Congenital heart defects and pulmonary arterial hypertension
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PART I
GENES, ENVIRONMENT AND HEREDITY IN CONGENITAL HEART DEFECTS

Chapter 2

Genetic aspects of congenital heart defects

W.S. Kerstjens-Frederikse, R.M.W. Hofstra

Translated and adapted from: “Aangeboren Hartafwijkingen bij Volwassenen”

Chapter 2

INTRODUCTION

Congenital heart defects (CHDs) occur in approximately 8 per 1000 live births (1:130). The huge improvement in diagnostics, therapy and care for patients with a CHD in the last decades has increased the number of adults living with a (corrected) CHD and the relative numbers of surviving adult patients is expected to increase further. The current estimated prevalence of adults with a CHD is 3 per 1000 persons in the Netherlands. In the last decade we have learnt that heredity plays an important role in the aetiology of CHD and it has become more and more clear that adult patients with CHD may have offspring with CHD. As a consequence, clinicians caring for patients with CHD have a responsibility to inform their patients about this aspect of their disorder. Knowledge about heredity is important because it may provide information on: (1) syndromic CHD affecting other organs, (2) prognosis, (3) risk for offspring having CHD, and (4) risks for relatives, who may be eligible for presymptomatic (genetic) testing.

Genetic counselling

A referral for genetic counselling is indicated when someone has questions about a congenital and/or hereditary disease present in him- or herself or in relatives. In the Netherlands, genetic counselling is provided by a medical specialist, a clinical geneticist. Genetic counselling addresses the nature of the disease, its prevalence, the availability of genetic testing, the interpretation of genetic test results, the recurrence risks for offspring, the health risks for relatives, and the options to reduce these risks.

Causes

CHDs may be present in patients with numeric chromosomal anomalies or small chromosomal anomalies, manifesting as a monogenic syndromic or non-syndromic disease, but also as a complex genetic disease. Numerical chromosomal anomalies, (for instance trisomy 21, Down’s syndrome) are amongst the earliest reported genetic causes for CHDs. These chromosomal anomalies cause 10% of the heart defects seen in live births. Though genetic in origin, these anomalies are usually new (de novo) in children and thus not inherited nor familial.

Small deletions and duplications in chromosomes, which cannot be detected by microscopic analysis, are detected by molecular techniques, such as multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (array CGH) or single nucleotide polymorphism array (SNP array) analysis. Small chromosomal anomalies probably cause approximately 15% of the cases of CHDs.

CHDs are a component of many, mostly rare, hereditary syndromes with multiple congenital malformations, for instance the autosomal dominant Noonan’s syndrome. Together, these monogenic syndromes contribute to approximately 5% of the cases of CHDs.

In the last two decades, quite a few pedigrees have suggested monogenic inheritance in non-syndromic CHDs (autosomal dominant, autosomal recessive, or X-linked) and several of the
associated genes have been discovered.\textsuperscript{4}

Formerly, the large group of non-syndromic CHDs was assumed to be non-genetic. However, at the end of the 20th century, several studies showed recurrence of non-syndromic congenital defects in pedigrees that was inconsistent with monogenic inheritance. The hypothesis of multifactorial inheritance was postulated (but has not yet been proven), assuming that these congenital defects were caused by a combination of mutations in several genes, together with several, mostly unknown, environmental factors. Environmental factors associated with CHDs are maternal diseases like diabetes, obesity, rubella infection, phenylketonuria, or the maternal use of alcohol, cigarettes, amphetamines, anti-epileptic drugs, some anti-depressant drugs or retinoic acid.\textsuperscript{2-3} More recently, the term “complex diseases” has been adopted for diseases that are not plainly chromosomal or monogenic but which still have a strong genetic component.

The classification of non-syndromic heart defects into monogenic or complex groups is probably an oversimplification. The concept of a spectrum of disease is more plausible, on one end of the spectrum consisting of monogenic defects caused by mutations in genes showing a high penetrance of disease and, at the other end, of complex defects caused by mutations in several genes with a middle or low penetrance of disease, which may or may not act in concert with environmental factors. Moreover, approximately 10\% of CHDs which were assumed to have a complex aetiology now appear to be caused by the occurrence of new monogenic mutations.

