Genomics and Epigenomics of Congenital Heart Defects: Expert Review and Lessons Learned in Africa

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Abstract

Congenital heart defects (CHD) are structural malformations found at birth with a prevalence of 1%. The clinical trajectory of CHD is highly variable and thus in need of robust diagnostics and therapeutics. Major surgical interventions are often required for most CHDs. In Africa, despite advances in life sciences infrastructure and improving education of medical scholars, the limited clinical data suggest that CHD detection and correction are still not at par with the rest of the world. But the toll and genetics of CHDs in Africa has seldom been systematically investigated. We present an expert review on CHD with lessons learned on Africa. We found variable CHD phenotype prevalence in Africa across countries and populations. There are important gaps and paucity in genomic studies of CHD in African populations. Among the available genomic studies, the key findings in Africa were variants in *GATA4* (P193H), *MTHFR 677TT*, and *MTHFR 1298CC* that were associated with atrial septal defect, ventricular septal defect (VSD), Tetralogy of Fallot (TOF), and patent ductus arteriosus phenotypes and 22q.11 deletion, which is associated with TOF. There were no data on epigenomic association of CHD in Africa, however, other studies have shown an altered expression of *miR-421* and *miR-1233-3p* to be associated with TOF and hypermethylation of CpG islands in the promoter of *SCO2* gene also been associated with TOF and VSD in children with non-syndromic CHD. These findings signal the urgent need to develop and implement genetic and genomic research on CHD to identify the hereditary and genome–environment interactions contributing to CHD. These projected studies would also offer comparisons on CHD pathophysiology between African and other populations worldwide. Genomic research on CHD in Africa should be developed in parallel with next generation technology policy research and responsible innovation frameworks that examine the social and political factors that shape the emergence and societal embedding of new technologies.

Keywords: congenital heart defects, genomics, epigenomics, global health, responsible innovation

Introduction

Cᴏɴɢᴇɴɪᴛᴀʟ ʜᴇᴀʀᴛ ᴅᴇꜰᴇᴄᴛs (CHD) are among the most common human congenital anomalies, occurring in an accepted approximation of 6 to 8 out of 1000 live-births (Hoffman and Kaplan, 2002; van der Linde et al., 2011) and accounting for nearly one-third of all major congenital anomalies. CHD are a group of structural heart and great vessel disorders present at birth.

This expert review examines the genes and genomic loci that are reportedly associated with the CHD phenotypic distribution in different populations. Based on these observations and literature analysis, we propose a case for a closer look at the African continent in regard to CHD biomarkers and CHD genomics, especially for neglected or understudied populations. In addition, we present an original enrichment analysis as part of our literature analyses so as to evaluate possible interactions between known genes that have been

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implicated in non-syndromic CHD showing the complexity of CHD.

Clinical Context for CHD

Errors in septation, proper partitioning of the great vessels, and valve formation are the most common aberrations in cardiac development. Frequently identified risk factors predisposing newborns to developing CHD include genetics factors such as consanguinity, advanced maternal age that is associated with aneuploidies, environmental factors such as a vitamin A (Botto et al., 2001) and folic acid-deficient diet during pregnancy, maternal drug/teratogen exposure, and previous obstetric history of abortions and still births (Abqari et al., 2016; Fung et al., 2013; Ul Haq et al., 2011).

The epidemiology of CHD varies across different populations with a recent study in China indicating approximately 11.1 per 1000 live births (Qu et al., 2016) are affected by CHD, which was higher than previously reported. The Metropolitan Atlanta Congenital Defects Program (MACDP) surveillance system in Atlanta, reported an overall prevalence of 81.4/10,000 births (Reller et al., 2008). A study in Northern England from 1985 to 2003 indicated a CHD livebirth prevalence of 79.7 per 10,000 livebirths (Dadvand et al., 2009).

