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Congenital heart defects and pulmonary arterial hypertension
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Chapter 6

The Cardiac Phenotype in Patients With a CHD7 Mutation


ABSTRACT

**Background:** Loss-of-function mutations in *CHD7* cause Coloboma, Heart Disease, Atresia of Choanae, Retardation of Growth and/or Development, Genital Hypoplasia, and Ear Abnormalities With or Without Deafness (CHARGE) syndrome, a variable combination of multiple congenital malformations including heart defects. Heart defects are reported in 70% to 92% of patients with a *CHD7* mutation, but most studies are small and do not provide a detailed classification of the defects. We present the first, detailed, descriptive study on the cardiac phenotype of 299 patients with a *CHD7* mutation and discuss the role of CHD7 in cardiac development.

**Methods and Results:** We collected information on congenital heart defects in 299 patients with a pathogenic *CHD7* mutation, of whom 220 (74%) had a congenital heart defect. Detailed information on the heart defects was available for 202 of these patients. We classified the heart defects based on embryonic cardiac development and compared the distribution to 1007 equally classified nonsyndromic heart defects of patients registered by EUROCAT, a European Registry of Congenital Anomalies. Heart defects are highly variable in patients with *CHD7* mutations, but atrioventricular septal defects and conotruncal heart defects are over-represented. Sex did not have an effect on the presence of heart defects, but truncating *CHD7* mutations resulted in a heart defect significantly more often than missense or splice-site mutations ($\chi^2, P<0.001$).

**Conclusions:** CHD7 plays an important role in cardiac development, given that we found a wide range of heart defects in 74% of a large cohort of patients with a *CHD7* mutation. Conotruncal defects and atrioventricular septal defects are over-represented in patients with *CHD7* mutations compared with patients with nonsyndromic heart defects.
INTRODUCTION
Congenital heart defects have a high birth prevalence, ≤7 per 1000 live births, and may occur in combination with noncardiac congenital anomalies. The current hypothesis is that most heart defects without noncardiac anomalies, referred to as nonsyndromic heart defects, are the result of a combination of environmental and genetic factors. In contrast, heart defects with noncardiac congenital malformations, which are also referred to as syndromic heart defects, are more often associated with genetic factors. One of the syndromes that causes heart defects and has a known genetic cause is CHARGE syndrome (Mandelian Inheritance in Man [MIM] no. 214800).

CHARGE syndrome is a highly variable combination of multiple congenital malformations with an incidence between 1 in 15 000 and 1 in 17 000 newborns. The acronym stands for Coloboma, Heart Disease, Choanal Atresia, Retardation of Growth and/or Development, Genital hypoplasia, and Ear abnormalities with or without deafness. Additional major features are cranial nerve defects like anosmia or facial palsy and inner ear defects including abnormalities of the semicircular canals. The clinical diagnosis of CHARGE syndrome can be made when the criteria of either Blake et al8 or Verloes are met. In 2004, loss-of-function mutations in the $CHD7$ gene (MIM *608892, Chromodomain Helicase DNA-binding protein 7) were identified as the major cause of CHARGE syndrome. CHARGE syndrome is usually a sporadic condition caused by de novo mutations, although it is rarely transmitted as an autosomal dominant disease. More than 90% of the patients who fulfill the clinical criteria of CHARGE syndrome have a mutation in the $CHD7$ gene, but $CHD7$ mutations can be found in atypical patients as well; ≥14% to 17% of the patients with a $CHD7$ mutation do not fulfill the clinical diagnostic criteria and are referred to as atypical CHARGE syndrome. However, until now every patient with a pathogenic $CHD7$ mutation has ≥2 main clinical features of CHARGE syndrome at careful clinical evaluation. In this study, we will focus on the heart defects in patients with a pathogenic $CHD7$ mutation, irrespective of their accompanying clinical features as part of their typical or atypical CHARGE syndrome.