Many genes associated with non-syndromic familial heart defects have been discovered by molecular studies in the past decade. This has lead to a better understanding of the aetiology of CHDs. The availability of advanced techniques able to detect small chromosomal aberrations has also contributed to the detection of loci and genes involved in CHDs. Several hundreds of genes, but also micro RNAs and epigenetic factors, like imprinting, methylation and chromatin remodelling, appear to be involved in the development of the foetal heart.\textsuperscript{6} All of the above strengthens the idea that the contribution of genetic factors to CHDs has been underestimated in the past. Current technologies in molecular genetics and bioinformatics will greatly facilitate the genetic analysis of these patients and enhance our understanding of the origin of CHDs in the near future.\textsuperscript{7}

\begin{table}[h]
\centering
\caption{Classification of genetic causes of congenital heart defects at birth}
\begin{tabular}{|l|c|}
\hline
\textbf{Category} & \textbf{Percentage} \\
\hline
numerical chromosomal anomalies & 10 \\
microdeletions/microduplications & 15 \\
monogenic syndromic diseases & 5 \\
monogenic non-syndromic diseases & 5-10 (?) \\
complex diseases & 60-65 (?) \\
\hline
\end{tabular}
\end{table}
Chromosomal anomalies

Numerical chromosomal anomalies

Numerical chromosomal anomalies are characterised by the occurrence of one or more complete extra chromosomes (trisomy, tetrasomy) or the lack of a complete chromosome (monosomy). Patients with trisomy 13 (Patau’s syndrome), trisomy 18 (Edwards’ syndrome), trisomy 21 (Down’s syndrome) and monosomy X (Turner’s syndrome) often have CHDs. Most patients with trisomy 13 or 18 do not reach adult age, but most live-born patients with trisomy 21 or Turner’s syndrome do. Approximately 45% of patients with Down’s syndrome have a CHD; this is most frequently an atrio-ventricular septal defect, atrial septal defect, ventricular septal defect, or Fallot’s tetralogy. For the cardiologist, the most important numerical chromosomal anomaly in adult patients is Turner’s syndrome. This syndrome should be considered in any female patient with a CHD and normal intelligence, short stature and/or delayed puberty. It is not exceptional for the diagnosis not to be made until adolescence. Turner’s syndrome is caused by monosomy X (a 45,X karyotype) in 40–60% of the patients. The other patients have a structural anomaly of an X- (or Y-) chromosome, or are mosaic, meaning that the mutation is not present in all the somatic cells of an individual. In

Features of Turner’s syndrome

- short stature
- delayed puberty
- nuchal webbing
- low hairline
- large internipple distance
- congenital heart defect, most often aortic coarctation
- lymphedema of hands and feet (in newborns)
- valgus deformity of the forearm
- renal anomalies (e.g. horseshoe kidney)

Turner’s syndrome this means that normal cell lines (46,XX) as well as abnormal cell lines (45,X) are present in one individual, while combinations with other cell lines, for instance 47, XXX, may also occur. This explains why the phenotype seen in Turner’s syndrome is quite variable – it is related to the proportion of normal and abnormal cell lines in the various tissues. However, the proportion of abnormal cell lines found in blood does not predict that found in other tissues. Though many women with Turner’s syndrome are infertile, pregnancies have been reported in several women with –probably mosaic-Turner’s syndrome. The disease may be detected by karyotyping, QF-PCR, array CGH or SNP array.

Microdeletions and Microduplications

Instead of a complete chromosome, a small part of a chromosome may be lacking (a deletion) or present as extra material (a duplication). Some of these small anomalies may be visible under the
microscope, but modern techniques (MLPA, SNP array, or array CGH) have a higher resolution for detecting these small copy number variations. The size of the deleted or duplicated chromosomal segment at the DNA level is usually large enough to contain several genes.

A deletion or duplication often arises de novo, meaning that it is not present in either parent. However, a person who has a deletion or duplication has a 50% chance of passing it on to offspring in each pregnancy. The phenotypic expression of the deletion or duplication may be highly variable within a family. It is important for the clinician to be able to recognise the effects of several deletions and duplications, in the first place because they are not particularly rare, and in the second place, because the severity of the extracardiac features may be highly variable. Quite often a microdeletion or microduplication is not diagnosed until adult age.

**Microdeletion 22q11.2, Velocardiofacial syndrome**

Microdeletion 22q11.2 is one of the most prevalent microdeletions (estimated prevalence 1:4000). The q-arm is the long arm of the chromosome, 11.2 marks the position on this long arm, the chromosome bands are numbered from the centromere. Historically several syndromes with overlapping features were clinically recognised, (DiGeorge syndrome, velocardiofacial or Shprintzen syndrome, asymmetric-crying face or Cayler syndrome, conotruncal anomaly face syndrome) which all appeared to be caused by a microdeletion 22q11.2.

