Inheritance of congenital heart disease

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Congenital heart defects (CHD) are the most common developmental anomalies and are the leading noninfectious cause of mortality in newborn babies. It has been estimated that between four and ten live-born infants per 1000 have a cardiac malformation (0.4 to 1.0%), 40% of which are diagnosed in the first year of life.[1,2] The European Registration of Congenital Anomalies (EUROCAT) reported a prevalence of 58.9/ 10,000 live births in the northern part of the Netherlands (0.6%). Hoffman estimated that the true prevalence of CHD may be as high as 53 per 1000 pregnancies (5.3%), including a 20% occurrence of heart defects in spontaneous abortion, a 10% occurrence in stillbirth, and a 1% occurrence in live birth.[3] (*Neth Heart J* 2005;13:88-91.)

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In spite of tremendous advances in diagnosis and treatment of congenital heart disease, the underlying causes of the majority of CHD are only partly understood. Prior epidemiological studies suggested that Mendelian disorders constituted a very small percentage of CHD and that multiple factors were responsible for the majority of cases.[4] However, recent studies have shown that CHD caused by single gene or single locus defects is more common than had been expected.[5] Furthermore, it has become apparent that a higher percentage of heart defects occur in the context of familial disease than previously recognised.[6]

Because many children with corrected congenital heart defects now reach adulthood and childbearing age, the birth prevalence of congenital heart defects, particularly of the more severe defects, may increase in subsequent years.

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Classification of causes

Chromosome disorders

At the moment, chromosome disorders are known to be the underling cause in 8 to 10% of newborn babies with congenital heart disease; at adult age this percentage is lower because many children with chromosomal defects die at a young age. Examples of patients with a numeric chromosomal defect who reach adult age are patients with Down's syndrome (complete atrioventricular septal defect) and Turner's syndrome (coarctation).

Mendelian disorders

Mendelian inheritance (single gene disorders) may be autosomal dominant, autosomal recessive or X-linked. Noonan's syndrome, Marfan's syndrome and Alagille's syndrome are examples of autosomal dominant disorders. Also some isolated cardiac disorders are single gene disorders, such as atrioventricular septal defects. Recent molecular genetic studies suggest that the genetic basis of congenital heart disease has been underestimated.[7,8] Known genes with associated heart defects and familial clustering of heart defects are presented in table 1. In table 2 the most frequent syndromes with congenital heart defects are mentioned.

Multifactorial inheritance

The majority of congenital heart defects (80 to 85%) can not be explained by chromosomal or single gene disorders at the moment. In these patients it is assumed that multifactorial causes play a role. Multifactorial inheritance is a model that assumes that a disease is caused by the interaction of several genetic and

Table 1. Known genes and most frequent heart defects.*

Aut.dom. NKX2.5 (CSX) (5q35), Schott et al. *Science* 1998	Atrial septal defect + conduction disorder
Aut.dom. GATA4 (8p), Garg et al. *Nature* 2003	Atrial septal defect without conduction disorder (Ventricular septal defect/atrioventricular septal defect)
Sporadic cases: FOG2 (8q22), Pizzuti et al. *Human Mutation* 2003	Fallot's tetralogy
X-linked: ZIC3 (Xq26) (+heterotaxia), Ware et al. *Am J Hum Genet* 2004 Aut.dom. PROSIT240 (12q24), Muncke et al. *Circulation* 2003 Aut.dom. CFC1 (2q21.1)(+heterotaxia), Golmuntz. *Am J Hum Genet* 2002	Transposition of the great arteries
Aut.dom. JAG1 (20p12), Eldadah et al. *Hum Molec Genet* 2003	Fallot's tetralogy
Aut.dom. CRELD1 (3p25.3), Robinson. *Am J Hum Genet* 2003	Atrioventricular septal defect
Aut.dom. Elastine (7q11), Metcalfe et al. *Eur J Hum Genet* 2000	Supravalvular aortic stenosis
Familial heart defects with unknown genes*	
Aut.dom. Gerboni et al. *J Med Genet* 1993	Coarction of aorta
Aut.dom. Bleyl et al. *Am J Hum Genet* 1995 (linkage 4pq)	Total abnormal pulmonary venous return
Aut.dom. Sheffield. *Hum Molec Genet* 1997 (linkage 1p31-21)	Atrioventricular septal defect
Aut.rec. Abushaban et al. *Pediatr Cardiol* 2003	Truncus arteriosus