The European surveillance of congenital anomalies, a network of population-based registers of congenital anomalies in Europe showed that CHD are the most common non-chromosomal anomaly with a prevalence of 5.8–6.5/1000 births (Bourdial et al., 2012; Dolk et al., 2010). In Asia, a study conducted in Iran, utilizing data over a 1-year period (2007–2008) showed a prevalence of 8.6 per 1000 live births, with an upward trend during this period (Nikyar et al., 2011). A nationwide study of birth prevalence of CHD in Norway over a 15-year period (1994–2009) showed a prevalence of 133.2 per 10,000 live births, which is on the high side compared to the average prevalence of 8/1000 live births (Leirgul et al., 2014).

Data on clinical epidemiology on CHD in Africa vary greatly due to differences in diagnostic methods and expertise. In the Niger Delta region of Nigeria, a 4-year prospective echocardiographic data for frequency and pattern of CHD showed a prevalence of 14.4 per 1000 children (Otaigbe and Tabansi, 2014). Recently, echocardiography data from a cardiac referral hospital in Cameroon showed that 27.2% of suspected heart diseases cases reported involved definite structural CHD (Nkoke et al., 2017). CHDs are usually found in the pediatric age group (0–15 years), however, it is not rare to see adults with corrected or uncorrected CHDs, especially in Africa. Some patients may not manifest any symptomatic characteristic of CHD and thus, the condition might not be noticed until complications arise later.

The variable CHD prevalence presented in the various studies across both developed and developing countries shows the complexity in clinical CHD epidemiology. Even in high resource countries, CHD can be missed at birth resulting in infant mortality (Ng and Hokanson, 2010; Wren et al., 2008). In developing nations, missed diagnoses has the potential to be much worse secondary to limited resources (Ekure and Adeyemo, 2015). Fortunately, with the advancement in prenatal cardiovascular diagnostics and corrective strategies such as cardiothoracic surgery, the number of infantile deaths due to CHD has declined, and more than 75% of children with CHD survive into adulthood, including those with complex abnormalities (Gilboa et al., 2010), in high resource countries; unfortunately, many countries in Africa do not share these success stories despite the improvement in health infrastructure secondary to financial and policy limitations.

CHD can be linked to recognizable genetic syndromes that are due to aneuploidy such as Down syndrome, copy-number variations such as 22q11.2 deletion syndrome and single gene disorders such as Noonan syndrome (Fahed et al., 2013). Isolated or sporadic CHD (also referred to as non-syndromic CHDs) make up most CHDs. Advances are being made to elucidate the etiology of these conditions due to progress in genomic technology and animal models; however, most non-syndromic CHD remains without a known etiology. In addition to genetic causes, environmental exposures and nutritional deficiencies of pregnant mothers during pregnancy has long been suspected as some of the plausible risk for non-syndromic CHD.

In addition to DNA coding genetic changes and environmental and nutritional associations with CHD, epigenetic mechanisms are a new area of investigation. Here, ''gene silencing'' in the parent are activated in the offspring leading to NS-CHD (Fahed and Nemer, 2012). Epigenetic changes resulting in gene enrichment may in part explain the incomplete penetrance and low recurrence rates in familial NS-CHD (Sifrim et al., 2016).

Syndromic CHDs such as Noonan or Alagille syndrome have a monogenic mode of inheritance (Prendiville et al., 2014). In contrast, most of the observed non-syndromic CHD (NS-CHD) occur sporadically and families with clear monogenic inheritance of non-syndromic CHDs are scarce (Garg et al., 2003; Kirk et al., 2007). Incomplete penetrance and genetic heterogeneity are thought to contribute to apparent non-Mendelian inheritance in affected families. Non-syndromic CHD are usually explained by a multifactorial inheritance model that comprises a multitude of susceptibility genes with low-penetrance mutations (common variants) or intermediate-penetrance mutations (rare variants) superposed on adverse environmental factors (Burn et al., 1998; Oyen et al., 2010; Roos-Hesselink et al., 2005).

