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Commentary

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# Genetic Mechanisms of Neurodevelopmental Risk in Congenital Heart Disease: Mostly Unknowns

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## *Running Title: Genetics of Neurodevelopmental in Congenital Heart Disease*

*Congenital heart disease (CHD) is the most common major congenital anomaly. As survival rates have improved in the past decades, neurodevelopmental delay and disability have been identified as among the most common non-cardiac conditions among people with CHD. This increased neurodevelopmental risk could be due to intrinsic patient factors, such as genetic risk and CHD type, or extrinsic factors such as operative exposures and nutritional status. Genetic risk contributes to the majority of CHD, including molecular diagnoses such as Trisomy 21 and 22q11 deletion syndrome. Both Trisomy 21 and 22q11 deletion syndrome are also associated with increased risk of neurodevelopmental delay or disability, but the precise molecular mechanisms underlying this risk is not well characterized. This is also true of single gene causes of both CHD and neurodevelopmental risk, such as CHD7. Future research should include patients with known genetic diagnoses or genomic data, which will better illuminate the complex contributions of genetics, extrinsic, and intrinsic factors to neurodevelopmental risk among people with CHD.*

**Keywords:** *Congenital heart disease; Genetics; Neurodevelopment*

## Introduction

Congenital heart disease (CHD) is the most common major congenital anomaly, occurring in approximately one percent of live births globally [1,2]. Yet, an underlying genetic etiology is identified in only 20 to 30 percent of people with CHD [3,4]. The role of genetic factors in CHD risk is demonstrated by the high recurrence rate within families and its association with genetic syndromes [5,6]. CHD is associated with a higher incidence of neurodevelopmental delay and disability (NDD) [7-11], and there has been recent interest in the contribution of genetics to these outcomes [12,13]. As the survival rate for individuals with CHD has significantly improved [14], the excess risk for impairments in motor skills, language abilities, and social-emotional functioning have been become more apparent [11,15-19]. Both factors intrinsic to an individual patient, such as genetic variants or structural type of CHD, as well as extrinsic factors, such as nutritional supports and anesthesia exposures, can influence the risk of NDD [20,21]. However, as few multicenter trials include patients with known genetic diagnoses or genomic data [22], we have a limited understanding of how genetic variation contributes to neurodevelopmental outcomes among individuals with CHD.

## Early Alterations in Neurodevelopment

Recent studies suggest that the effects of CHD on brain development begin in utero [23-25]. Fetal brain volume as measured by magnetic resonance imaging is decreased in CHD, and in the overall cohort those with lower brain volume had lower scores for cognitive, language, motor, and adaptive functioning at two years of age [26,27]. In a multivariable model adjusting for socioeconomic status and postnatal factors such as surgical bypass time and length of initial hospitalization, fetal brain volume remained the most consistent predictor of neurodevelopmental outcomes, explaining 18% to 45% of the variance in outcomes. Similarly, studies utilizing pre-operative MRIs of infants with

CHD have demonstrated evidence of early ischemic injury prior to CHD surgery [11,23,28]. These findings underscore the importance of considering prenatal factors in the assessment of neurodevelopmental risk.

The impact of certain risk factors for adverse neurodevelopmental outcomes has also been investigated in CHD patients, including timing of major surgery and anesthesia exposure [29-31], and fetal or postnatal hypoxic injury in cyanotic phenotypes [26,27,32-34]. There are multiple mechanisms by which CHD affects brain development, including intrinsic factors, e.g. genetics and CHD type [12,13], as well as extrinsic factors such as surgical/medical interventions, inflammatory responses, and environment exposures [15,20,23] (Figure 1).