Before the identification of $CHD7$, 2 studies focused specifically on the cardiac phenotype in a group of patients with the clinical diagnosis of CHARGE syndrome. Both studies identified conotruncal heart defects as a common heart anomaly in this syndrome. Arch vessel anomalies and atrioventricular septal defects (AVSDs) were over-represented in 1 of the studies. However, at that time, the $CHD7$ gene had not been discovered, and the diagnosis of CHARGE syndrome was hampered by its highly variable clinical presentation. As a consequence, these studies are liable to ascertainment bias toward the more severe end of the clinical spectrum. Thus, studies on prevalence and phenotype should preferably be performed in patients with a proven $CHD7$ mutation. Since the identification of $CHD7$ as a cause of CHARGE syndrome, 5 other groups have looked at the phenotype in patients with a $CHD7$ mutation, revealing a wide range of prevalence of congenital heart defects from 70% to 92%. However, these were small studies containing at most 60 patients, and the studies did not focus on classifying the heart defects.
We present the first, detailed, descriptive study on cardiac phenotype in 299 patients with a proven pathogenic CHD7 mutation, using a classification system based on current developmental and epidemiological insights. We also compare our results with 1007 nonsyndromic heart defects and discuss the role of CHD7 in embryonic cardiac development.

POPULATION, MATERIAL, AND METHODS

Population and Data Collection

We aimed to collect detailed clinical information on 344 patients with a pathogenic CHD7 mutation, irrespective of whether they were known to have a congenital heart defect. These patients were referred for CHD7 analysis on a diagnostic basis to the DNA laboratory in Nijmegen, The Netherlands, between 2004 and 2009, because their local doctors suspected them of CHARGE syndrome. CHD7 analysis was performed using methods as described previously.18 Patients were derived from The Netherlands (34%) and other European countries (54%) but also from Northern America (6%) and other continents (6%). Detailed information on the congenital heart defects was collected via the local doctors or via our Dutch outpatient clinic for CHARGE syndrome. We used a datasheet that included questions on all the possible clinical features of CHARGE syndrome, but with a special focus on the cardiac evaluation and, if present, documentation of the congenital heart defect, age at diagnosis, and any heart surgery. We studied reports of cardiac ultrasound, reports of cardiac surgery, autopsy reports, and medical charts if available.

Written informed consent for the collection of medical information was obtained from all patients or their legal representatives. The accredited Medical Ethics Review Committee of the University Medical Center Groningen waived full ethical evaluation because, according to Dutch guidelines, no ethical approval is necessary if medical information that was already available is used anonymously and no extra tests have to be performed.

Classification

All heart defects caused by CHD7 mutations were classified by 2 pediatric cardiologists (L.K. and G.J.D.M.S.) using Botto’s embryonic development- and epidemiology based classification system for congenital heart defects.19 Because patent ductus arteriosus (PDA) and arch vessel anomalies cannot be included in Botto’s classification, we added these defects using the overlapping Society of Thoracic Surgeons’ classification modified by Riehle-Collauraso.20 Both classification systems are made up of 3 levels: a detailed, a main, and a large. On the detailed level, the heart defects are based on the International Pediatric and Congenital Cardiac Codes and described as specifically as possible. On the main level, some detailed heart defects are grouped together, like the different types of AVSDs. On the large level, different defects are further combined based on their developmental origin. For example, double outlet right ventricle, tetralogy of Fallot, and truncus arteriosus are grouped together within the large level of conotruncal. We aimed to have one large-level defect for each patient whenever possible. When we did have 2 large-level defects instead, each large-level
The cardiac phenotype in patients with a CHD7 mutation was counted separately, so the total number of heart defects at the large level exceeds the number of patients.

PDA and intra-atrial shunts were considered a heart defect if they persisted beyond the age of 6 months or if surgery was indicated.

Control Group
We compared the distribution of the cardiac phenotypes with that of 1007 cases with nonsyndromic congenital heart defects collected for a regional population-based birth defects registry (European Registry of Congenital Anomalies [EUROCAT] Northern Netherlands) from 1997 to 2008. This database holds detailed information on pregnancy outcomes and maternal characteristics of >80% of all live births, stillbirths, and terminations of pregnancy with congenital anomalies that are born in the Northern Netherlands. Data collection for this registry, and specifically for the registration of congenital heart anomalies, has been described in detail by Baardman et al. All cases with nonsyndromic congenital heart defect did not have other congenital anomalies or abnormal genetic test (if performed).

Statistical Methods
We compared sex and mutation type between the CHD7-mutated patients with and without a heart defect using the χ2 test in SPSS PAW Statistics 18. The χ2 test was also used to compare the cardiac phenotypes in patients with a CHD7 mutation with those in the EUROCAT group with a nonsyndromic congenital heart defect. The significance level was set at P=0.05.