Non-syndromic CHD phenotypes worldwide have also been linked to parental consanguinity (Stavsky et al., 2017) and recessive etiology (McGregor et al., 2010). Genes that have been implicated in CHD can be categorized into ligand receptors, transcriptional factors, and structural/contractile proteins (Wessels and Willems, 2010) (Table 1).

These genes (Table 1) are expressed in different stages of fetal heart development and perturbations at different times in different genes could potentially affect formation of the heart structure (Cao et al., 2016; Sanchez-Castro et al., 2016; Xiong et al., 2013; Yoshida et al., 2016). Sequencing of genes encoding transcription factors such as *GATA4*, *NKX2-5*, and *TBX5* in NS-CHD has identified variants that affect heart development. We now know that the molecules in these pathways affect both spatial and temporal gene expression patterns (Munshi, 2012; von Gise and Pu, 2012), and that disrupting these pathways results in abnormal heart development. However, there are variable phenotypes associated with any of these causal genes due to other influencing factors.

The complexity of CHD may be linked to embryonic cardiac development that involves multiple pathways with extensive cross-talking and promiscuous ligand–receptor

TABLE 1. GENES INVOLVED IN HEART DEVELOPMENT ASSOCIATED WITH CONGENITAL HEART DEFECTS

Gene	Cytogenic location	Function	Mim number	Chd associated phenotype	Reference
Transcription genes					
CITED2	6q24.1	Transcriptional modulator/ co-activator	602937	ASD, VSD	MacDonald et al. (2013)
FOXH1	8q24.3	Forkhead activin signal transducer-1	603621	VSD, TGA	Barnes and Black (2016)
FOXP1	3p13	Forkhead box P1 protein	605515		Bekheirnia et al. (2017)
GATA4	8p23.1	Zinc-finger transcription factor	600576	ASD, TOF, PDA, AVSD	Ang et al. (2016)
GATA6	18q11.2	Zinc-finger transcription factor	601656	ASD, TOF, PDA, AVSD	Li et al. (2014a)
IRX4	5p15.33	Iroquois homeobox 4 transcription factor	606199	VSD	Cheng et al. (2011)
MED13 L	12q24.21	Mediator complex transcriptional co-activator	608771	d-TGA	Asadollahi et al. (2013)
NKX2-5	5q35.1	Homeobox-containing transcription factor	600584	ASD, AVSD, TOF, VSD	Xu et al. (2017)
NKX2-6	8p21.2	Homeobox-containing transcription factor	611770	TA	Wang et al. (2015)
TBX5	12q24.21	T-box genes transcription factors	601620	VSD	Chen et al. (2017)
TBX20	7p14.2	T-box genes transcription factors	606061	ASD	Hu et al. (2013)
ZFPM2/ FOG2	8q23.1	Zinc-finger transcription factor/coactivator	603693	TOF	Zhang et al. (2014)
ZIC3	Xq26.3	Zinc-finger transcription factor	300265	Congenital heart defects	Cowan et al. (2014)
Structural proteins					
ACTC1	15q14	Cardiac smooth muscle actin	102540	ASD	Greenway et al. (2014)
MYH6	14q11.2	Cardiac muscle myosin Heavy chain	160710	ASD	Posch et al. (2011)
MYH7	14q11.2	Cardiac muscle myosin Heavy chain	160760	Left ventricular noncompaction	Khodyuchenko et al. (2015)
MYH11	16p13.11	Smooth muscle myosin heavy chain	160745	PDA	Harakalova et al. (2013)
NOTCH1	9q34.3	Transmembrane protein	109730	AVD, LVOTO	Theodoris et al. (2015); Preuss et al. (2016)
Other					
CRELD1	3p25.3	Cell adhesion	607170	AVSD	Guo et al. (2014)

ASD, atrial septal defect; VSD, ventricular septal defects; TGA, transposition of the great arteries; TOF, tetralogy of fallot; AVSD, atrioventricular septal defects; PDA, patent ductus arteriosus; TA, tricuspid atresia; AVD, aortic valve disease; LVOTO, left-ventricular outflow tract obstructions.

interactions, secondary signal transduction pathways, and a network of transcription factors that determines the expression of cardio-specific effector genes (Fahed and Nemer, 2012). Of special interest to developing countries, dietary issues such as deficient periconceptional folic acid supplementation (which is critical for neural tube formation) may also contribute to the complexity of CHD. Maternal polymorphisms of ''pharmacogenes'' of folic acid metabolism especially *methylene tetrahydrofolate reductase* (*MTHFR*) such as *MTHFR* (*677C>T*) has been classified as a risk factor for CHD (Pishva et al., 2013; Van Beynum et al., 2006).