* Most families with congenital heart defects (the above included) do not show Mendelian inheritance!

environmental factors (such as maternal diabetes, maternal infections, alcohol, drugs and smoking).

Genetic mechanisms hampering classification

Several genetic mechanisms contribute to the difficulties in recognising the genetic causes of congenital heart disease.

Genetic heterogeneity

Tetralogy of Fallot (ToF) is a common type of congenital heart disease. Although the anatomic features are clear, at least five different genetic causes of ToF have been identified: approximately 16% of patients with ToF have a deletion of chromosome 22q11, nearly 7% have trisomy 21 (Down's syndrome), and a smaller number of ToF patients have mutations in NKX2.5, FOG2 or JAG1 (Alagille's syndrome).[9,10] So a genetic cause has been identified in nearly one third of ToF patients; additional genetic causes remain to be identified.

Reduced penetrance

Reduced penetrance refers to a situation where an individual who appears normal carries a disease causing gene mutation in a dominant gene. This is observed in familial anomalous pulmonary venous connection, familial atrioventricular septal defect and other familial congenital heart disease.[5]

Variable expression

Variable expression refers to the situation that individuals with the same genetic defect show variable

Table 2. Most frequent syndromes with congenital heart defects.*

Down's, Pateau's, Edwards' syndrome (Trisomy 21, 13, 18)
Turner's syndrome (45,XO)
Velocardiofacial syndrome (microdeletion 22q11 (TBX1))
Holt-Oram syndrome (TBX5)
Noonan's syndrome (PTPN11)
Williams syndrome (microdeletion 7q11)
Alagille's syndrome (JAG1)
VACTERL association
CHARGE association
Oculo-auriculo-vertebral spectrum

* Reviews of these syndromes can be found in genetic textbooks.

Table 3. Recurrence risks for offspring of patients with a congenital heart defect.

Specific lesion	Offspring recurrence rate (if non-syndromatic)	Associated syndromes
Atrial septal defect	3-5%	Holt-Oram upper limb deformity autosomal dominant
	Familial ASD with long PR higher	
Ventricular septal defects	2-5%	Down's syndrome
	Occasionally familial	Holt-Oram
Atrioventricular septal defect (complete)	10-14% in affected mother	Down's syndrome in >50%
Pulmonary stenosis	3-5%	Noonan, congenital rubella, Williams, Alagille
Tetralogy of Fallot	3-5%	Deletion of chromosome 22q11 (16%)
Aortic valve stenosis	12-20% in affected mother	Scheie's syndrome
	5% in affected father	
	Bicuspid valve may be familial	
Subaortic stenosis	Familial cases described	Shone's syndrome (left heart abnormalities)
Coarctation	May be familial	22q11 deletion
	Association with bicuspid aortic valve	
Patent arterial duct	No information	Congenital rubella
Ebstein's anomaly	6% in affected mother	Rare
	Familial occurrence documented	Associated with maternal lithium use
Complete transposition of the great arteries	2%	None
	Rare familial recurrence	
Congenitally corrected transposition	3-5%	None

phenotypes. The variety of observed malformations caused by mutations in NKX2.5 and the fact that the gene is expressed throughout the heart suggest that this gene may affect a number of pathways in cardiac development.

