inheritance with very low penetrance have been described (23,24). Recent studies in mice support the hypothesis that both copies of one gene (recessive) and one copy of a second gene (dominant) may be needed for full expression of the phenotype (34). This mode of inheritance has recently been shown to operate in the genetically heterogeneous condition of Bardet-Biedl syndrome (32). It is likely this or similar digenic models may apply to other types of CHD.

Sixty-seven of the mothers in the study had a detailed assessment by a clinical geneticist. In 15 (22%) of the 67 families, additional first-, second-, or third-degree relatives were found to have CHD, confirming the value of clinical genetics input. This adds weight to the theory that dominantly inherited susceptibility genes with incomplete penetrance are likely to be responsible for a high proportion of recurrences. Further genetic investigation of these families for mutations in candidate genes is likely to be fruitful and may lead to the isolation of key developmental genes. However, DNA samples from affected individuals in these families need to be stored prospectively in order for this strategy to be successful.

Acknowledgments

We thank all the families who agreed to participate in this study.

Reprint requests and correspondence: Dr. John M. Simpson, Consultant in Fetal and Paediatric Cardiology, Fetal Cardiology Unit, 15th Floor, Guy’s Hospital, London, United Kingdom SE1 9RT. E-mail: John.Simpson@gsst.sthames.nhs.uk.

REFERENCES


34. Oh SP, Li E. Gene-dosage-sensitive genetic interactions between inversus viscerum (iv), nodal, and activin type IIB receptor (ActRIIB) genes in asymmetrical patterning of the visceral organs along the left-right axis. Dev Dyn 2002;224:279–90.