CHD continue to remain a critical health issue in Africa as the continent works to achieve the sustainable development goals (SDG) of reducing child mortality. A few decades ago, CHD diagnoses were not common in Africa. With improvements in health service delivery and healthcare professional training (Budzee et al., 2010), CHD diagnosis and treatment at an early age is allowing for children with CHD to live (Ejim et al., 2013; Methlouthi et al., 2016; Nkoke et al., 2017; Sadoh et al., 2016; Sani et al., 2007).

Despite the variation in different phenotypes of CHD diagnosed in the health facilities across Africa, the genetic basis of CHD in African populations remains a great challenge.

Literature Search

Article sources and databases employed

A comprehensive search method of published articles up to February 2018 was completed using PubMed (National Library of Medicine)/Medline and Google Scholar. Search terms included ''genetics,'' ''congenital heart defects,'' ''Africa,'' ''epidemiology,'' ''diagnosis,'' ''CHD,'' ''burden,'' ''non-syndromic,'' ''transcriptional factors,'' and ''congenital heart malformations.'' Authors that are known to have published in the field were specifically searched for and relevant articles included. Our search enabled us to discuss

in detail the burden of CHD in Africa and understand the importance of genetic architecture in African populations.

Selection criteria

Abstract reviews were performed for relevant published articles related to CHD and relevant full articles were retrieved in this review (Fig. 1).

A total of 4108 articles were consulted after search; exclusion criteria were performed based on article relevance to the expert review and articles that were not written in English. Subsequently, 125 articles that gave required information were included in this review. The inclusion criteria focused on academic, research, clinical case studies, and reports describing prevalence; clinical phenotypes; and genetics related to non-syndromic CHD. We must state, there were articles that fit these criteria except authors could not get the full articles or abstracts not in English and so were excluded. Articles for genes involved in non-syndromic CHD were used. Studies that found no causative associations between CHD and genetic variants were excluded.

Data collection

A summarized version of the different studies is presented in different sections of this review to elaborate the importance of such a review to, especially, populations in health transition in Africa. The following information is used for the summary, country of study, city, cohort, study type, encountered CHD phenotypes, and genes.

Key Findings from the Literature Search

The CHD odyssey in Africa

The last decade has seen the publication of several clinical epidemiological studies showing the differential prevalence of various subtype of CHD across different African populations, which is summarized in Table 2.

A search for studies conducted in African populations found no study on birth incidence or population prevalence. Very rarely, genetic causes were investigated with the 22q11 deletion syndrome being the most investigated, in three independent studies in Cameroon, Rwanda, and South Africa (Table 2).

The trends and patterns of CHD in Nigerian children over a 51-year period (1964–2015) were recently published showing the most prevalent forms of CHD as ventricular septal defect (VSD) accounting for 40.6% of all CHDs, 11.3% as atrial septal defect (ASD), 11.8%, as Tetralogy of Fallot (TOF), and 18.4% as patent ductus arteriosus (PDA) (Abdulkadir and Abdulkadir, 2016). This study also reported decline in the occurrence of pulmonary stenosis (PS) and a 6% increase in the burden of VSD over 5 decades. These recent findings agree with a previous study on mortality related to CHD in Nigerian children, which indicated that VSD, PDA, and TOF were the most common causes of mortality (Akang et al., 1993).

