

THE GENETICS OF HYPOPLASIA OF THE LEFT HEART

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Congenital heart disease affects 8 babies in every thousand born alive, and is one of the major causes of infant mortality and morbidity. At the time of diagnosis, the major issues for parents relate to survival and outcome. Sooner or later, however, they will have concerns regarding the aetiology of the cardiac defect. Establishing the aetiology of congenital malformations becomes extremely important when parents ask:

- “What caused it?”
- “Why did it happen to us?”
- “Will it happen again, either to us or to our children?”

These questions can be answered accurately only if the aetiologies are understood and clearly identified. The answers become especially important for “lethal” malformations, such as hypoplasia of the left heart, that carry high rates of morbidity and mortality. If there is potential for a genetic aetiology, then a significant risk of recurrence may influence future reproductive decisions of the parents.

It seems likely that hypoplasia of the left heart is aetiologically heterogeneous, with both environmental and heritable factors contributing to the phenotype. This chapter discusses the evidence that a proportion of individuals with hypoplasia of the left heart have a genetic aetiology, and the impact that this might have on them and their families.

EXISTING GENETIC EVIDENCE

There is an increase in the risk of recurrence of congenital heart disease in families where one individual has

hypoplasia of the left heart. For a couple who have had one child with a nonsyndromic congenital cardiac malformation, the probability that it will happen again in a subsequent pregnancy, called sibling recurrence risk, is approximately 2% to 3%.¹ For parents of a child with hypoplasia of the left heart, the sibling risk of recurrence is significantly above the “population risk” of one in 5000 live births, and has been estimated to be as high as 13.5%,² although no large prospective studies have been reported.

Patterns of Inheritance of Hypoplasia of the Left Heart

Patterns of inheritance have been difficult to determine because of the severity of the phenotype, but available evidence suggests that there may be more than one pattern. Familial recurrence has been reported in consanguineous marriages with affected pairs of siblings, and this suggests an autosomal-recessive pattern.³ Autosomal-dominant inheritance has been suggested for nonsyndromic obstructive left-sided lesions,⁴ and there are reports of an increased incidence of valvular lesions in parents of children with the hypoplasia of the left heart. Brenner and colleagues⁵ found that one-eighth of children had one parent with a bicuspid aortic valve and/or aortic stenosis. This is consistent with an autosomal-dominant pattern of inheritance with a variable phenotype, as has been seen in other conditions such as the DiGeorge and Holt-Oram syndromes, both of which include cardiac malformations. Transmission of hypoplasia of the left heart from parents to offspring, however, has not been reported, although this may not be surprising for such a severe phenotype that was lethal prior to the advent of cardiopulmonary bypass

TABLE 4.1. Chromosomal abnormalities associated with hypoplasia of the left heart (HLH)

| <i>Chromosomal abnormality and birth incidence</i> | <i>% CHD in newborns</i> | <i>% HLH</i> |
|--|--------------------------|-------------------|
| 45,X (Turner syndrome) 1/5000 | 23% ¹² | 15% ¹² |
| 47,XX/XY+13 (Patau syndrome) 1/12,000 | 82% | |
| 47,XX/XY+18 (Edwards syndrome) 1/5000 | 85% | ~6% |
| 47,XX/XY+21 (Down syndrome) 1/650 | 40% | |
| 46,XX/XYdel(22)(q11) (DiGeorge syndrome) 1/4000 | ~60% | Low |
| 46,XX/XYdel(11)q | 65% | 13% |

CHD, congenital heart disease.

surgery. The observation of Brenner and colleagues,⁵ nonetheless, raises the possibility that an autosomal-dominant gene exists that is associated with a much wider phenotype.

Specific Chromosomal Abnormalities are Associated with Hypoplasia of the Left Heart

Chromosomal analysis of individuals with hypoplasia of the left heart usually proves normal, although several associated chromosomal anomalies have been specifically reported (Table 4.1). Of these the most notable are Turner's syndrome, or 45,X, and the common trisomies of chromosomes 13, 18, and 21.