A well-known example of variable expression is in microdeletion 22q11.2. The features of this microdeletion syndrome may vary from subtle abnormalities, as mild velopharyngeal insufficiency being the only feature, to the serious DiGeorge syndrome, with congenital heart defect, mental retardation, hypocalcaemia and severe immunodeficiency. Cardiovascular abnormalities seen in patients with 22q11.2 deletion are often abnormalities in the outflow tract, such as truncus arteriosius, interruption of the aortic arch, pulmonary atresia, ventricular septal defect and tetralogy of Fallot.

Genomic imprinting

For many congenital heart defects the risk of the offspring getting the same disorder is higher if the mother has a heart defect than the father.[5] This is probably caused by a phenomenon called genomic imprinting. Genomic imprinting means that a certain part of the genome is modified in the germ cells with an 'imprint' that turns certain genes on or off, dependent on the gender of the person. This imprint is reversible in the next generation.

Recurrence risks and prenatal diagnosis

Recurrence risks for offspring of patients with a congenital heart defect depend on the cause of the defect (table 3).

Most patients with a chromosomal defect are not reproductive, although some women with Turner's syndrome do have the possibility of having children. The recurrence risks of these chromosomal defects depend on the precise diagnosis and exceed the scope of this paper.

The offspring of patients with Mendelian or single gene disorders (autosomal dominant, autosomal recessive or X-linked recessive) have increased recurrence risks. For autosomal dominant traits the risk that the offspring is a mutation carrier is 50%. Because of reduced penetrance and variable expression the true risk of a heart defect may be lower. For autosomal recessive disorders the offspring risk is low because usually the carrier risk is low. In X-linked disease the situation is more complicated as males have only one X-chromosome and females have two. The offspring risk may vary as it depends on the gender of the parent and the level of expression in female carriers.

In multifactorial inheritance the recurrence rate of heart defects in the offspring of an affected parent may vary between 1.5 and 14% with higher rates if the affected parent is a female and if more family members are affected.[4] Several studies have recently reported

large families with congenital heart defects with high risks of recurrence.[11-20] To estimate the recurrence risk for an individual couple it is essential to perform a thorough family investigation.[21]

Cardiac structural anomalies and functional problems in the foetus can be detected by prenatal echocardiography from 16 weeks of gestation or earlier. Many defects are already visible at that time, although not all defects will be detected.[22] Prenatal diagnosis by chorion villus biopsy or amniocentesis is only an option in cases with a known chromosomal or Mendelian (single gene) defect.

The future is nearby

Dividing causes of congenital heart defects into chromosomal, Mendelian (single gene) and multifactorial disease is a simplification. The possibility that phenotype variability of single gene disorders is due to complex interactions between other genetic factors and/or environmental factors is a logical extension of the concept that simple Mendelian traits are, in fact, complex traits. On the other hand presumed complex traits may sometimes be due to a single gene disorder with low penetrance.

Considerable interest has developed in identifying the modifying genetic and environmental factors. Identification of the factors that modify the phenotype of single gene disorders will enhance our appreciation of the clinical diversity of congenital heart defects.[23-26] More genetic research is necessary for further identification of the genes. Many studies suggest a long list of (candidate) genes. Environmental factors such as maternal smoking, maternal exposition to drugs and supplements of folic acid and other nutritional factors are also subject of extensive research.

In conclusion

The interactions of genetic and environmental factors in patients with congenital heart defects are still a topic of research. Hopefully this will lead to a better understanding of the aetiology of these defects and consequently to the availability of better information to patients about the risk of their offspring. In the end this may lead to prevention of a substantial part of these defects in the future. Further research in this field is necessary. ■