A hospital-based necropsy study on CHD over an 8-year period in Nigeria demonstrated, the most common conditions were VSDs, ASDs, TOF, PDA and transposition of great
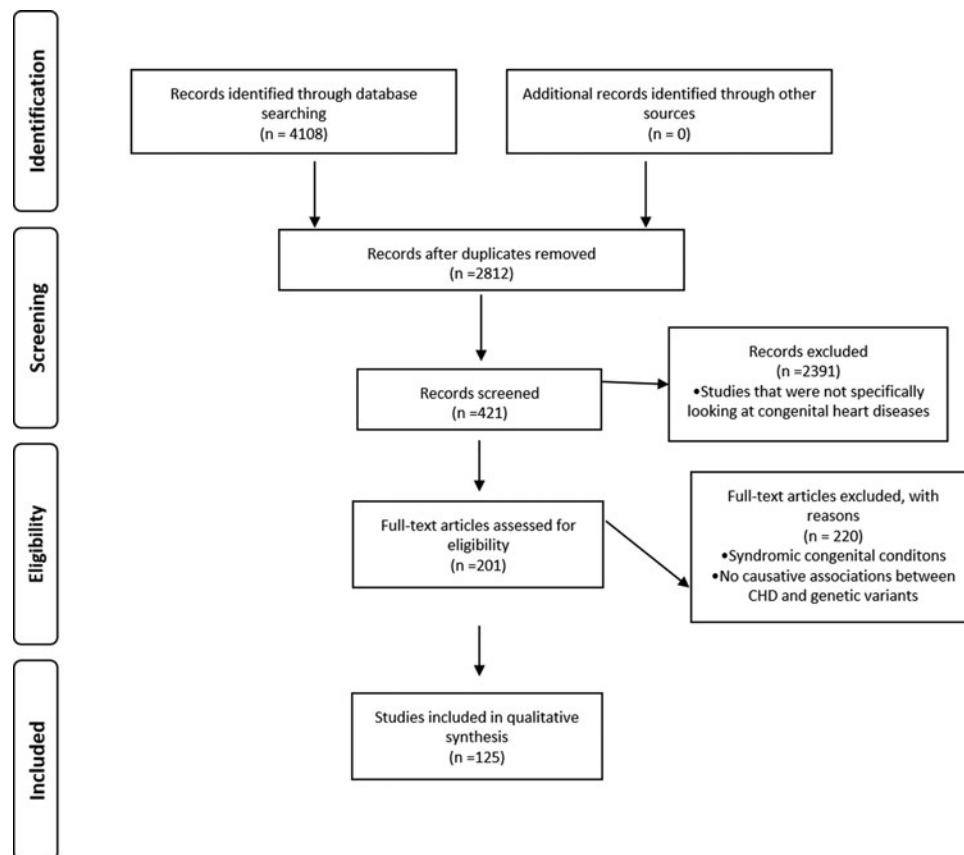

FIG. 1. Summary of search and selection of the literature review used in the review.