RESULTS
We were able to collect information on heart defects in 299 of the 344 live born patients (87%) with a CHD7 mutation: 165 males (55%) and 134 females (45%). Of these patients, 47 (16%) died postnataally (median age 1 month). Congenital heart defects were present in 220 of the 299 patients (74%): 115 males (52%) and 105 females (48%). The prevalence of heart defects in male and female CHD7 mutation carriers was thus 70% and 78%, respectively (P=0.09; Table). To correct for incomplete data, we also calculated the prevalence range by correcting for the 45 patients of the 344 patients for whom we had no data (nonresponders). If we assume that none or all of these 45 patients had a heart defect, respectively, the prevalence ranges from 64% (=220/344) to 77% (=265/344). The prevalence ranges from 60% (=115/191) to 74% (=141/191) for males and from 69% (=105/153) to 81% (=124/153) for females.

The types of CHD7 mutations in the 299 patients were mostly nonsense (38%) and frame shift mutations (33%), although missense mutations (12%), splice-site mutations (16%), and deletions (1%) also occurred. Heart defects were found more frequently in patients with truncating mutations and deletions (80%) than in patients with missense and splicesite mutations (58%) (P<0.001; Table).

Of the 45 patients in whom heart defects were not known, 30 had truncating mutations and 15 had
missense or splice-site mutations. Thus, the corrected prevalence of heart defects ranges from 70% to 82% for the group with a truncating mutation or deletion and from 49% to 64% for the patients with missense and splice-site mutations.

We had sufficient information for classifying the heart defects in 202 of the 220 (92%) patients. The classification showed that the cardiac phenotypes in our cohort were variable, with almost all groups of the classification system being represented. None of the patients had heterotaxy or cardiomyopathy. Conotruncal heart defects, septal defects, AVSD, left ventricular outflow tract obstruction, and right ventricular outflow tract obstruction occurred both isolated and in combination with other large-level defects (Figure 1). The most common large-level heart defects were conotruncal defects, septal defects, and AVSD (Figure 2).

Among the conotruncal defects, we found different main-level heart defects (Table I in the online-only Data Supplement). Many were arch vessel anomalies, either isolated (n=15) or in combination with other conotruncal or other heart defects (n=25). Examples of arch vessel anomalies were an aberrant subclavian artery (n=18) or a right aortic arch (n=19). A tetralogy of Fallot was relatively frequent (n=23), whereas interrupted aortic arch (n=3), double outlet right ventricle (n=7), transposition of the great arteries (n=5), and truncus arteriosus (n=3) were less frequently seen.

We had information about cardiac surgery for 139 patients: 88 (63%) had undergone cardiac surgery, whereas in 3 patients surgery was not yet necessary and 12 patients had died before the operation could be performed. Thus, in 36 patients (26%) with a heart defect, cardiac surgery was not necessary.

Comparing the cardiac phenotype of CHD7 mutation with the nonsyndromic heart defects at the large level showed that the type of heart defects differed significantly between both groups (P<0.001; Figure 2). AVSD (13% versus 2%), conotruncal defects (31% versus 8%), and PDA (8% versus 2%) were over-represented in the CHD7 mutation group (Figure 2). At the main level, significantly more arch vessel anomalies (40/202 versus 3/1007, P<0.001) and tetralogy of Fallot (23/202 versus 49/1007, P<0.001) were present in patients with a CHD7 mutation.

### Table. Distribution of Heart Defects Between Sex and Mutation Type

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<td>Nontruncating</td>
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<td>15</td>
</tr>
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<td></td>
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<tr>
<td>P&lt;0.000†</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Truncating mutations include nonsense mutations, frame shift mutations, and deletion. Nontruncating mutations are missense mutations and splice-site mutation. †P value based on χ2 test. ‡The male:female distribution in the unknown group (1.4:1) did not deviate significantly from the patients with available information on heart defects (1.2:1). The same is true for the truncation:nontruncation mutation ratios (2.0:1 and 2.6:1, respectively).
DISCUSSION

This study suggests that CHD7 is important in cardiac development because heart defects have a remarkably high penetrance in patients with pathogenic CHD7 mutations of 74% (range, 64%–77%). The type of heart defects in these patients is variable. Heart defects occur equally in men and women but are seen significantly more often in patients with a truncating CHD7 mutation.

