Consanguinity and Congenital Heart Disease Susceptibility

Subjects: Health Care Sciences & Services | Cardiac & Cardiovascular Systems

Contributor: Salam Massadeh

Congenital heart disease (CHD) encompasses a wide range of structural defects of the heart and, in many cases, the factors that predispose an individual to disease are not well understood, highlighting the remarkable complexity of CHD etiology. Evidence of familial aggregation of CHD has been demonstrated in different communities and for different cardiac lesions. Consanguinity, particularly among first cousins, is an added risk factor for these families, particularly in societies where it is considered a common cultural practice, as confirmed in previous studies conducted in Saudi Arabia and other countries.

congenital heart disease consanguinity Saudi Arabia autosomal recessive autosomal dominant

1. Introduction

Despite rising awareness, congenital heart disease (CHD) is still a major cause of significant morbidity and mortality. It is clinically defined as a group of structural malformations present at birth and characterized by abnormal development of the heart and may be induced by environmental influence, altered gene function, or stochastic factors [1][2]. It is the most frequently diagnosed congenital disease affecting about 0.8–1.2% of live births worldwide [3]. Incidence and mortality from CHD vary globally. In the recent years, patterns, prevalence, and risk factors for CHD among newborns in Saudi Arabia have been studied. Interestingly, Kurdi et al. found in a three-year cohort case-control study that the prevalence rate for CHD was as high as 14.8 per 1000 births [4]. A plausible explanation for this comparable rate is consanguineous mating (inbreeding), a prominent phenomenon of the Arab countries that is widely accepted and practiced, particularly among first cousins. From a genetic standpoint, inbreeding has significant genetic implications for the offspring of inbred populations as it renders the genomes of the offspring autozygous due to identical chromosomal segments inherited from both parents. It is known form previous research that children born to closely related parents are at higher risk, approximately 2.0–2.5 times, of congenital malformations than the offspring of unrelated parents [5]. First-cousin marriage has been found to aggravate the estimation of malformation risk to 5–8% [6]. In Saudi Arabia, epidemiological reports have estimated that first-cousin marriages among families of children with CHD (41.6%) were significantly higher than the general population (28.4%) [7]. Therefore, the incidence of autosomal recessive congenital anomalies is expected to be higher in such highly inbred populations. Moreover, it has been shown that consanguinity increases the frequency of homozygosity for autosomal dominant traits, such as familial hypercholesterolemia, and possibly increases the prevalence of complex multifactorial conditions such as CHD [8].

Owing to the fact that Saudi Arabia has one of the highest consanguinity rates among Arab countries (>50%) besides its high fertility rate, it represents fertile ground for exploring the relevance of consanguinity to basic human genetics and applied clinical genetics [9]. Tracing back the biparental inherited recessive mutations of the same ancestral haplotype on which they reside has provided one of the most potent tools in interrogating the role of consanguinity in autosomal recessive disorders. Alkuraya has discussed a combination of techniques for mapping novel recessive disease genes.

2. Consanguinity and CHD

The most detrimental consequences of consanguinity are frequent occurrences of autosomal recessive diseases in the offspring, leading to increased morbidity and mortality rates [10][11]. Encounters between people with two or more of these abnormal genes are frequently causing the presence of combination of pathogenic variant genes influencing the clinical presentation. Monies et al. reported the clinical exome sequencing (CES) on >2200 previously unpublished Saudi families as a first-tier test, highlighting 155 genes to be recessive, disease-related candidates in the Saudi population [9]. Autosomal-recessive variants account for 77.2% variants, 98.4% homozygous, and 41.3% founder variants [9]. The percentage of the genome rendered homozygous by consanguinity seems to be directly proportional to the degree of consanguinity [12]. In a population with a high consanguinity rate, the homozygous gene pool will inevitably include defective alleles. On the other hand, a similar mutation rate in consanguineous populations leads to increased allelic and even locus heterogeneity incidences. This is exemplified by Kamal et al. with a report of four novel mutations in the *ALMS1* gene among Saudi patients with very rare autosomal recessive Alstrom disease presenting allelic heterogeneity in this inbred population [13].