There is no clear relation between the phenotype and the size of the deletion. The $TBX1$ gene is located in the deleted area and the deletion of one copy of this gene appears to explain most of the features, including the cardiovascular defects. The clinical expression coupled to this microdeletion

<table>
<thead>
<tr>
<th>Features of microdeletion 22q11.2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Craniofacial</strong></td>
<td></td>
</tr>
<tr>
<td>• microcephaly</td>
<td></td>
</tr>
<tr>
<td>• narrow palpebral fissures, periorbital fullness</td>
<td></td>
</tr>
<tr>
<td>• hypoplastic alae naseae</td>
<td></td>
</tr>
<tr>
<td>• small ears with thickened helix</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>• mainly conotruncal anomalies: truncus arteriosus, interruption of the aortic arch type B, Fallot’s tetralogy, pulmonary valve atresia, right sided aortic arch</td>
<td></td>
</tr>
<tr>
<td>• ventricular septal defect</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>• renal hypoplasia or agenesis</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
</tr>
<tr>
<td>• hypotonia (often transient)</td>
<td></td>
</tr>
<tr>
<td><strong>Mental</strong></td>
<td></td>
</tr>
<tr>
<td>• mild mental retardation, though this is highly variable and approximately half of the children attend normal elementary school</td>
<td></td>
</tr>
<tr>
<td>• psychiatric diseases (psychosis, schizophrenia)</td>
<td></td>
</tr>
</tbody>
</table>

1 Only a few features may be present, but no one feature is obligatory.
is highly variable and may consist of subtle facial dysmorphic features and hypernasal speech, but may just as well be a full blown DiGeorge syndrome with severely disturbed T-cellular immunity due to a hypoplastic thymus gland, hypocalcemia due to hypoplastic parathyroid glands, microcephaly, cleft palate, a conotruncal heart defect (truncus arteriosus and interruption type B the most frequent). Typical features of the velocardiofacial syndrome are hypernasal speech, with or without cleft palate, narrow palpebral fissures, a long face and a conotruncal heart defect (VSD, right-sided aortic arch, Fallot’s tetralogy). Psychiatric diseases (schizophrenia, psychosis) are frequent.\(^9\)

**Partial tetrasomy 22, Cat-eye syndrome**

Total anomalous pulmonary venous return is the typical heart defect for cat-eye syndrome, but other heart defects may occur. Coloboma of the iris (a defect in the iris tissue resulting in an abnormal shape of the pupil, a cat-eye) and anal atresia are the most frequent extracardiac-features. Most patients have a normal intelligence. Cat-eye syndrome is caused by tetrasomy 22, most often through an extra chromosome containing a duplicated part of chromosome 22 and two centromeres. The tetrasomy is often mosaic.\(^9\)
Partial tetrasomy 22 may be detected by karyotyping, array CGH or SNP array.

**Microdeletion 20p11.2, Alagille syndrome**

The microdeletion 20p11.2 is associated with Alagille syndrome. Most patients have a pulmonary valve stenosis or Fallot’s tetralogy. Extracardiac features are intra-and extrahepatic atresia or hypoplasia of the biliary ductus, leading to a variable severity of cholestasis. Subtle facial features: prominent forehead, deep set eyes, narrow nose, are present, as well as anomalies of the eye (posterior embryotoxon) and the vertebra (butterfly shaped vertebra). The causative gene in the deleted chromosomal area is Jagged-1 (*JAG1*). Mutations in *JAG1* are more frequent than microdeletion 20p11.2 in patients with Alagille syndrome. Mutations in *JAG1* are also detected in patients with Fallot’s tetralogy, without other features of Alagille syndrome.\(^9\)
Microdeletion 20p11.2 may be detected by Fluorescent-in-Situ-Hybridization (FISH), array CGH or SNP array.