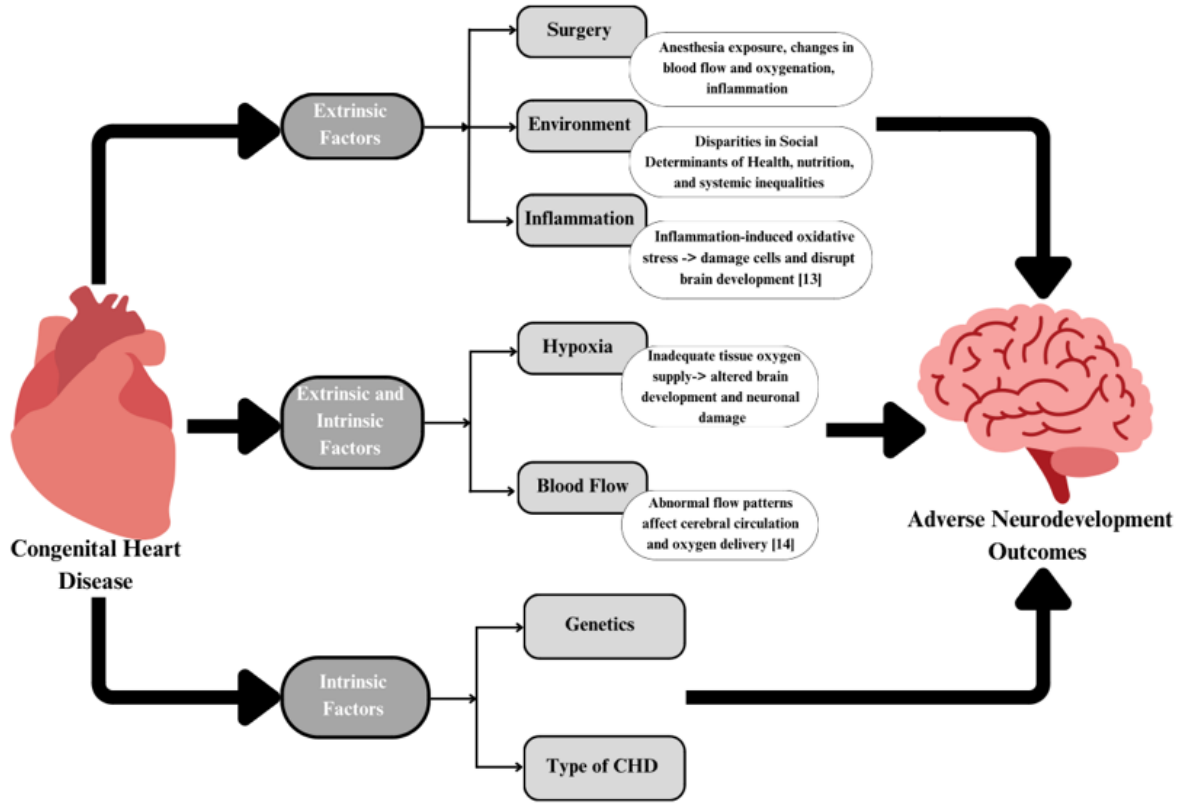


**Figure 1:** Summary of factors that could influence neurodevelopment among persons with congenital heart disease. Intrinsic factors are those which are not currently easy to modify, such as patient genetic variants or the structural type of CHD. However, the downstream mechanisms by which these factors impact NDD may be targets for therapeutic interventions. By contrast, many extrinsic factors could be targeted directly to mitigate NDD risk.

Additionally, factors such as hypoxia and altered blood flow [20,35,36], which can be considered both intrinsic and extrinsic to CHD, have been identified as potentially modifiable factors that may impact brain development in CHD individuals. As genetic causes of CHD could also directly cause NDD via influences on in utero brain development, or by impacting neuronal resiliency during exposure to stressors such as hypoxia or surgery, it remains unclear to what extent the variability in outcomes due to early life exposure are attributable to intrinsic genetic risk.

## Genetic Risk and Neurodevelopment

The relationship between CHD, genetics, and neurodevelopment is complex. Roughly 440 genes are known to cause human CHD, including genes encoding transcription factors (*GATA4, NKX2-5, TBX5*), cell signaling molecules (*NOTCH1*), structural proteins (*VEGF*), chromatin modifiers (*KMT2D*), and cilia-related proteins (*NODAL*) [4,37-40]. Genetic variants that cause CHD may also directly influence brain development [3,11,13,41]. For example, specific genetic variants such as copy number variants involving 1q21.1, 16p12.1-11, and 8p23.1 have been identified in people who have high rates of both CHD and neurodevelopmental disorders. Due to limited integration of genetic risk in clinical studies of CHD outcomes, the exact mechanisms by which genetic changes alter human development are often not known [39,42,43].

Two common genetic causes of CHD, Trisomy 21 [44-47] (T21, also known as Down syndrome) and 22q11 deletion syndrome [48-51] (22q11DS, also known as DiGeorge or velocardiofacial syndrome), are associated with increased risk of both CHD and neurodevelopmental delay or disability. As both disorders result in the dysregulation of many genes, it could be that either

single genes or multiple genes lead to the shared risk to heart and brain development. Human chromosome 21 contains more than 500 genes, including *DSCAM* (Down Syndrome Cell Adhesion Molecule) and *COL6A* (Collagen VI). Overexpression of *DSCAM* and *COL6A* leads to CHD in mice [3,52], while copy number variants involving *DSCAM* have been associated with intellectual disability, autism, and bipolar disorder [53]. Similarly, the *TBX1* gene within the 22q11DS locus is associated with CHD [54]. Findings from mouse models have also revealed that loss of *TBX1* results in deficits in social interaction and communication, impaired working memory, and heightened anxiety [55,56]. In one study, people with 22q11DS had a longer interoperative bypass time, highlighting the potential interaction between intrinsic genetic variants and extrinsic medical factors [57.] Further research into the multifaceted impact of genes relevant to T21 and 22q11DS on both cardiac and neurological development holds promise for developing targeted interventions for individuals with CHD.

Once single-gene disorder that often includes CHD and neurodevelopmental disorders is CHARGE (ocular coloboma, heart malformations, atresia of the choanae, retardation of growth, genital hypoplasia, and ear abnormalities). CHARGE is an autosomal dominant disorder resulting from variants in *CHD7*, a chromatin helicase [58-60]. Developmentally, *CHD7* is expressed in the neural crest, and this broad expression is hypothesized to account for the observed pleiotropy [61,62]. However, there is limited understanding of genotype-phenotype associations to explain the variation in neurological and psychiatric outcomes for individuals with CHARGE who also have CHD.

## Conclusion

In conclusion, even among established genetic causes of CHD, we have a limited understanding of the molecular and cellular mechanisms underlying the shared risk to heart and neurodevelopment. Beyond genetics, the role of extrinsic factors, such as the in-utero environment [23] and social determinants of health [63] also contribute to the complexity of neurodevelopmental outcomes among people with CHD. Modifying NDD risk factors, such adjunctive therapies during surgery that maximize neuroprotection [64] or pharmacogenetically-informed medication choices that reduce off-target effects [65], provide opportunities for novel interventions to reduce NDD. As many studies exclude participants with known genetic diagnoses, we have a limited understanding of the relationship which NDD risk factors may be relevant to patients with genetic disorders such as T21 or 22q11DS, nor the molecular mechanisms by which any risk factor is contributing to NDD. Designing studies to include prenatal, genetic, and postnatal factors are needed to build a more comprehensive model of the interplay between these factors and ensure that results can be translated to meaningful clinical interventions. Future research should aim to comprehensively consider the interplay of genetics, extrinsic, and intrinsic factors.

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