Chehab et al. performed one of the largest cohort studies to date (>1500 patients) to assess the connection between consanguinity and CHD incidence. This cohort was represented by 19% of first-degree cousins, 5.9% of second-degree cousins, and 2.1% of other parental consanguinity. Comparatively, the consanguineous contributions in the control group without CHD were: 14% (first degree cousins), 5.9% (second degree cousins), and 3.6% (other parental consanguinity), showing a significant difference between the two groups. However, consanguinity rates vary greatly between different types of CHD. The highest incidences of atrial septum defect (ASD), tetralogy of Fallot (TOF), and valvular aortic stenosis (AS) were among the defects with consanguineous parents, supporting the theory that these defects may be caused by recessive genes [14]. The prevalence of consanguinity among patients with CHD is also evidenced in many other studies [7][15][16]. Monies et al. [15] have undertaken the most extensive study on the spectrum of mutational genetic diseases in the Saudi population in the diagnostic setting. The random selection of tested families representing all regions of the Kingdom aided the inference of essential patterns of genetic diseases in a highly consanguineous Saudi population relevant to the broader community of diagnostic NGS labs worldwide. The first 1013 Saudi families' first report was tested with seven gene panels and whole-exome sequencing (WES). A breakdown of the diagnostic yield by indication shows marked variability, with the highest yield being multiple congenital malformations in the prenatal setting followed by skeletal dysplasia. The duo testing of couples with deceased children was associated with a high diagnostic yield, reaching 83% when novel candidate genes are counted. Autosomal recessive pathogenic and likely pathogenic

mutations accounted for 71% cases and 97% homozygous cases, consistent with the high rate of consanguinity (78% of 482 families that provided the consanguinity information) in this cohort. Of the recessive positive cases, 33% were due to founder mutations [15]. This report has highlighted the role of consanguinity in identifying important patterns of genetic diseases in the Saudi population that are relevant to the international community. The study has also highlighted the need for in-depth research to understand the Saudi population's gene pool using NGS technologies. Parental consanguinity has been well proven to play a significant role in the prevalence of congenital heart disease in the Saudi population [16][17]. A study on a group of 1028 consecutive CHD patients identified through the Congenital Heart Disease Registry at King Faisal Specialist Hospital in the central region of Saudi Arabia, Riyadh, indicated that the proportion of first-cousin mating among CHD patients is significantly higher than that of first-cousin intermarriages reported in the general population. This study suggested that first-cousin consanguinity was significantly associated with ventricular septal defect (VSD), ASD, atrioventricular septa l defect (AVSD), pulmonary stenosis (PS), and pulmonary atresia (PA). Therefore, in a population with a high degree of inbreeding, consanguinity may exacerbate underlying genetic risk factors with prevalence of recessive component as causation of some cardiac defects [7]. Most recent cross-sectional studies found the prevalence of CHD in SA ranging between 2.1 and 10.7 per 1000 persons with VSD ranging from 29.5 to 39.5% followed by ASD (8.9% to 18.1%) and PS (6% to 12.4%). It was also stated that CHD occurrence in Saudi Arabia was significantly associated with Down's syndrome, consanguinity, and maternal diabetes [17]. Comprehensive data on cohort studies conducted over the span of 25 years to identify the prevalence of CHD in the Saudi population indicated the significance of consanguinity as a risk factor, as summarized in **Table 1**.

Table 1. Spectrum of epidemiological and consanguinity-associated congenital heart disease (CHD) studies in Saudi Arabia.

Study Reference	City	Study Setting	Data Collection Year	CHD Sample Size	Findings
Prevalence and Relative Frequency Studies					
[18]	AlQassim	Hospital	1988–1991	320	Relative frequency of VSD (38.5%) was higher ASD (11.5%), Pulmonary Stenosis (PS) (9%), PDA (8%) and AVSD (5%)
[19]	AlMadina	Hospital	1992–1995	1209	VSD (29.7%), ASD (26%), PS (16.1%) and PDA (13.2%)