TABLE 2. SPECTRUM OF CONGENITAL HEART DEFECTS PHENOTYPES IN AFRICAN COUNTRIES

Country	City	Study cohort	Study	Chd phenotypes and clinical prevalence (%)	Genetic study results	References
Angola	Luanda	Children Adolescents	Clinical	CoA (2.1), TGA (2.1) PDA (35), PS (16.8), TOF (1.4), TA (1.4), VSD (49), DORV (1.4)	ND	Manuel et al. (2014)
	Luanda	Children	Clinical	ASD (6.2), VSD (39.5, AVSD, AVCDD, TGA, PDA (33.8)	ND	Nunes et al. (2017)
Burkina Faso	Bobo-Dioulasso	Children	Clinical	ASD, AVSD, DORV, TGA, TO, VSD	ND	Tougouma et al. (2016)
Cameroon	Yaoundé	Children	Genetic	TOF, TA	22q11.2 deletion	Wonkam et al., (2017)
		Children	Clinical	i-VSD (38.8), TOF (26.1), i-PS (2.6), DORV (2.1), i-ASD (2.8), AVSD (7.3)	ND	Tantchou Tchoumi et al. (2011);
		Adult				Tantchou Tchoumi and Butera (2013)
	Yaoundé	Adolescent	Clinical	Shone's anomaly	ND	Nkoke et al. (2014)
	Yaoundé	Children	Clinical	VSD (37.2), PS (15.0), PDA (13.7), ASD (11.1), TOF (8.2), AVCD (5.3), TA (1.5), TGA + ASD (0.6)	ND	Chelo et al. (2016)
		Adolescent				
	Yaoundé	Children Adolescent	Clinical	ASD (17.0), VSD (30.0), PDA (18.9), AV-Canal (2.3), TOF (5.3), PS (29.1) TGA (<1.0)	ND	Nkoke et al. (2017)
Egypt		Children	Genetic	ASD (28.7), VSD (32.5), PDA (17.5)	MTHFR 677TT, 1298CC	Zidan et al. (2013)
		Adults (Mothers) Neonates infants	Clinical	PAVSD (6.2), VSD (50.8), TOF (4.6), AVSD (6.2), DORV (1.5)	ND	Udink ten Cate et al. (2013)
	Cairo	Adults	Clinical	ASD, VSD, TOF	ND	Farouk et al. (2015)
	Cairo	Children???	Genetic	ASD, VSD, AVSD, AVCDD	GATA4 gene variants	Al-Azzouny et al. (2016)
			Genetic	VSD (47.3), ASD (16.4), TOF (7.3), PS (3.6)	GATA4 gene exon 1 (P193H)	Shaker et al. (2017)
Ghana	Accra	Adults	Clinical	ASD (26.0), VSD (34.0), PDA (12.0), TOF (12.0)	ND	Edwin et al. (2017)
Libya	Accra	Children	Clinical	TOF, PA-VSD, DORV	ND	Edwin et al. (2016)
	Tripoli	Children Adolescent	Clinical	ASD (23.0), AVSD (19.0), VSD (14.0)	ND	Elmagrpy et al. (2011)
Malawi	Blantyre	Pediatric	Clinical	ASD (2.0), AVSD (5.2), DORV/TGA (4.4), TOF (10.0), VSD (24.0), PDA (7.2), PS (1.2)	ND	Kennedy and Miller (2013)
Morocco	Casablanca	Pediatric Adolescents	Clinical	AVSD (29.0), ASD (19.9), TOF (5.4), VSD (21.5), PDA (16.7)	ND	Benhaourech et al. (2016)

(continued)

TABLE 2. (Continued)

