# Frequently Asked Questions, Part II
# More about Copy number variants (CNVs), Variants of Uncertain Significance (VUS) in Chromosome Microarrays, with a special focus on Congenital Heart Defects (CHDs)

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**How common are genetic disorders in children with CHDs?**

Congenital heart defects are the most common form of birth defects, affecting almost 1% of all newborns. Genetic factors play a role in most CHDs, which are typically isolated and nonsyndromic, and inherited as multifactorial traits, in which gene-environmental interactions contribute to the etiology. However, about 30% of all CHDs, including some of the isolated and many of the syndromic forms, are caused by single-gene disorders or chromosomal anomalies, such as aneuploidy or CNV.

**Is chromosome microarray a first-line test for CHD?**

Conventional chromosome analysis can detect aneuploidies like Trisomy 21 or Turner syndrome in about 10% of children with CHDs. However, smaller CNVs or microdeletions and microduplications, are beyond the resolution of the microscope used for traditional chromosome analysis. Because chromosome microarray can detect these smaller CNVs, it has become the preferred first test, in most situations, for children with congenital anomalies of all types, including heart defects.

**When is chromosome analysis, rather than microarray, the preferred test?**

Chromosome analysis is a better first-line test when an aneuploidy is suspected or when there is a family history of multiple miscarriages or infertility when a balanced translocation is suspected. Both conventional chromosome analysis and microarray testing can detect aneuploidy. However, microarrays, which analyze DNA rather than whole chromosomes, cannot identify translocations, inversions or other structural chromosome rearrangements, whereas, in conventional cytogenetics, the microscopic analysis of banded chromosomes examines explicitly the shape and morphology of chromosomes.

**How common are CNVs in children with CHD?**



Children with CHDs and other extracardiac congenital anomalies account for 20-30% of all CHDs. In this group, 15-20% have pathogenic CNVs. Children with apparently isolated CHDs also have more pathogenic or likely pathogenic CNVs when compared with the general population. The number of CNVs in this group is 4-10% depending on the study. Both *de novo* and familial CNVs are more common in children with CHD. It is important to understand that a CNV can act as one of many contributory traits in a multi-hit model, or it can be the principal cause of a CHD.

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**Can the same pathogenic CNV be associated with more than one type of cardiac defect?**

Several recurrent de novo CNVs are associated with more than one type of CHD. Example: The classic 3Mb deletion of 22q11.2 that includes TBX1 is seen in >10% of Tetralogy of Fallot, 35% of truncus arteriosus, and 50% of interrupted aortic arch type B. However, some CNVs are specific to one type of cardiac defect. For instance, large CNVs on the X-chromosome are found in males with coarctation of the aorta.

**Can a CNV in the same chromosome region cause CHD both as a microduplication and as a microdeletion?**

Yes. Dosage sensitivity for critical genes may work both ways, as copy number gain or loss may disturb the same pathway.

Example: Microduplications and microdeletions for the same regions of 1q21.1 (*GJA5)*, 3p24.1 (*TGFBR2*), 8p23.1 (*GATA4*) and 22q11.2 (*TBX1*) have been reported in CHDs.

**Are recurrent CNVs seen in both isolated and syndromic CHDs?**

The same recurrent CNVs are seen in children with both isolated and syndromic CHD. It may be that the syndromic forms of CHDs have a wider phenotype, including milder forms, that we are just starting to appreciate, or it may be that other modifying factors may contribute to the range of phenotypes that are expressed by a CNV in a given gene or chromosome region.

**Why is a CNV diagnosis important in the care of children with CHDs?**

Outcomes for CHDs vary with the type and severity of the cardiac defect, the presence or absence of associated anomalies and with the underlying cause. Early identification of genetic diagnosis can alter the clinical course of a child with a CHD. Children with CHD caused by a pathogenic CNV have more complications and a less favorable prognosis than their similarly affected peers without CNVs. Identifying these children early gives medical providers the chance to offer more appropriate care.

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**Practical applications:**

1. Recognize that recurrent CNVs associated with CHDs include important genes for cardiogenesis.

    a. Patients with isolated CHDs can have the same CNVs that are responsible for syndromic cardiac defects.

2. Utilize online resources (OMIM, www.omim.org; DECIPHER, rarechromo.org) for more information about recurrent and novel CNVs and the genes within them.


*References:*

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