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CLASSIFICATION OF VENTRICULAR SEPTAL DEFECTS (VSDS) ON THE BASIS OF GENETICS

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Contribution
SS conceived the idea. Data collection and manuscript writing was done by SS, S, and SH. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Ventricular Septal Defects (VSDs) account for 30% to 60% of all congenital heart diseases in neonates. VSDs are one of the commonest abnormalities, affecting human heart and has been the focus of interest in several studies since years. Strong evidence regarding the involvement of genes in causing VSDs has been accumulated over the years. The classification based on genetics, including three types of VSDs; VSD1, VSD2 and VSD3, is the focus of this paper.

Keywords: Congenital Heart Disease, Ventricular Septal Defect, Tetralogy of Fallot

INTRODUCTION

Human heart develops after a complex series of events and pathways. The events should run in a correct sequence, if there is any disturbance in the process, it will lead to a number of heart defects.[1] Congenital cardiac malformations are clinically categorized into more than 18 different types; the most common among these is the Ventricular septal defect (VSD).VSDs account to 30% to 60% in neonates, suffering from congenital heart disease and are one of the primitive abnormalities, affecting the human heart.[2-4] It has been extensively investigated in several studies since years. Such a defect results in the mixing of blood in the right and left ventricle of heart. Most forms of VSD can be corrected by surgery.[5, 6]

VSD can be divided into either isolated VSD (no extra cardiac symptoms) or syndromic (associated with other congenital cardiac defects and extra cardiac symptoms). This heart defect also exists as a component of several complex malformations, including Tetralogy of Fallot (TOF) and univentricular heart.[2] Untreated VSDs lead to the ventricular dysfunction, cardiac enlargement, Eisenmenger's syndrome, pulmonary hypertension, delayed development of fetal brain and ultimately cardiac death.[2, 7, 8] It is a prominent cause of morbidity and mortality in infancy.[9]

A previous study published in 1977 with the title of "Natural history of Ventricular septal defects" reported, the size of defect/hole matters a lot in VSDs cases. In early age, spontaneous closure of smaller defects usually occurs but the chances of closure become significantly less with the increasing age (years).[10] The rate of spontaneous closure vary depending upon different cases and studies but the range of closure is almost 11 to 70%.[11, 12]

Classification of VSD

For the purpose of unifying reporting system all over the world and evaluating the genetic causes of defect, extended classification system of VSDs is present. This classification system is based on the location, number, types and genetics of the defect.[4] European Association for Cardiothoracic Surgery, provides the nomenclature of VSD on bases of defect's location (Figure 1). This nomenclature comprises of four different types;[6]

- Type 1 Sub-arterial,
- Type 2 Perimembranous or paramembranous
- Type 3 Inlet or atrioventricular canal
- Type 4 Muscular