**Microdeletion 7q11.23, Williams (Williams-Beuren) syndrome**

Williams syndrome is characterised by supravalvular aortic stenosis (SVAS), mental retardation, a specific behavioural pattern described as “cocktail-party-behaviour”, specific facial features, and hypercalcemia. It is caused by a microdeletion at 7q11.23. The genes elastin (*ELN*), RFC2 and Limkinase are located in the deleted area. The *ELN* gene is associated with SVAS and mutations in *ELN* have been reported in families with autosomal dominant SVAS but without other features of Williams syndrome.\(^9\)
Microdeletion 7q11.23 can be detected by FISH, array CGH or SNP array.
Microdeletion or microduplication 1q21.1

Microdeletion or microduplication of 1q21.1 causes a highly variable phenotype and may feature several CHDs, including aortic valve stenosis and aortic coarctation. Short stature, mild mental retardation, microcephaly, cataracts, and subtle facial features (epicanthal folds, widely spaced teeth) may be present. The microdeletion may be detected in apparently healthy parents, but is not detected in random healthy controls. Microdeletion or microduplication of 1q21.1 can be detected by array CGH or SNP array.

Monogenic defects

Syndromes with heart defects and monogenic inheritance

Monogenic syndromic heart defects may have very subtle extracardiac features that can easily be missed. However, it is important that cardiologists who deal with young adults are aware of these syndromes because the risk for offspring may be high (50% in autosomal dominant disease) and the severity of the syndromes can be highly variable. Hundreds of syndromes featuring heart defects have been reported in the medical literature. Here, we briefly summarize the features of only the most frequent autosomal dominant syndromes that are not associated with (severe) intellectual disability.

Non-syndromic heart defects with monogenic inheritance

A rapidly increasing number of families suffering from hereditary, non-syndromic, CHDs are being detected by targeted family studies. This is particularly seen in AVSD, ASD-II, in heart defects associated with heterotaxy and in left-sided heart defects (bicuspid aortic valve (BAV), aortic valve stenosis (AVS), coarctation of the aorta (COA) and hypoplastic left heart syndrome (HLHS). Several families with AVSD have been reported with a pedigree compatible with autosomal dominant inheritance with incomplete penetrance, and in some of these families a mutation in CRELD1 has been detected. Mutations in the NKX2.5 and GATA4 genes are reported in familial ASD-II, often associated with electrical conduction anomalies or pulmonary valve stenosis, respectively.
### Table 2. Some autosomal dominant syndromes with heart defects that are not associated with intellectual disability

<table>
<thead>
<tr>
<th>Disease (gene)</th>
<th>Most frequent heart defect</th>
<th>Most common other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alagille syndrome <em>(JAG1, NOTCH2)</em></td>
<td>pulmonary artery stenosis</td>
<td>mild craniofacial anomalies, intrahepatic bile duct atresia</td>
</tr>
<tr>
<td>Aneurysm-osteoarthritis syndrome <em>(SMAD3)</em></td>
<td>aortic aneurysm, tortuosity</td>
<td>early osteoarthritis</td>
</tr>
<tr>
<td>Char syndrome <em>(TFAB2B)</em></td>
<td>persistent ductus arteriosus</td>
<td>duck-bill lips</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome <em>(COL3A1 and many other genes)</em> Several types, some are autosomal dominant</td>
<td>atrial septal defect, mitral valve prolapse, rupture of large- and medium-sized arteries</td>
<td>easy bruising, skin fragility, joint hypermobility</td>
</tr>
<tr>
<td>Holt-Oram syndrome <em>(TBX5)</em></td>
<td>septal defects</td>
<td>thumb anomalies, variable anomalies of the forearm</td>
</tr>
<tr>
<td>Loeys-Dietz syndrome <em>(TGFBR1, TGFBR2, TGBF2)</em></td>
<td>aortic aneurysm, tortuosity</td>
<td>hypertelorism, bifid uvula/cleft palate; aneurysms in various arteries</td>
</tr>
<tr>
<td>Long QT-syndrome <em>(KCNN1, KCNH2, SCN5A and many other genes)</em></td>
<td>prolonged QT-interval, ventricular arrhythmias</td>
<td>syncope, sudden cardiac death</td>
</tr>
<tr>
<td>Lymphedema Distichiasis-syndrome <em>(FOXC2)</em></td>
<td>Fallot’s tetralogy</td>
<td>lymphedema, distichiasis (= double row of eye lashes)</td>
</tr>
<tr>
<td>Marfan syndrome <em>(FBN1, TGFBR1, TGFBR2)</em></td>
<td>aortic root dilatation/dissection, valve anomalies</td>
<td>pectus deformity, arachnodactyly, lens dislocation</td>
</tr>
<tr>
<td>Myotonic dystrophy <em>(DM1)</em></td>
<td>several arrhythmias</td>
<td>myotonia, muscle weakness, cataract, frontal balding</td>
</tr>
<tr>
<td>Neurofibromatosis type I <em>(NF1)</em></td>
<td>pulmonary valve stenosis</td>
<td>café-au-lait spots, cutaneous neurofibromas</td>
</tr>
<tr>
<td>Noonan syndrome <em>(PTPN11 and many other genes in MAPK-pathway)</em></td>
<td>pulmonary valve or artery stenosis, ASD, hypertrophic cardiomyopathy</td>
<td>Short stature, short neck with webbing, pectus excavatum and/or carinatum</td>
</tr>
<tr>
<td>Tuberous sclerosis <em>(TSC1, TSC2)</em></td>
<td>rhabdomyomas of the heart</td>
<td>depigmented skin lesions, periungual fibromas, adenoma sebaceum, intracerebral calcifications</td>
</tr>
</tbody>
</table>