As recorded in the human cytogenetics database,⁶ one-eighth of all 11q23 deletions have hypoplasia of the left heart, and an additional one-tenth have mitral stenosis, which may represent the mild end of a left-sided obstructive phenotype. Computational analyses of the material contained within this database, calculating the association of single congenital malformations with cytogenetic regions, revealed that 11q23 has a very significant association with hypoplasia of the left heart.^{7,8} This was confirmed independently,⁸ and more recently a critical region was defined within 11q25 by investigating overlapping deletions of different sizes in 3 children with hypoplasia of the left heart.⁹ This approach has narrowed the gene or genes causing the cardiac defect to within the terminal 8 megabases of 11q25.

Hypoplasia of the Left Heart Occur as Part of Genetically Determined Syndromes

Hypoplasia of the left heart has been reported as part of several other syndromes (Table 4.2), and they may have important implications for prognosis. In this context, it is important to define the term "syndrome" as a recognisable pattern of malformations or disease that typically affects multiple systems of organs or tissues. Although hypoplasia of the left heart is fre-

quently referred to as "hypoplastic left heart syndrome," in the strictest sense it represents maldevelopment of only one organ, namely the heart, and therefore should be grouped as a nonsyndromic cardiac malformation.

Although most of the syndromes listed in Table 4.2 are clinically distinct and easily recognisable, this may not be the case if hypoplasia of the left heart is diagnosed prenatally. The aetiological basis for some of these syndromes has yet to be determined. For others, specific genes have already been implicated, such as *TBX5* with Holt-Oram syndrome, and *CRB* (CRE binding protein gene) with Rubinstein-Taybi syndrome. This is further proof that the phenotypes making up hypoplasia of the left heart can result from mutations in more than 1 gene.

Animal Models of Human Disease

The advent of transgenic technology in animals, particularly in mice, in which targeted genes may be either switched off or overexpressed, has provided significant insight into the molecular mechanisms of congenital malformations. Over the past 10 years, many genes have been disrupted. The resulting murine phenotypes include those with cardiac defects resembling or identical to those in humans. This is not surprising, given the similarities in mammalian embryonic development. The challenge will be to use these clues to determine the genes in which dysfunction or mutation causes cardiac malformations in humans.

PRACTICAL CLINICAL IMPLICATIONS

Whilst the investigation of the genetic basis of hypoplasia of the left heart is intellectually challenging, what are the implications for the parents and family of a child? The need for evidence to answer the many questions arising at the time of diagnosis is great. In addition, as rates of survival improve for children treated surgically, attention to factors influencing the quality of life increases.

TABLE 4.2. Syndromes and the Online Mendelian Inheritance in Man (OMIM) number for each, in which hypoplasia of the left heart has been described (number of reported cases, where known); main clinical features, mode of inheritance, locus to which the syndrome maps, and the causative gene are tabulated