The main strength of our study is the size of our patient cohort. Previous phenotypic studies by other groups on patients with a CHD7 mutation were based on 131 patients in total only, whereas our results are based on a large group of 299 patients.13–17 This is also the first study that has specifically focused on heart defects in patients with a CHD7 mutation, and it used an embryonic development-based classification system to classify the heart defects in these patients. We classified the heart defects as accurately as possible, asking for original reports of cardiac ultrasound and surgery; however, these were not always available. In ≈60% of the cases, we had to base our classification of the defect on the description given by the physician who requested the CHD7 mutation analysis.

Figure 1. Overlapping classification of heart defects at the large level in patients with CHD7 mutations. The congenital heart defects of the patients with a CHD7 mutation, which were classified in >1 category, are shown at the larger level of the classification system. The groups other (n=2) and patent ductus arteriosus (n=19) were not included because these heart defects were only classified in one category. AVSD indicates atrioventricular septal defects; LVOTO, left ventricular outflow tract obstruction; and RVOTO, right ventricular outflow tract obstruction.
who was not usually the cardiologist. This lack of information might have resulted in a reporting bias, and, in particular, the description of heart defects at the detailed level of the classification system might be incomplete. Such a reporting bias probably had less effect at the main and large levels, where the defects were combined into broader, less-specific groups based on their developmental origin, and most errors at the detailed level would have been filtered out.

Figure 2. Distribution of congenital heart defects caused by CHD7 mutations and nonsyndromic heart defects from the EUROCAT registry. The distributions of (A) 239 congenital heart defects in a group of 202 patients with a CHD7 mutation, and (B) 1007 nonsyndromic congenital heart defects collected by EUROCAT, using the classification of Botto et al.19 The cardiac phenotypes differ significantly between both groups (P<0.001). AVSD, conotruncal defects, and PDA are over-represented in patients with CHD7 mutations compared with patients with nonsyndromic heart defects. AVSD indicates atrioventricular septal defects; LVOTO, left ventricular outflow tract obstruction; PDA, patent ductus arteriosus; and RVOTO, right ventricular outflow tract obstruction.

In studies like this, we should always be aware of an ascertainment bias resulting from under-reporting of patients without a heart defect. We tried to minimize this by stating in the patient information material that we were mainly, but not solely, interested in cardiac defects, and we explicitly stated that to estimate an accurate occurrence of heart defects, it was very important for us to be sent information on patients without a heart defect. Nonetheless, we also calculated prevalence ranges assuming that none and all of the 45 nonresponding patients had a heart defect. The prevalence of heart defects found (74%, range 64%–77%) closely resembles the prevalence of 77% reported by Zentner et al in their review of all 254 patients with CHD7 mutations that were described in literature earlier but within the lower end of the range of reported prevalences (70%–92%) in patients with a CHD7 mutation reported in other original phenotypic studies.4, 13–17, 22 This is most likely because of a referral bias toward the more severe end of the clinical spectrum in previous
The cardiac phenotype in patients with a CHD7 mutation

studies, that is, mildly affected patients being less likely referred for CHD7 analysis. Although this bias can never be ruled out completely, the unbiased nature of our patient cohort is reflected by the low mutation-detection rate of 41% in our center, indicating a low threshold for performing CHD7 analysis and thus avoiding a bias to the severe end of the clinical spectrum.

We compared our data on cardiac phenotypes in patients with a CHD7 mutation with data on nonsyndromic heart defects collected by the regional, population-based, birth defects registry, EUROCAT Northern Netherlands (Figure 2). The patients with a nonsyndromic heart defect all originated from The Netherlands, whereas our data of patients with a CHD7 mutation were collected internationally (see Methods). In other, more internationally based, registries on heart defects, the prevalence data on cardiac phenotype show a major overlap with the Dutch EUROCAT data, so we feel our control population is representative. Although none of the patients in our control population had been screened for CHD7 mutations, they were all known to have a heart defect without anomalies in other organ systems. As mentioned before, thus far, no CHD7 mutations have been detected in patients presenting with only one CHARGE feature, including patients with isolated heart defects. Therefore, it is not likely that our control cohort is enriched for CHD7 mutations. Furthermore, we can extract from the prevalence data on CHD7 mutations (1:15 000–17.000) and isolated heart defects (1:140) that at the most, 1% of our control cohort will have a pathogenic CHD7 mutation. This will hardly influence the classification of the heart defects in our control cohort. To fully exclude the contribution of CHD7 mutations to isolated (conotruncal) heart defects, large series of patients should be sequenced.