A third important group of highly hereditary heart defects are the left-sided structural heart defects, also designated “left ventricular outflow tract obstructions” (BAV, AVS, COA, HLHS). When first-degree relatives (parents and sibs) of a paediatric index patient are screened echocardiographically, one or more relatives appear to have a heart defect in 20% of the index cases. Most often this defect is a BAV and most often it was unknown.\(^\text{15}\) A mutation in \(\text{NOTCH1}\) is detected in some of these families.\(^\text{16}\)

CHDs are genetically heterogeneous, meaning that one CHD may be caused by a mutation in one of several different genes. The number of known genes associated with CHDs is increasing rapidly and medical professionals who address heredity issues with patients need to have up-to-date knowledge. The rapid advances in molecular technologies and bioinformatics will provide us with a huge amount of data in the coming years, so it will be a challenge to combine and to interpret these data for the benefit of individual patients.
### Table 3. Some genes associated with non-syndromic monogenic heart defects

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Heart defect(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTA2</td>
<td>10q23.31</td>
<td>TAAD</td>
</tr>
<tr>
<td>CFC1</td>
<td>2q21.1</td>
<td>TGA, DORV, HTX</td>
</tr>
<tr>
<td>CRELD1</td>
<td>3p25.3</td>
<td>AVSD, HTX</td>
</tr>
<tr>
<td>ELN</td>
<td>7q11.23</td>
<td>SVAS</td>
</tr>
<tr>
<td>GATA4</td>
<td>8p23.1</td>
<td>ASD-II, AVSD, VSD</td>
</tr>
<tr>
<td>GDF1</td>
<td>19p13.11</td>
<td>DORV, TOF, TGA</td>
</tr>
<tr>
<td>JAG1</td>
<td>20p11.2</td>
<td>TOF</td>
</tr>
<tr>
<td>MED13L</td>
<td>12q24.21</td>
<td>TGA</td>
</tr>
<tr>
<td></td>
<td>14q11.2</td>
<td>ASD</td>
</tr>
<tr>
<td>MYH6</td>
<td>14q11.2</td>
<td>Ebstein, LVNC</td>
</tr>
<tr>
<td>MYH7</td>
<td>14q13.11</td>
<td>TAAD + PDA</td>
</tr>
<tr>
<td>NKX2-5</td>
<td>5q35.1</td>
<td>ASD-II + AV-conduction defects, TOF</td>
</tr>
<tr>
<td>NODAL</td>
<td>10q22.1</td>
<td>HTX</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>9q34.3</td>
<td>AVS, BAV</td>
</tr>
<tr>
<td>TAB2</td>
<td>6q25</td>
<td>TOF, PVS, AVS</td>
</tr>
<tr>
<td>ZFPM2</td>
<td>8q23.1</td>
<td>TOF</td>
</tr>
</tbody>
</table>

ASD atrial septal defect; AVS aortic valve stenosis; AVSD atrial ventricular septal defect; BAV bicuspid aortic valve; DORV double outlet right ventricle; HTX Heterotaxy; LVNC left ventricular non-compaction; PDA persistent ductus arteriosus; PVS pulmonary valve stenosis; SVAS supravalvular aortic stenosis; TAAD thoracic aortic aneurysm/aortic dissection; TGA transposition of the great arteries; TOF Fallot's tetralogy; VSD ventricular septal defect.

**Websites:**
- Database of genomic variants: [http://projects.tcag.ca/variation/](http://projects.tcag.ca/variation/)
- University of California Santa Cruz Genome browser: [http://genome.ucsc.edu/](http://genome.ucsc.edu/)
References


