



“Clinical and molecular effects of CHD7 in the heart”

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<https://doi.org/10.1002/ajmg.c.31590>

AUTHORS AND THEIR CONNECTION TO THE CHARGE SYNDROME FOUNDATION:



Nicole Corsten-Janssen, MD, is a clinical geneticist at University of Groningen, University Medical Center Groningen, Department of Genetics. She is a protégé of Conny van Ravenswaaij-Arts and continues to work with the CHARGE Center in the Netherlands.

For her PhD, Nicole studied heart defects in CHARGE syndrome from a clinical point of view. She has conducted research and presented at multiple CHARGE syndrome conferences.



Peter Scambler, MD, is head of the Section of Developmental Biology of Birth Defects at UCL Great Ormond Street Institute of Child Health, London. His research examines the developmental genetics of 22q11.2 deletion and CHARGE syndromes, including collaborations with Conny van Ravenswaaij-Arts, Albert Basson, and others in the greater CHARGE community.

SUMMARY OF THE PAPER:

Abstract: Heart defects are a frequent cause of both illness and death in CHARGE syndrome (CS). Here we review the clinical and molecular aspects of *CHD7* that are related to the cardiovascular manifestations of the syndrome. The types of heart defects found in CS are variable. When compared to patients with isolated heart defects, those with *CHD7* mutations show a higher percentage of atrioventricular septal defects and outflow tract defects, including aortic arch anomalies. Mouse models confirm a role for *Chd7* in multiple processes during heart development, including formation of great vessels, atrioventricular cushion development and septation of the outflow tract. Emerging knowledge about the function of *CHD7* in the heart indicates that it may act in concert with transcription factor genes (e.g. *TBX1* and *SMADs*) to regulate genes such as *p53* and the cardiac transcription factor *NKX2.5*.

Additional summary: In this paper, the authors focus on the effect of *CHD7* in the heart from a clinical point of view and relate it to what is known about molecular development of the heart using mouse and other animal models. Heart defects are reported in about 75% of individuals with CS due to pathogenic *CHD7* mutations. Individuals with missense or splice-site mutations have a lower rate of heart defects (58%) than those with truncating mutations (80%). Figure 1 shows the relative frequency of various heart defects in individuals with CS compared to those with isolated (nonsyndromic) heart defects. *CHD7* mutations have not been found in individuals with isolated heart defects, but they have been identified in a small percentage of individuals with heart defects with other anomalies (without obvious CS). *The authors recommend that genetic panels for syndromic heart defects should include CHD7.*

There follows a description of heart embryology, along with a figure illustrating what is known about specific pathways where *Chd7* is active during heart development, particularly involving the tumor-suppressor protein p53. Loss of *CHD7* appears to activate p53. In one mouse model, partially deactivating p53 resulted in fewer CS features in the *Chd7* mice. Other complex pathways where *CHD7* is thought to be involved are presented, with complex descriptions of the animal models.

From here the authors turn to the clinical overlap between CS and other syndromes with heart defects. Table 2 is a large table showing the overlap in features of CS and seven other syndromes. They conclude by saying that the cardiac phenotype in patients with a *CHD7* mutation is variable, with a relative over-representation of AVSD and outflow tract defects including aortic arch anomalies. *Chd7* deficient mice have a cardiac phenotype similar to human CS. Molecular studies have shown some underlying mechanisms and genetic interactions during cardiac development that give rise to congenital heart defect in patients with *CHD7* mutations and overlapping heart syndromes.

WHAT DOES THIS MEAN TO FAMILY/PERSON WITH CHARGE?

This paper will not change anything directly in terms of care. But it shows the progress that is being made towards the understanding of the complex embryology of the heart, the role of *CHD7*, and the interaction of *CHD7* with other genes and pathways. The table of CS and seven other syndromes with overlapping features is very interesting – everything is interconnected.

SHOULD I READ IT? SHOULD ONE OF MY DOCTORS READ IT?

Much of the middle portion of the paper is complex lab information that may be difficult to understand. If you are interested in cardiac embryology and animal models, this is for you. The beginning and the end present more information about clinical findings, which may be of interest to more people. If your child has atypical CS or may have a different diagnosis, Table 2 showing overlapping features may be of interest.

FULL CITATION:

Corsten-Janssen N, Scambler PJ. Clinical and molecular effects of *CHD7* in the heart. *Am J Med Genet Part C Semin Med Genet.* 2017;175C:487–495. <https://doi.org/10.1002/ajmg.c.31590>