References

1 Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J* 2004;**147**:425-39.
2 Moller JH, Allen HD, Clark EB, et al. Report of the task force on children and youth. *Circulation* 1993;**88**:2479-86.
3 Hoffman JI. Incidence of congenital heart disease: II Prenatal incidence. *Pediatr Cardiol* 1995;**16**:155-65.
4 Nora JJ, Nora AH. The evolution of specific genetic and environmental counseling in congenital heart disease. *Circulation* 1978; **57**:205-13.
5 Burn J, Brennan P, Little J, Holloway S, Coffey R, Somerville J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. *Lancet* 1998;**351**:311-6.
6 Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol* 1997;**30**:1809-12.
7 Delot EC. Control of endocardial cushion and cardiac valve maturation by BMP signaling pathways. *Mol Genet Metab* 2003; **80**:27-35.
8 McFadden DG, Olson EN. Heart development: learning from mistakes. *Curr Opin Genet Dev* 2002;**12**:328-35.
9 Bonnet D. Genetics of congenital heart disease. *Arch Pediatr* 2003; **10**:635-9.
10 Gelb BD. Recent advances in the understanding of genetic causes of congenital heart defects. *Front Biosci* 2000;**5**:D321-33.
11 Digilio MC, Casey B, Toscano A, et al. Complete transposition of the great arteries: patterns of congenital heart disease in familial precurrence. *Circulation* 2001;**104**:2809-14.
12 Abushaban L, Uthaman B, Kumar AR, et al. 'Familial truncus arteriosus: a possible autosomal recessive trait'. *Pediatr Cardiol* 2003;**24**:64-6.
13 Clementi M, Notari L, Borghi A, et al. Familial congenital bicuspid aortic valve: a disorder of uncertain inheritance. *Am J Med Genet* 1996;**62**:336-8.
14 Udwadia AD, Khambadkone S, Bharucha BA, et al. Familial congenital valvar pulmonary stenosis: autosomal dominant inheritance. *Pediatr Cardiol* 1996;**17**:407-9.
15 Grossfeld PD, Lucas VW, Sklansky MS, et al. Familial occurrence of pulmonary atresia with intact ventricular septum. *Am J Med* 1997;**72**:294-6.
16 Schunkert H, Brockel U, Kromer EP, et al. A large pedigree with valvuloseptal defects. *Am J Cardiol* 1997;**80**:968-70.
17 Petsas AA, Anastassiades LC, Constantinou EC, et al. Familial discrete subaortic stenosis. *Clin Cardiol* 1998;**21**:63-5.
18 Grange DK, Balfour IC, Chen SC, et al. Familial syndrome of progressive arterial occlusive disease consistent with fibromuscular dysplasia, hypertension, congenital cardiac defects, bone fragility, brachysyndactyly and learning disabilities. *Am J Med Genet* 1998; **75**:469-80.
19 Gelb BD, Zhang J, Sommer RJ, et al. Familial patent ductus arteriosus and bicuspid aortic valve with hand anomalies: a novel heart-hand syndrome. *Am J Med Genet* 1999;**87**:175-9.
20 Brown C, Sane DC, Kitzman DW. Bicuspid aortic valves in monozygotic twins. *Echocardiography* 2003;**20**:183-4.
21 Gill HK, Splitt M, Sharland GK, Simpson JM. Patterns of recurrence of congenital heart disease: an analysis of 6640 consecutive pregnancies evaluated by detailed fetal echocardiography. *JACC* 2003;**42**:923-9.
22 Cardiovascular Genetics for Clinicians. Editors: Doevendans, PA Wilde AAM. Kluwer, October 2001, ISBN 1-4020-0097-9.
23 Garg V, Kathiriya IS, Barnes R, et al. GATA4 mutations cause human congenital heart defects and reveal an interaction with TBX5. *Nature* 2003;**424**:443-7.
24 Kaynak B, von Heydebreck A, Mebus S, et al. Genome-wide array analysis of normal and malformed human hearts. *Circulation* 2003;**107**:2467-74.
25 Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management. Part I: from etiology to diagnostic strategies. *Circulation* 2003;**108**:628-35.
26 Hasham SN, Willing MC, Guo DC, et al. Mapping a locus for familial thoracic aortic aneurysms and dissections (TAAD2) to 3p24-25. *Circulation* 2003;**107**:3184-90.