

## GENETIC PERSPECTIVE OF THE CONGENITAL HEART DISEASE

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**Contribution**

SA conceived the idea. Data collection and manuscript writing was done by SA and KA. All the authors contributed equally to the submitted manuscript.

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Congenital heart diseases (CHDs) are the structural abnormalities that may occur in the heart, greater veins and arteries or may include the septum between the ventricles and atria that mainly happen during the developmental stages of the heart in the neonates. It is the most frequent birth defect affect 1% of all infants.<sup>1,2</sup> The CHDs includes following major categories: septation defects, cyanotic heart diseases and left sided obstruction defects. The septation defects can be further divided into ventricular septal defects (VSDs), atrioventricular septal defects (AVSDs) and atrial septation defects (ASDs). The cyanotic heart disease occurs due to many defects such as tetralogy of Fallot (TOF), Ebstein's anomaly of the tricuspid valve, double outlet right ventricle, pulmonary atresia, total anomalous pulmonary venous connection and tricuspid atresia. The left sided obstructive lesions involves the hypoplastic left heart syndrome, interrupted aortic arch, aortic stenosis, mitral stenosis and aortic coarctation.<sup>3</sup>

Globally, each year, 1.35 million infants are born with the congenital heart defects. Many studies suggested that the overall incidence of the congenital heart disease is relatively similar across the populations. It is considered as one of the major causes for stillbirths and early fetal demises. The prevalence of congenital heart defects varies across the globe due to the parental consanguinity e.g. the prevalence of CHDs in Asia is 9.3 per 1000 live births and in North America it is 8.1 per 1000 live birth.<sup>4</sup>

In Pakistan approximately 40,000 children per year are born with CHD.<sup>5</sup> A study conducted by the Hassan et al. reported the prevalence approximately 4 per 1000 live births, and the VSDs showed the highest percentage i.e. 29%. The reason for the low numbers than the actual figures includes that the many cases may not become clinically evident due to the very small atrial or ventricular defects. Second, they excluded the stillborn fetuses as in abortuses and intrauterine deaths the malformations appear 5% higher as compared to the live born infants. Third, diagnosis of 50-60% cases after 1 month of birth.<sup>6</sup> In Pakistan, the diagnosis of the CHD cases in most of the cases late. There are several factors which contribute toward the delaying of this process such as socioeconomic constraints and the dearth of adequately trained health system. Thus, there is an immediate need to improve the public awareness and develop an efficient referral system in low income and lower middle income countries for early diagnosis and management of the congenital heart disease cases.<sup>7</sup>

It is a multifactorial disease, which is broadly classified into the two major components one is the environmental and second includes genetic factors. The non-genetic factors occur during the fetal development, such as chemical teratogens exposure (e.g. retinoic acid), viral infections (e.g. rubella) and maternal diseases (e.g. diabetes) has been well established in causing the congenital heart diseases.<sup>8</sup> The genetic architecture of CHD is not completely understood.<sup>9</sup> After the first report regarding the significant genetic contribution of congenital heart diseases in the 1950s, much research in the field of genetics in the development of CHDs has been done and in the 1960s the notable work of James Nora on multifactorial inheritance was published.<sup>10</sup> Over the past ten to fifteen years the understanding of the genetic factors contributing in CHDs has advanced at a rapid pace, particularly the availability of molecular techniques has facilitated the gene discoveries such as copy number variants (CNVs). Moreover, for the confirmed diagnosis the next generation sequencing (NGS) is now commonly available and used by the cardiologist, molecular geneticist and genetic counselors.<sup>11</sup>

The genetic pattern of congenital heart diseases is heterogeneous. The mutations in CHDs could be familial or sporadic in nature. Familial congenital heart diseases occur as X-linked trait, autosomal dominant and autosomal recessive that are expressed with the variety of clinical manifestations and are highly penetrant. These mutations can cause early mortality and reduced reproductive fitness. These mutations are mostly *de novo* in nature if these are X-linked or dominant, and particularly dominant *de novo* mutations are the key contributors to the congenital heart defects. Moreover, the sporadic dominant mutations in neonates are responsible for the high rate of recurrence. The alternative genetic models include the polygenic variants and autosomal recessive far less is understood about them but there is strong evidence that recessive alleles can increase 2 to 3 fold risk of CHD phenotypes in population due to the parental consanguinity.<sup>12</sup>

The association of chromosomal syndromes with CHDs led to the classification of these congenital heart defects into two broad categories: isolated CHDs (Non-syndromic) and syndromic CHDs.<sup>12</sup>

Non-syndromic CHDs etiology can be elucidated by the multifactorial model of inheritance. The genetic predisposition is polygenic, however a single locus is considered to be implicated. The changes in the number of copies of particular sequences which is known as copy number variants identified as a major contributing factor in CHDs. The previous evidence suggests that the pathogenic CNVs are involved in the AVCDs, TOF and left sided lesions. The Mendelian monogenic transmission pattern has also been observed for the AVCD, ASDs and left sided obstructive lesions.<sup>13</sup>

Gene mutations that responsible for the isolated congenital heart defects can be categorized into 3 functional classes one is the cardiac structural proteins, second is the transcriptional regulation and the third is the signal transduction. The significance of genetic polymorphisms in the genes involved in the transcription was explained by the studies conducted on the following candidate genes: IRX4, GATA5, NKX2-5, GATA4, NKX2-6, GATA6, ZIC3 and TBX20. In addition, depending on whether the mutation is loss or gain it can result in increase or decrease the physiological levels of encoded proteins.<sup>1</sup> The gene mutations responsible for CHD results in haploinsufficiency which strongly suggests that for the normal heart formation gene dosage is critical.<sup>14</sup>

The second major category is syndromic CHD in which 30% of patients can be affected by the Mendelian syndromes, chromosomal abnormalities such as mutation that cause abnormality causing loss or addition of the complete chromosome known as aneuploidy and non-Mendelian associations. The most frequent chromosomal abnormalities investigated by using the fluorescent in SITU hybridization analysis are the 22q11.2 deletion DiGeorge with conotruncal heart defects. The standard karyotype use for the classic chromosome anomalies in Turner syndrome, Down syndrome, Patau syndrome and Edwards's syndrome. Each of these anomalies associated with the particular types of CHDs, as occurring for aortic coarctation and Turner syndrome or AVCD and Down syndrome. Monogenic syndromes typically associated with congenital heart defects such as Noonan syndrome, Cornelia de Lange syndromes, Alagille, Kabuki, Holt–Oram, CHARGE, Marfan, and Ellis–van

Crevelde. Malformation associations include the: VACTERL, Cantrell and Goldenhar.<sup>13</sup>

The research on the congenital heart diseases shows remarkable progress with vital inferences. It has been proven that the congenital heart disease is a pleiotropic, heterogeneous and multifactorial disease involving complex interactions between genes and the environment. The point mutations in the majority of cases cause the isolated CHDs whereas, aneuploidy or large duplication or deletion results in syndromic CHD. The process of normal heart development can be disturbed due to defect in a gene which is the part of heart development pathway. Moreover, the advancement in the molecular biology techniques involving NGS leads to the identification of the role of genes involve in causing the CHDs and hence help in diagnosis and treatment of this fatal disease.

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