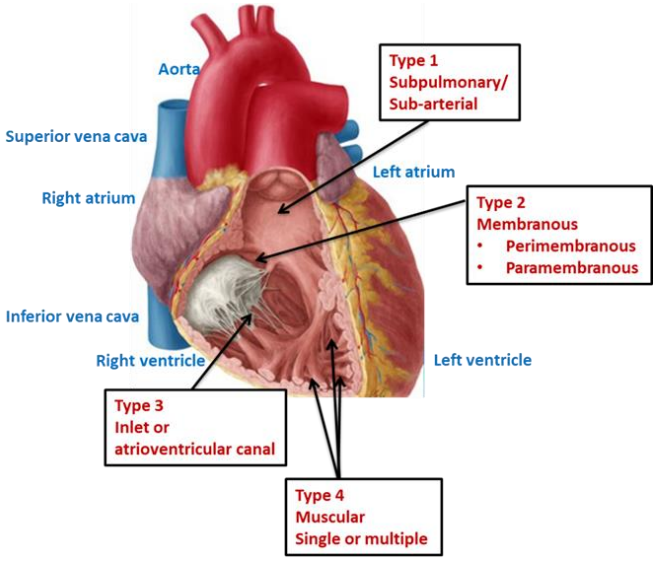

Figure 1: Nomenclature of VSD on bases of defect's location

In the infundibular portion of the right ventricular, type 1 defects lie beneath the pulmonary valve. In Asian populations, prevalence of type 1 defect is higher, reaching up to 30%. Spontaneous closure is uncommon in type 1 defects.[13] There are further two subtypes of type 1 defects, (Type Ia) *without* pulmonary infundibular stenosis, (Type Ib) *with* pulmonary infundibular stenosis.[14] Type 2 defects account up to 70% of all defects.[13] As name indicated, type 2 VSD located in the membranous portion of the ventricular septum. Perimembranous or paramembranous are further subtypes of type 2 defects.[15] Type 3 defects account for 5% in all defects, and lie in the right ventricular septum at posterior inlet portion correspond to outlet portion of left ventricular septum.[13] The defect expands superiorly to membranous septum. Type 4 defect is muscular defect and this includes a variety of single or multiple defects in the muscular septum.[16]

Muscular defects comprise about 15-20% of all defects.[13] Frequently, type 4 defects are present in multiple numbers. Muscular defects are more likely to close spontaneously, by the development of septal muscles.[5] Furthermore, the classification based on number of VSDs in heart consists of two classes, single VSD and multiple VSDs.[4] The mortality rate of single VSD closure is less than 1%. In postoperative period, multiple VSDs escalate the mortality rate up to 7%. Smaller VSDs are restrictive due to presence of pressure gradient across the ventricle while the larger VSDs said to be nonrestrictive due to the equal pressure in left and right ventricular. Smaller restrictive VSD remains asymptomatic in infants.[5, 17]

Classification on basis of genetics

Abnormally developed interventricular septum, is a complex pathogenic process implicated due to the environment as well as genetic risk factors. Evidences highlight the major genes involved in VSDs. The classification based on genetics, including three types of VSDs; VSD1, VSD2 and VSD3. According to Online Mendelian Inheritance in man (OMIM), ClinVar, UniprotKb/swiss-prot and genetic testing registry the unaccompanied genetic cause of VSD1 is *GATA4* gene (https://www.omim.org/entry/614429?search=VSD&highlight=vsd).

GATA transcription factors are a family of DNA binding proteins having zing finger domains that bind to the consensus sequence (5'-AGATAG-3'/'5-WGATAR-3') GATA of the target gene. GATA family consists of GATA1, GATA2, GATA3, GATA4, GATA5 and GATA6.[18] Among them, GATA4, 5 and GATA 6 predominantly express in human embryonic heart. Zinc finger cardiogenic transcription factor (GATA4) plays a critical role in cardiogensis.[18] GATA4 is an essential component that regulates the septal development and cardiomyocyte proliferation.[19] In humans, *GATA4* gene is located on chromosome 8p23.1-p22 and contains 7 exons that encode for a protein of 442 amino acids (Table 1).[2, 20-22]

Gene expression in cardiomyocytes is regulated by the coordinated effect of GATA4 with TBX5, both bind to the cardiac super enhancer. Another important task completed by the complex of GATA4 and TBX5 is the down regulation of endothelial and endocardial gene expression.[19] Cardiac myocyte enlargement promotes by the cooperation of GATA4 with NKX2-5 (Figure 2).[23] Certain genetic variants of GATA4 are reported that can altered protein function and structure by change of even single amino acid (Table 2 and 4).

Table 1: Exons of Genes (GATA4, CITED2 and NKX2-5)

Exon	Start	End	Length (bases)
VSD 1: Exons of GATA4 gene			
ENSE00002176206	11,676,959	11,677,063	105
ENSE00002156958	11,700,511	11,700,778	268
ENSE00003674454	11,748,916	11,749,085	170
ENSE00001612139	11,750,111	11,750,236	126
ENSE00000924803	11,755,046	11,755,133	88
ENSE00000924802	11,756,935	11,757,083	149
ENSE00002182412	11,758,293	11,760,000	1708
VSD 2: Exons of CITED2 gene			
ENSE00003737459	139,374,605	139,374,413	193
ENSE00003733992	139,373,952	139,373,469	484
ENSE00003711761	139,373,297	139,373,074	224
VSD 3: Exons of NKX2-5 gene			
ENSE00002134783	173,235,311	173,234,750	526
ENSE00002124364	173,234,140	173,234,048	93