A major advantage of our control population is that we were able to select exclusively nonsyndromic patients with heart defects and the heart defects could be classified using the same development-based system. The response rate for the Dutch EUROCAT registry is high, 80%; nonetheless, there may be a reporting bias. Mild heart defects may be underreported in the registry because they become apparent later in life (after the age of 16 years, which is the reporting limit for this registry) or remain undetected. Thus, in the group of nonsyndromic heart defects, PDA, septal defects, and some arch vessel anomalies might be under-represented compared with patients with a CHD7 mutation. In contrast to the general population, patients with a CHD7 mutation will all undergo extensive cardiac examination irrespective of their cardiac symptoms. The higher frequency of PDAs, in 8% of the heart defects caused by CHD7 mutations versus 2% in nonsyndromic heart defects of the EUROCAT registry, is thus most likely a reporting artifact of the registry. In contrast, the higher frequency of septal defects in the EUROCAT data (43%) compared with the CHD7 mutation carriers (24%) is in this respect remarkable because, just as for PDAs, the prevalence of septal defects in the EUROCAT registry is likely to be underestimated. Also, the difference in prevalence of arch vessel anomalies between the CHD7 patients (40/202=20%) and the EUROCAT group (3/1007=0.3%) is so large that it cannot be explained by the difference in method of data collection alone.

The cardiac phenotypes in patients with a proven CHD7 mutation are similar to those previously reported in CHARGE patients with a heart defect whose CHD7 status is unknown;
conotruncal defects are the most common heart defect, followed by AVSD, arch vessel anomalies, and PDA.\textsuperscript{11,12} These results are not surprising because most clinically typical CHARGE patients have a CHD7 mutation. Although AVSD and conotruncal defects are over-represented in CHARGE syndrome, the heart defects among \( CHD7 \) mutation carries are variable, with all types being represented (Figure 2). For clinical practice, this means that one should always be aware of other features of CHARGE syndrome, like coloboma, choanal atresia, cranial nerve dysfunction, balance problems, characteristic ear anomalies (triangular conchae or cup ear), or hypogonatropic hypogonadism, in patients with congenital heart defects especially in patients with AVSD and conotruncal defects.\textsuperscript{5,24}

Several types of heart defects are found in animal models with heterozygous \( CHD7 \) mutations: ventricular septal defects in adult mice,\textsuperscript{25,26} ventricular septal defects and defects of the pharyngeal arch arteries in mouse embryos,\textsuperscript{27} and abnormal positioning of the truncus arteriosus and cardiac outflow tract in Xenopus laevis (African clawed frog).\textsuperscript{28} This finding suggests that \( CHD7 \) must be involved in several steps of the cardiac embryogenesis, and especially in the formation of the outflow tract and the atrioventricular cushion. How \( CHD7 \) haploinsufficiency exactly causes heart defects is not known, and the function of \( CHD7 \) in general is only now emerging.

The latest studies show that CHD7 regulates gene expression by enhancer-mediated transcription and ribosomal RNA biogenesis in the nucleolus.\textsuperscript{29,30} They also suggest that CHD7 binds to several sites on the DNA with different protein complexes in a tissue- and time-specific manner, regulating various target genes.\textsuperscript{29,30} The continuum of influences of CHD7 at different levels and in different cell types could explain the clinical variability seen in different organ systems of individuals with CHARGE syndrome, including the broad spectrum of heart defects.\textsuperscript{31,32} CHD7 probably regulates the expression of cardiac transcription factors by chromatin remodeling.\textsuperscript{33,34} The proteins of interest in cardiac development with respect to CHD7 are the ATP-dependent chromatin-remodeling protein complex Polybromo- and BRGI-associated factor containing complex and the histone acetyl transferase p300.\textsuperscript{33,34} p300 has been shown to colocalize with CHD7 at enhancer elements in mouse embryonic stem cells, and Polybromo- and BRGI-associated factor containing complex is a protein partner of CHD7 in human neural crest-like cells.\textsuperscript{28,29} CHD7 has been shown to be important for neural crest cell migration, and one hypothesis on the pathogenesis of heart defects is that CHARGE syndrome is a neurocristopathy.\textsuperscript{28,35}