Study Reference	City	Study Setting	Data Collection Year	CHD Sample Size	Findings
Prevalence and Relative Frequency Studies					
[20]	Asir	Hospital	1994–1996	335	VSD (32.5%), PDA (15.8%); ASD (10.4%); PS (10.1%); AVSD (3.6%) and mitral valve prolapse (3.6%); CoA (3.3%); obstructive aortic valve lesions (2.7%); TOF (4.5%); common ventricle (2.7%); PA with VSD (1.8%); D-transposition of the great arteries (1.5%); Ebstein anomaly (1.5%) and PA (1.2%).
[21]	Nation-wide	National registry	1998–2002	5865	The Southwestern region exhibits the highest burden of CHD. AlBaha with a prevalence estimate of 748/100,000.
[22]	Hofuf	Hospital	1997–2000	740	VSD was the most common defect (39.5%), followed by ASD (11.5%), PS (8.9%), PDA (8.6%), AVSD (3.5%), TOF (4.2%), CoA (2.7%), AS (3.5%)
[23]	Nation-wide	Household	2004–2005	95	The highest prevalence in the central region (27/10000). Northern and Eastern had a prevalence of (25/10,000) while the Southwestern region had a prevalence of 21/10,000. VSD was the most common defect (10/10,000).
[24]	AlMadina	Hospital	2007–2008	4348	CHD represents 34.4% of all cardiac problems. VSD represented 34.5% of all CHD diagnoses, followed by ASD (8.9%), PS (7.9%), PDA (6%), AVSD (3.8%), TOF (3%), AS (3.5%), CoA (2.8%), TGA (3.5%), and others (26%)

Study Reference	City	Study Setting	Data Collection Year	CHD Sample Size	Findings
Prevalence and Relative Frequency Studies					
[25]	Albaha	Hospital	2005–2010	2610	VSD (29.6%), PDA (9.5%), ASD (9.3%), PS (7.9%), AVSD (6.0%), TOF (4.7%), COA (3.4%), AS (3.0%), and TGA (1.9%)
[4]	Riyadh	Hospital	2010–2013	1179 CA cases	The birth prevalence of CA was 412/10 000 births, driven mainly by CHD (148/10,000). Isolated CHD found in 62.5%, distributed as VSD (28%), ASD (25.3%), PA and PS (6.8%) and severe CHD (20.4%)
[26]	Albaha	Hospital	2016–2017	2961	CHD was diagnosed in 49 patients of the positive test group, (1.7%) distributed as 5 (0.2%) patients with VSD, and 44 (1.5%) patients with large symptomatic PDA.
[27]	AlMadina	Hospital	2017–2019	1127	The acyanotic CHDs were the predominant lesions, accounting for 84.8% of all cases, while the cyanotic types accounted for 13%. PDA VSD, ASD, CoA and AVSD represented 27.9%, 24.8%, 18.9%, 6.4%, and 4.4% of the total cases, respectively. TOF (8.7%), followed by TGA (1.7%) and TA (1.1%), were the most common cyanotic CHDs.
Consanguinity-Associated Studies					
[7]	Riyadh	CHD Registry	1998	949	There was a significantly higher incidence of CHD among first-cousin marriages (41.6%) in comparison to the general population (28.4%).

transposition of the great arteries; CA, congenital anomaly.3. The Genetic Landscape of Non-Syndromic CHD.

Evidences of a genetic component in CHDs are familial recurrence and their association with inherited microdeletion syndromes [1]. Numerous CHD cases are known to be chromosomally abnormal, particularly those

Study Reference	City	Study Setting [32]	Data Collection Year	CHD Sample Size	Findings
Prevalence and Relative Frequency Studies					
[28]	Riyadh	CHD Registry	1998	891	It was found that consanguinity was significantly higher in the sample (40.4%) than in the general population (28.4%). Some forms of CHD are significantly associated with consanguinity, such as VSD, ASD, AVSD, PA, and PS, but not TOF, TA, AS, COA, or PDA.
[29]	Dhahran	Hospital	1996–2000	37 families	There were 23 consanguineous marriages (62%) in these families. Dilated cardiomyopathy was more common in consanguineous marriages; 26 cases vs. 2 in non-consanguineous marriages
[16]	Nation-wide	Household	2004–2005	11,554	CHD was the only disease associated with first cousin consanguinity in 56% of respondents.