| | | | | |
|--|--|---|---------------------|--------------------|
| Holt-Oram syndrome 142900 | Symmetrical radial ray abnormalities | Natowicz et al. 1988 ¹³ | Dominant | 12q21 <i>TBX5</i> |
| Smith-Lemli-Opitz syndrome (4) 270400 | Genital abnormalities, learning disability | Natowicz et al. 1988 ¹³ | Recessive | 7q32.1 |
| Ellis-van Creveld syndrome 225500 | Postaxial polydactyly, skeletal abnormalities | Schinzel 1983 ⁶ | Recessive | 4p16 |
| Saldino-Noonan syndrome 263560 | Short ribs, polydactyly, skeletal abnormalities | Johnson et al. 1982 ¹⁴ | Recessive | |
| Apert syndrome (1) 101200 | Craniosynostosis, syndactyly | Natowicz et al. 1988 ¹³ | Dominant | 10q25 <i>FGFR2</i> |
| Cerebrocostomandibular syndrome (1) 117650 | Severe micrognathia and posterior "rib gap" | Kirk and Ades 1998 ¹⁵ | Recessive/dominant | |
| Beckwith syndrome 130650 | Overgrowth, macroglossia, abdominal wall defects | Greenwood et al. 1975 ¹⁶ | Dominant | 11p15 |
| CHARGE syndrome 214800 | Coloboma, choanal atresia, ear abnormalities, developmental delay, genital anomalies | Hall 1979, ¹⁷ Cryan et al. 1987 ¹⁸ | | |
| FG syndrome 305450 | X-linked mental retardation, macrocephaly, dysmorphism | | X-linked recessive | Xq12-21? |
| Day-Salvatore-McLean (1) | Skeletal abnormalities, blepharophimosis | Day-Salvatore and McLean 1998 ¹⁹ | | |
| Gianotti (2 sibs) 600460 | Cleft palate, genital anomalies, ectrodactyly | Gianotti et al. 1995 ²⁰ | Recessive | |
| Holzgreve 236110 | Renal agenesis, cleft palate, skeletal anomalies | Holzgreve 1984 ²¹ | | |
| Hurst | Leptomeningeal angiomas, absent olfactory tracts, clefts | Hurst et al. 1992 ²² | | |
| Kaufman (2 sibs) | Vertebral and renal anomalies | Kaufman et al. 1972 ²³ | Recessive | |
| Kennerknecht 202660 | Agonadism, multiple internal malformations | Kennerknecht et al. 1995 ²⁴ | Recessive | |
| McPherson-Clemens (2 sibs) 601165 | Cleft lip and palate, intestinal malrotation | Mc Pherson and Clemens 1996 ²⁵ | Recessive | |
| Medeira | Neural tube defect, cleft lip and palate, limb reduction | Medeira et al. 1994 ²⁶ | | |
| Neish-Roberts(2 sibs) | Nephromegaly, distinctive facies | Neish and Roberts 1992 ²⁷ | | |
| Short rib polydactyly syndrome type 3 | Small thorax, polydactyly | | Recessive | |
| SHORT syndrome 269880 | Rieger anomaly, short stature, characteristic facies | | Dominant, recessive | |
| X-linked cardiac valvular dysplasia 314400 | Congenital cardiac valve dysplasia | Newbury-Ecob et al. 1993 ²⁸ | X-linked recessive | |
| Rubinstein Taybi syndrome (3) 268600 | Distinctive facies, broad halluces and thumbs | Bartsch et al. 1999, ²⁹ Hannauer et al. 2002 ³⁰ | Dominant | 16p13 <i>CRB</i> |
| Toriello-Carey 217980 | Agenesis corpus callosum, Robin sequence, facial anomalies, hypotonia | Czarnecki et al. 1996 ³¹ | ? X-linked | |

Prenatal Diagnosis—Investigating the Cause and Prognosis of the Affected Fetus

Hypoplasia of the left heart, in some centres, can now be diagnosed prenatally in over nine-tenths of affected fetuses.¹⁰ Genetic advice regarding management of both the pregnancy and the parents is most important in this situation. Most centres offer fetal karyotypic analysis, along with detailed sonographic investigation to determine whether there are additional congenital malformations.¹¹

Fetal karyotypic analysis, usually obtained by sampling the amniotic fluid, may provide valuable information regarding the cause of the problem, and thus the prognosis and risk of recurrence in future pregnancies. In the series of Brackley et al.,¹¹ one-twentieth of cases that had karyotypic analysis had aneuploidy as the cause of the left-sided hypoplasia. If aneuploidy is the cause, the couple may be offered a low risk of recurrence, in addition to details about the general noncardiac prognosis.

Detailed fetal ultrasonic examination may also provide vital information. Apart from obvious implications for management, the presence and nature of additional extracardiac malformations might suggest a syndromic diagnosis, or arouse suspicion of a specific chromosomal abnormality prior to receiving the result of karyotypic analysis.

If no chromosomal abnormality is found, and sonography shows other structural malformations, how might this affect fetal prognosis, and long-term outcome? Brackley et al.¹¹ studied a series of cases diagnosed prenatally, and reported that the frequency of additional congenital anomalies was increased above that in the general population, although insufficient longitudinal data were available to provide prognostic advice.