Cardiac neural crest cells migrate from the neural tube into the caudal pharyngeal arches, and a subset migrates into the distal cardiac outflow tract.\textsuperscript{36} These cells are known to be important for the development of the pharyngeal arches, the septation of the outflow tract, and closure of parts of the cardiac septum. Ablation of premigratory cardiac neural crest cells in animal models results in conotruncal cardiac abnormalities, like persistent truncus arteriosus and malalignment of the outflow tract.\textsuperscript{36,37} Whether neural crest cells also contribute to other portions of the heart like the atrioventricular valves is debated.\textsuperscript{37,38} Conotruncal defects and AVSD are over-represented in patients with a \( CHD7 \) mutation, which supports the neural crest hypothesis. However, not all heart defects in patients with \( CHD7 \) mutations can be explained by neural crest cell involvement such as
The cardiac phenotype in patients with a CHD7 mutation

hypoplastic left heart syndrome and AVSD. Moreover, rescue of Chd7 expression in neural crest cells of heterozygous mouse embryos did not rescue the defects of the pharyngeal arch arteries, whereas rescue of Ch7 expression in both neural crest cells and the pharyngeal ectoderm led to a normal phenotype of the pharyngeal arch arteries. Thus, CHD7 has an effect on cardiac development via other cardiac cell types as well. Irrespective of these observations, CHD7 seems to be involved in the signaling pathways that regulate the migration or differentiation of cardiac neural crest cells during cardiac development.

Further research is necessary to fully understand how CHD7 affects cardiac development and which other genes are involved in this pathway. What can be concluded from the functional and clinical studies is that the level of CHD7 must be strictly regulated for normal development, including cardiac development. This is supported by our finding that patients with a truncating mutation in CHD7 more often have a congenital heart defect than patients with a less detrimental, missense, or splice site mutation. Nonetheless, in patients with the same mutation, phenotypes differ strikingly, even in monozygotic twins. In our cohort, patients with the same mutation had different heart defects within the different groups of the development-based classification. So, the clinical variability is not explained by the type of CHD7 mutation alone in line with the multivariable effect of CHD7 mentioned above, which changes during development and between tissues.

In conclusion, the prevalence of heart defects in 74% of our patients with CHD7 mutation show that the CHD7 protein is important for cardiac development. Haploinsufficiency, especially because of truncating mutations, results in variable heart defects with a relative over-representation of AVSDs and conotruncal defects, supporting a potential role of CHD7 in the migration or differentiation of neural crest cells in the developing heart. However, the variability of the heart defects suggests a pleiotropic effect of CHD7 mutations, which is not only attributable to a defect of the neural crest cells’ lineage.

Unraveling the role of the CHD7 gene in the developing heart and identifying the signaling pathways influenced by CHD7 could significantly contribute to our knowledge on the mechanisms playing a role in congenital heart disease, which is one of the most frequent congenital anomalies seen in humans. For clinical practice, we advise cardiologists to be aware of other features of CHARGE syndrome in patients with congenital heart defects, especially if the patient has an AVSD or conotruncal defect.

Acknowledgments

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REFERENCES


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## Supplementary Table 1. Classification of congenital heart defects in 202 patients with a CHD7 mutation at Botto's main and large levels

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### The cardiac phenotype in patients with a CHD7 mutation

The classifications at the main and large levels of Botto’s system are shown for the 202 patients with a congenital heart defect and CHD7 mutation.

Abbreviations:
- Abn AV: abnormal atrioventricular valve
- AS: aortic stenosis
- ASD: atrial septal defect
- AVA: arch vessel anomaly
- AVSD: atrioventricular septal defect
- BAV: bicuspid aortic valve
- Coarctation: coarctation of the aorta
- DORV: double outlet right ventricle
- Ebstein: Ebstein anomaly
- HLHS: hypoplastic left heart syndrome
- HRHS: hypoplastic right heart syndrome
- IAA: interrupted aortic arch
- IVS: intact ventricular septum
- LAVV: left atrioventricular valve
- LVOTO: left ventricular outflow tract obstruction
- PA: pulmonary atresia
- PDA: persistant ductus arteriosus
- PS: pulmonary stenosis
- PVS: pulmonary valve stenosis
- RVOTO: right ventricular outflow tract obstruction
- SAS: supravalvular aortic stenosis
- SV: single ventricle
- TA: tricuspid atresia
- TAPVR: total anomalous pulmonary venous return
- TGA: transposition great arteries
- TOF: tetralogy of Fallot
- Truncus: truncus arteriosus
- VSD: Ventricular septal defect

#### REFERENCES