Table 2: Genetic Variation of GATA4 and NKX2-5, causing amino acid change

Serial	Amino Acid change	Variation ID
VSD1; GATA4 gene Variation		
1	p.Ala6Val	VAR_067605
2	p.Arg43Trp	VAR_067606
3	p.Gly296Arg	VAR_067613
4	p.Glu359Lys	VAR_067617
5	p.Ser429Thr	VAR_067622
6	p.Ala442Val	VAR_067623
VSD2; NKX2-5 gene		
1	p.Pro59Ala	VAR_067586
2	p.Pro283Gln	VAR_067587

A gene strongly affiliated with the VSD2 is CREB-binding protein Cbp/P300 Interacting Transactivator with Glu/Asp rich Carboxy-Terminal Domain 2 (CITED2).[24, 25] Pertinent phenotype of VSD with this gene is perimembranous ventricular septal defect (HP: 0011682). *CITED2* gene is localized on chromosome 6q24.1, consisting on 3 exons encoding for the protein of 270 amino acids (Table 1). Variants of *CITED2* gene decrease the ability to mediate the expression of genes, crucial for heart development (VEGF and PITX2C) (Table 3).[26]

Homeodomain-containing transcription factor encoded by a gene *NKX2-5*, plays a crucial role in cardiogensis. NKX2-5 is a gene associated with VSD3. *NKX2-5* gene is located on chromosome 5q34; consists of 2 exons that translate protein of 324 amino acids (Table 1). *NKX2-5* is an essential gene for cardiac morphogenesis and normal cardiac development that's why it is a candidate gene for determining structural heart anomalies.[9, 27, 28] Myocardial lineage differentiation is regulated by the *NKX2-5* gene. It acts as a transcriptional activator in cooperation with GATA4.[23, 29] Genetic variations affect the gene expression of *NKX2-5* (Table 2 and 4).