Country	City	Study cohort	Study	Chd phenotypes and clinical prevalence (%)	Genetic study results	References
Nigeria	Abidjan	Children, Adolescents, Adults	Clinical	ASD (13.8), AVSD (7.7), CoA (2.3), TGA (3.8), PDA (7.7), PS (8.1), TOF (8.8), VSD (38.6),	ND	Métras et al. (1979)
	Ibadan	Pediatric	Clinical	VSD (35.0), PDA (22.0), TOF (10.0), ASD (7.5), PS (9.0), CoA (2.0)	ND	Jaiyesimi and Antia (1981)
	Kano	Children	Clinical	i-VSD	ND	Asani et al. (2005)
	Ilesa	Pediatric	Clinical	TOF	ND	Okeniyi and Kuti (2008)
	Lagos	Children	Clinical	TOF (16.9), PDA with ASD (8.3)	ND	Animasahun et al. (2015); Animasahun et al.(2016)
	Enugu	Children, Adults	Clinical	ASD, VSD, TOF,	ND	Ejim et al. (2013)
	Lagos Abuja	Children	Clinical	ASD (8.7), AVSD (8.2), DORV (0.6), PDA (12.1), TGA (1.5), TOF (7.8), VSD (46.6), TA (1.2), Tricuspid atresia (2.1)	ND	Sadoh et al. (2013)
	Enugu	Children	Clinical	i-VSD (21.5), TOF (9.2), AVSD (4.2), TA (4.2), i-ASD (2.8), DORV (2.8), PDA (2.8)	ND	Chinawa et al. (2013)
	Port Harcourt	Children	Clinical	ASD (2.5), AVSD (2.4), DORV (0.9), PDA (14.5), TGA (3.6), TOF (8.6), TA (0.9), VSD (27.1), Tricuspid atresia (0.9)	ND	Otaigbe and Tabansi (2014)
	Benin City	Children	Clinical	VSD (50.0), PDA (14.29), TA (21.43), Tricuspid atresia (7.17)	ND	Sadoh and Osarogiagbon (2013)
	Lagos	Children	Clinical	Single ventricle physiology hearts (15.7), ASD/VSD/PDA (13.9), TGA (13.9), TA (12.6), PS (12.2), VSD/PS (4.8), CoA 94.8)	ND	Ekure et al. (2017)
Rwanda	Kigali	Children	Clinical	PDA (53.3), ASD (3.0), PV (23.3)	ND	Senga et al. (2013)
	Kirehe, Southern Kayonza districts	Children	Clinical	ND	ND	Kwan et al. (2013)
	Kigali	Adults Adolescents	Clinical Genetic	ASD, AVSD, CoA, Dextrocardia, MVP, PDA, PS, TOF, TA, VSD	7q11.23, deletion, 22q11.2 deletion, 13qter deletion	Teteli et al. (2014)
Senegal		Children	Clinical	VSD (25.0), TOF (13.0)	ND	Diop et al. (1996)
South Africa	Soweto	Children	Clinical	VSD (2.07), PS (0.17), ASD (0.42)	ND	McLaren et al. (1979)
	Cape Town	Children	Genetics	ND	22q11.2 deletion (4.8)	De Decker et al. (2016)
	Bloemfontein	Adults	Clinical	Septal defects (ASD, VSD, AVSD)-(41.2), TOF (1.3), CoA (9.0), PDA (3.9)	ND	Long et al. (2016)

(continued)

TABLE 2. (CONTINUED)

Country	City	Study cohort	Study	Chd phenotypes and clinical prevalence (%)	Genetic study results	References
Sudan	Khartoum	Pediatric adolescent	Clinical	AVSD (48.0), VSD (23.0), TOF (6.0), PDA (7.0)	ND	Ali (2009)
Tunisia		Consanguineous Family	Clinical Genetic	ASD, AVCD	*PMM D5S394 & D5S2069* overlapping *NKX2-5* gene	Nouira et al. (2008)
	Sfax	Children	Clinical	ASD (12.9), VSD (31.0), TOF (6.2), TGA (2.7), CoA (4.3),	ND	Abid et al. (2014)
Togo	Lomé	Pediatric Adolescents	Clinical	VSD (24.0), PDA (21.0), AVSD (9.0), ASD (18.0), TOF (19.5)	ND	Kokou et al. (1996)
Uganda	Kampala	Pediatric Adolescents	Clinical	VSD (36.3), PDA (27.2), TGA (4.5), TOF (2.27), PS (4.5)	ND	Caddell and Connor (1966)
	Kampala	Children	Clinical	ASD (20.0), VSD (15.0), PDA (6.6), TOF (3.3), CoA (1.6)	ND	Wood et al. (1969)
	Kampala	Children	Clinical	VSD, PDA, TOF, ASD	ND	Freers et al. (1996)
	Kampala	Children	Clinical	VSD, PDA, TOF, ASD	ND	Ellis et al. (2007)
	Kampala	Pediatric Adolescents	Clinical	Cyanotic (28.9), Acyanotic (71.1)	ND	Batte et al. (2017)
	Kampala	Adults	Clinical	VSD (23), AVSD (13), TOF (13)	ND	Grimaldi et al. (2014)