6. Jaber, L.; Merlob, P.; Bu, X.; Rotter, J.I.; Shohat, M. Marked Parental Consanguinity as a Cause for Increased Major Malformations in an Israeli Arab Community. Am. J. Med. Genet. 1992, 44, 1–6.
7. Becker, S.; Al Halees, Z. First-Cousin Matings and Congenital Heart Disease in Saudi Arabia. Public Health Genom. 1999, 2, 69–73.
8. Teebi, A.S.; Teebi, S.A. Genetic Diversity among the Arabs. Community Genet. 2005, 8, 21–26.
9. Monies, D.; Abouelhoda, M.; Assoum, M.; Moghrabi, N.; Rafiullah, R.; Almontashiri, N.; Alowain, M.; Alzaidan, H.; Alsayed, M.; Subhani, S.; et al. Lessons Learned from Large-Scale, First-Tier Clinical Exome Sequencing in a Highly Consanguineous Population. Am. J. Hum. Genet. 2019, 104, 1182–1201.
10. Khoury, M.J.; Cohen, B.H.; Chase, G.A.; Diomond, E.L. An epidemiologic approach to the evaluation of the effect of inbreeding on prereproductive mortality. Am. J. Epidemiol. 1987, 125, 251–262.
11. Roberts, D.F. Genetic Disorders among Arab Populations. J. Med. Genet. 1997, 34, 704.

12. Woods, C.G.; Cox, J.; Springell, K.; Hampshire, D.J.; Mohamed, M.D.; McKibbin, M.; Stern, R.; Raymond, F.L.; Sandford, R.; Malik Sharif, S.; et al. Quantification of Homozygosity in Consanguineous Individuals with Autosomal Recessive Disease. Am. J. Hum. Genet. 2006, 78, 889–896.
13. Kamal, N.M.; Sahly, A.N.; Banaganapalli, B.; Rashidi, O.M.; Shetty, P.J.; Al-Aama, J.Y.; Shaik, N.A.; Elango, R.; Saadah, O.I. Whole Exome Sequencing Identifies Rare Biallelic ALMS1 Missense and Stop Gain Mutations in Familial Alström Syndrome Patients. Saudi J. Biol. Sci. 2020, 27, 271–278.
14. Chehab, G.; Chedid, P.; Saliba, Z.; Bouvagnet, P. Congenital Cardiac Disease and Inbreeding: Specific Defects Escape Higher Risk Due to Parental Consanguinity. Cardiol. Young 2007, 17, 414–422.
15. Becker, S.M.; Al Halees, Z.; Molina, C.; Paterson, R.M. Consanguinity and Congenital Heart Disease in Saudi Arabia. Am. J. Med. Genet. 2001, 99, 8–13.
16. Hamamy, H. Consanguineous Marriages. J. Community Genet. 2012, 3, 185–192.
17. Monies, D.; Abouelhoda, M.; AlSayed, M.; Alhassnan, Z.; Alotaibi, M.; Kayyali, H.; Al-Owain, M.; Shah, A.; Rahbeeni, Z.; Al-Muhaizea, M.A.; et al. The Landscape of Genetic Diseases in Saudi Arabia Based on the First 1000 Diagnostic Panels and Exomes. Hum. Genet. 2017, 136, 921–939.
18. El Mouzan, M.I.; Al Salloum, A.A.; Al Herbish, A.S.; Qurachi, M.M.; Al Omar, A.A. Consanguinity and Major Genetic Disorders in Saudi Children: A Community-Based Cross-Sectional Study. Ann. Saudi Med. 2008, 28, 169–173.
19. Alenezi, A.M.; Albawardi, N.M.; Ali, A.; Househ, S.M.; Elmetwally, A. The Epidemiology of Congenital Heart Diseases in Saudi Arabia: A Systematic Review. J. Public Health Epidemiol. 2015, 7, 232–240.
20. Fahed, A.C.; Gelb, B.D.; Seidman, J.G.; Seidman, C.E. Genetics of Congenital Heart Disease: The Glass Half Empty. Circ. Res. 2013, 112, 707–720.
21. Antonarakis, S.E.; Lyle, R.; Dermitzakis, E.T.; Reymond, A.; Deutsch, S. Chromosome 21 and Down Syndrome: From Genomics to Pathophysiology. Nat. Rev. Genet. 2004, 5, 725–738.
22. Bondy, C.A. Turner Syndrome 2008. Horm. Res. Paediatr. 2009, 71, 52–56.
23. Pont, S.J.; Robbins, J.M.; Bird, T.M.; Gibson, J.B.; Cleves, M.A.; Tilford, J.M.; Aitken, M.E. Congenital Malformations among Liveborn Infants with Trisomies 18 and 13. Am. J. Med. Genet. Part A 2006, 140, 1749–1756.
24. Al-Hassnan, Z.N.; Albawardi, W.; Almutairi, F.; AlMass, R.; AlBakheet, A.; Mustafa, O.M.; AlQuait, L.; Shinwari, Z.M.A.; Wakil, S.; Salih, M.A.; et al. Identification of Novel Genomic Imbalances in