If a chromosomal abnormality is not visible, and the sonographic scan is normal, what are the chances that a syndromic diagnosis will be made postnatally, with implications for the health of the child? In our own detailed clinical study, we assessed 44 infants and children with normal chromosomes and no additional anomalies. None of these had a recognised syndromic diagnosis, although one patient had a dysmorphic facial appearance suggestive of an undiagnosed syndrome. These findings are consistent with most cases of hypoplasia of the left heart being nonsyndromic. Thus, although published reports associate the cardiac phenotype with many syndromes (Table 4.2), most are limited to single cases.

Postnatal Diagnosis—Investigating the Cause and Prognosis of the Afflicted Infant

When a neonate presents with hypoplasia of the left heart, questions and investigations relating to aetiology

often take less precedence over decisions regarding surgical or nonsurgical management. This may be unfortunate on some occasions, as there may be a short window of time in which to obtain samples for investigation. Consultation with clinical geneticists may be advised if the child has multiple congenital anomalies in case specific diagnostic investigations are required, as in the case of Smith-Lemli-Opitz syndrome.

Chromosomal analysis may also be indicated, or more specific molecular cytogenetic analysis. As in the case of prenatal diagnosis, the results of these tests could answer questions relating to aetiology, prognosis, and the risk of recurrence. Although reported, left heart hypoplasia is an uncommon association with the DiGeorge or velocardiofacial syndrome phenotypes. Additional investigation for 22q11 deletion by fluorescent chromosome in situ hybridisation, therefore, is unlikely to show a deletion. Nevertheless, should additional features suggesting 22q11 deletion be observed, such as cleft palate, velopharyngeal insufficiency, or evidence of maldevelopment of the thymus or parathyroid glands, further analysis may be offered, as the diagnosis carries important implications in management for both the child and the family, such as the likelihood of deafness or a renal anomaly, and an increased risk of recurrence.

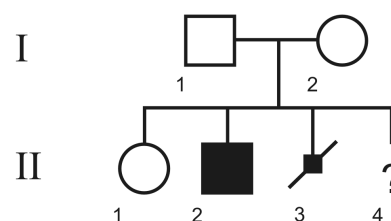


FIGURE 4.1. A healthy, nonconsanguineous couple with no family history of congenital heart disease wishes to know the chances of a future child (II.4) having hypoplasia of the left heart. Both of their affected boys have had isolated hypoplasia of the left heart, and have normal chromosomes. Patient II.2 is surviving, but III.3 was a male fetus that did not survive. This pedigree could be consistent with autosomal-recessive inheritance, with a risk of recurrence of 25%; X-linked recessive inheritance, with a risk of 25%; submicroscopic chromosomal rearrangement, a cryptic translocation for example, or autosomal-dominant inheritance with a variable phenotype. It is also consistent with a nongenetic cause for the phenotype. For a couple that have had 2 children with hypoplasia of the left heart, the empirical risk for the recurrence of any type of congenital cardiac malformation is likely to be between 15% and 20%. This, however, is an averaged “group risk” such that the risk for an individual couple may be as high as 25%, for autosomal-recessive, or 50%, for autosomal-dominant inheritance. Detailed antenatal echocardiography was offered.

Unbalanced chromosomal rearrangements, resulting in the loss or gain of specific chromosomal regions, may be the cause of the phenotype. Indeed, the identification of a critical region within 11q25 would suggest that translocations should be specifically investigated, as they can be associated with a significant risk of recurrence depending on the precise chromosomal rearrangement.

As with prenatally diagnosed patients, there is an increase in incidence of extracardiac malformations. In our unpublished postnatal series, 6 of 50 children with normal chromosomes had additional congenital anomalies, with 5 of the 6 requiring surgery. One patient was thought to have a possible syndrome, with potential adverse developmental consequences. For any fetus or child with hypoplasia of the left heart who does not survive, postmortem examination may identify unsuspected congenital malformations that could have implications for counselling the parents regarding the aetiology and the risk of recurrence.