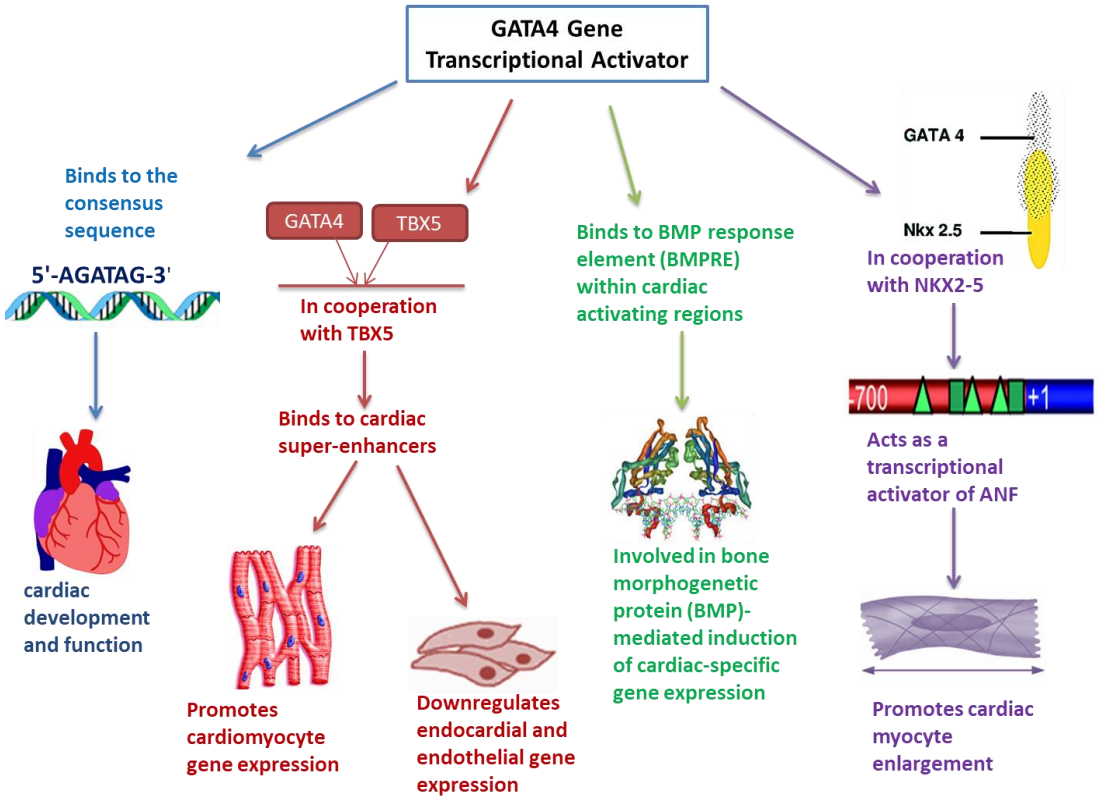

Figure 2: Functions of GATA4 gene

Table 3: Genetic Variation of CITED2 gene

No.	SNP ID	Variation	Type
1	rs1064797329 5	GCTGCTG/GCTG/GC TGCTGCTG	Coding sequence variant, in frame deletion, in frame insertion
2	rs1554233859 5	G/A	Coding sequence variant, missense variant
3	rs1000375923 5	A/C	Upstream transcript variant
4	rs1000475052 5	A/C/G	Upstream transcript variant
5	rs1001122499 5	G/A/C	Upstream transcript variant

Table 4: Genetic Variation (single nucleotide variant) of GATA4 and NKX2-5

No.	Variation	Significance	SNP ID	Location
GATA4 gene Variation (single nucleotide variant)				
1	NM_002052.4(GATA4): c.487C> T (p.Pro163Ser)	Conflicting interpretations of pathogenicity	rs387906769	Chromosome 8, 11566308: 11566308
2	NM_002052.4(GATA4): c.487C> T (p.Pro163Ser)	Conflicting interpretations of pathogenicity	rs387906769	Chromosome 8, 11708799: 11708799
3	NM_002052.4(GATA4): c.1075G> A (p.Glu359Lys)	Pathogenic	rs368489876	Chromosome 8, 11614521: 11614521
4	NM_002052.4(GATA4): c.1075G> A (p.Glu359Lys)	Pathogenic	rs368489876	Chromosome 8, 11757012: 11757012
5	NM_002052.4(GATA4): c.1325C> T (p.Ala442Val)	Pathogenic	rs146017816	Chromosome 8, 11615980: 11615980
6	NM_002052.4(GATA4): c.1325C> T (p.Ala442Val)	Pathogenic	rs146017816	Chromosome 8, 11758471: 11758471
7	NM_002052.4(GATA4): c.1220C> A (p.Pro407Gln)	Conflicting interpretations of pathogenicity	rs115099192	Chromosome 8, 11615875: 11615875
8	NM_002052.4(GATA4): c.1220C> A (p.Pro407Gln)	Conflicting interpretations of pathogenicity	rs115099192	Chromosome 8, 11758366: 11758366
9	NM_002052.4(GATA4): c.886G> C (p.Gly296Arg)	Pathogenic	rs104894073	Chromosome 8, 11607722: 11607722
10	NM_002052.4(GATA4): c.886G> C (p.Gly296Arg)	Pathogenic	rs104894073	Chromosome 8, 11750213: 11750213
NKX2-5 gene Variation (single nucleotide variant)				
1	NM_004387.3(NKX2-5): c.848C> A (p.Pro283Gln)	Uncertain significance	rs375086983	Chromosome 5, 172659699: 172659699
2	NM_004387.3(NKX2-5): c.848C> A (p.Pro283Gln)	Uncertain significance	rs375086983	Chromosome 5, 173232696: 173232696
3	NM_004387.3(NKX2-5): c.175C> G (p.Pro59Ala)	Pathogenic	rs387906775	Chromosome 5, 172661912: 172661912
4	NM_004387.3(NKX2-5): c.175C> G (p.Pro59Ala)	Pathogenic	rs387906775	Chromosome 5, 173234909: 173234909
5	NM_004387.3(NKX2-5): c.769C> G (p.Pro257Ala)	Pathogenic	rs387906776	Chromosome 5, 172659778: 172659778
6	NM_004387.3(NKX2-5): c.769C> G (p.Pro257Ala)	Pathogenic	rs387906776	Chromosome 5, 173232775: 173232775
7	NM_004387.3(NKX2-5): c.824C> T (p.Pro275Leu)	Uncertain significance	rs1060503097	Chromosome 5, 173232720: 173232720

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