Saudi Patients with Congenital Heart Disease. Mol. Cytogenet. 2018, 11, 9.

25. Lamb, A.N.; Rosenfeld, J.A.; Neill, N.J.; Talkowski, M.E.; Blumenthal, I.; Girirajan, S.; Keelean-Fuller, D.; Fan, Z.; Pouncey, J.; Stevens, C.; et al. Haploinsufficiency of SOX5 at 12p12.1 Is Associated with Developmental Delays with Prominent Language Delay, Behavior Problems, and Mild Dysmorphic Features. Hum. Mutat. 2012, 33, 728–740.
26. Hussein, I.R.; Bader, R.S.; Chaudhary, A.G.; Bassiouni, R.; Alquaiti, M.; Ashgan, F.; Schulten, H.-J.; Al Qahtani, M.H. Identification of De Novo and Rare Inherited Copy Number Variants in Children with Syndromic Congenital Heart Defects. Pediatr. Cardiol. 2018, 39, 924–940.
27. Alharbi, K.M.; Al-Mazroea, A.H.; Abdallah, A.M.; Almohammadi, Y.; Carlus, S.J.; Basit, S. Targeted Next-Generation Sequencing of 406 Genes Identified Genetic Defects Underlying Congenital Heart Disease in Down Syndrome Patients. Pediatr. Cardiol. 2018, 39, 1676–1680.
28. Dasouki, M.J.; Wakil, S.M.; Al-Harazi, O.; Alkorashy, M.; Muiya, N.P.; Andres, E.; Hagos, S.; Aldusery, H.; Dzimiri, N.; Colak, D. New Insights into the Impact of Genome-Wide Copy Number Variations on Complex Congenital Heart Disease in Saudi Arabia. OMICS A J. Integr. Biol. 2020, 24, 16–28.
29. Shaheen, R.; Al Hashem, A.; Alghamdi, M.H.; Seidahmad, M.Z.; Wakil, S.M.; Dagriri, K.; Keavney, B.; Goodship, J.; Alyousif, S.; Al-Habshan, F.M.; et al. Positional Mapping of PRKD1, NRP1 and PRDM1 as Novel Candidate Disease Genes in Truncus Arteriosus. J. Med. Genet. 2015, 52, 322–329.
30. Jaiyesimi, F.; Ruberu, D.K.; Misra, V.K. Pattern of Congenital Heart Disease in King Fahd Specialist Hospital, Buraidah. Ann. Saudi Med. 1993, 13, 407–411.
31. Baht, B.; Sheikh, A.; Khan, A.; Dad, M. Pattern of Congenital Heart Disease among Children in Madina Munawara. Saudi Heart Assoc. 1997, 9, 16–19.
32. Abbag, F. Pattern of Congenital Heart Disease in the Southwestern Region of Saudi Arabia. Ann. Saudi Med. 1998, 18, 393–395.
33. Greer, W.; Sandridge, A.L.; Al-Menieir, M.; Al Rowais, A. Geographical Distribution of Congenital Heart Defects in Saudi Arabia. Ann. Saudi Med. 2005, 25, 63–69.

Retrieved from https://encyclopedia.pub/entry/history/show/47344