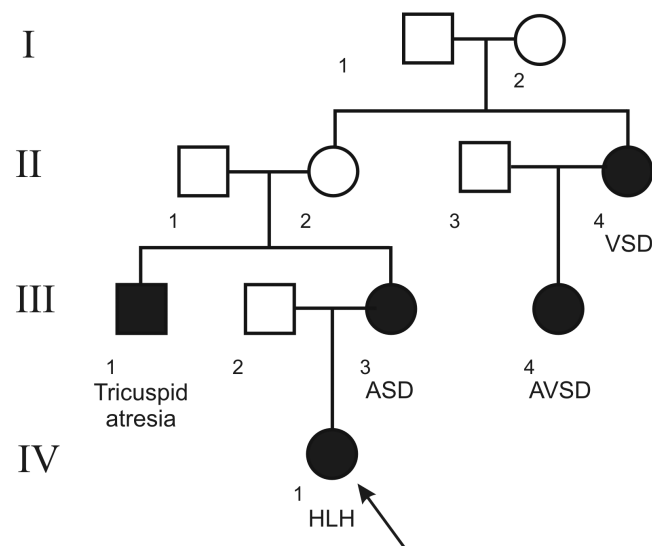


FIGURE 4.2. Our patient, II.2, wishes to know the cause of congenital heart disease in her family. Her children are nondysmorphic and have normal karyotypes. The family history suggests that a dominant gene with variable penetrance is the cause of the congenital cardiac anomalies in this family. Our patient should be offered echocardiography to exclude asymptomatic congenital cardiac disease. Patient III.1 also wishes to know the chances of having a child with a congenital cardiac anomaly. The chance of him transmitting the unidentified gene causing the cardiac phenotype in his family is 50%. The pedigree illustrates that gene carriers can have a phenotype ranging from an apparently normal heart to hypoplasia of the left heart. Although this complicates risk assessment, at a practical level detailed fetal echocardiography should be offered in all at-risk pregnancies.

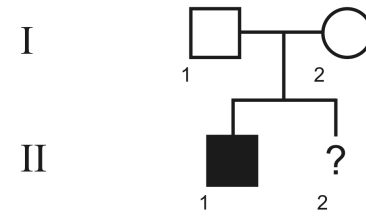


FIGURE 4.3. A healthy, nonconsanguineous couple wishes to know the chances of recurrence of hypoplasia of the left heart. There is no family history of congenital heart disease. Their son has isolated hypoplasia of the left heart and normal chromosomes, with no 22q11 deletion. It is estimated that recurrence of congenital cardiac anomalies occurs in about one-tenth of pregnancies where one previous child has hypoplasia of the left heart, albeit that this is not based on large prospective studies. It is unclear whether the cause of cardiac defect is genetic or nongenetic. There are reports of dominant inheritance of left-sided obstructive lesions with variable penetrance.⁴ It is possible that a recessive or a dominant gene is causing the problems in this family. A detailed family history, therefore, should be taken, looking for evidence of congenital cardiac malformations. The role of parental echocardiography in risk assessment is unclear. It may identify asymptomatic patients with congenital cardiac anomalies, suggestive of dominant inheritance. It may also reveal anatomical variants, the significance of which is uncertain, such as an aortic valve with two leaflets. A couple in this situation has a risk of recurrence of any type of congenital cardiac anomaly of between 5% and 10%. This takes account of all of the possible causes of hypoplasia of the left heart. Detailed fetal echocardiography will be offered.

Offering Advice on the Risk of Recurrence

Assessment of the risk of recurrence is based on the family history; clinical examination of the child, which may identify a specific syndrome; and the results of investigations, such as chromosomal analysis or the postmortem report.

For most couples, an empirical risk of recurrence will be offered. There are possible problems and pitfalls (Figs. 4.1–4.3) that highlight the potential demand for specific investigations to identify families with a higher risk of recurrence.

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