22qDS, 22q11.2 deletion syndrome; PMM, polymorphic microsatellite markers; AVCD, atrioventricular conduction defect; NS-CHD, non-syndromic congenital heart defects; NR, not reported; MTHFR, methylene tetrahydrofolate reductase; AVCDD, A-V canal disturbance defect; DCMP, dilated cardiomyopathy; EMF, endomyocardial fibrosis; HTN HD, hypertensive heart disease; RHD, rheumatic heart disease; IHD, ischemic heart disease; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; PFO, patent foramen ovale; PA, pulmonary atresia; HDC, hypokinetic dilated cardiomyopathy; PT, pericardial tamponade; PAVSD, pulmonary atresia with ventricular septum defect; ND, not determined; RAA, right aortic arch; MD, mirror dextrocardia; AS, aortic stenosis; PVS, pulmonary valve stenosis.

arteries (TGA) with a combined overall prevalence being 22.2% at age 2 months (Thomas et al., 2013). TOF, the most common cyanotic CHD, has a prevalence of 4.9/1000 among children presenting at the Lagos State University Teaching Hospital from 2007 to 2015 (Animasahun et al., 201611). Mozambique, a sub-Saharan African country with a life expectancy at birth of 50 years is also faced with CHD challenges requiring the involvement of nongovernmental organizations to make arrangements for free surgery, reported a 9.65% CHD-related mortality at a median age of 23 months over a 10-year period (2001–2011) (Mirabel et al., 2017).

Arthur (1995) reported over two decades ago that sudden deaths due to cardiac heart diseases in children in Accra, Ghana were quite common. A 2-year study conducted in Ghana on conotruncal heart defect (TOF, pulmonary atresia with ventricular septal defect (PA-VSD), double-outlet right ventricle (DORV), common arterial trunk, and transposition of the great arteries) repair and outcomes after treatment reported that 20% of the 6168 heart defects were of conotruncal anomalies (Edwin et al., 2016). This indicates that Ghana is gradually being able to diagnose CHD conditions due to trained staff and improved infrastructure. At the same time, Ghana is experiencing an increased CHD burden as seen by the increase in new cases diagnosed within a recent 2-year period.

A 1200 patient cohort in Cameroon presenting with abnormal echocardiogram during a 2-year period showed that approximately 52% of children under 10 years had CHD mostly relating to PDA, TOF, and septal defects (Jingi et al., 2013). In the East African country of Kenya, a 5-year retrospective study at the Kenyatta National Hospital showed that the most common CHDs for children (average age 1.5 years) were VSDs, ASDs, PDAs, TOF, and TGA (Awori and Ogendo, 2013).

A prospective cross-sectional study conducted at the pediatric cardiology and inpatient clinic in El Fayoum University hospital showed approximately ASDs and VSDs made up 30% of cases among children less than 12 years with a mortality of 4.8% among the same cohort (Atwa and Safar, 2014). Prevalence of CHD in Tunisia is 6.8 per 1000 live births with common CHD diagnosed conditions been VSD, ostium secundum ASD, pulmonary valve abnormalities, coarctation of the aorta, TOF, and TGA (Abid et al., 2014) with a 23% mortality rate over a 1-year period before access to surgery.

Despite the clinical epidemiological spectrum of CHD in Africa displaying variable prevalence of CHD phenotypes with the common occurrence being VSD, ASD, and TOF not much has been done in terms of genetics/genomic studies, which can influence our understanding of epidemiological data obtained.

Genetic basis of non-syndromic CHD: global populations

Variations in transcriptional factors and CHD. With the understanding that CHD development is a multifactorial condition involving both genetic predisposition and environmental influences, it is becoming important that the genetic factors predisposing newborns to heart malformations be investigated. There has been a tremendous progress in understanding the molecular mechanisms involved in cardiac development that has enabled researchers and the clinical community to make prediction on plausible genetic markers for CHD.

Previous studies have shown an evolutionary conserved programme of cardiogenesis initiated by complex interactions of transcription factors with their regulators, receptors, ligands, signaling pathways, and protein networks (Fahed and Nemer, 2012). Some of these factors involved in the process including *CRELD1*, *GATA4*, *NKX2.5*, *TBX5*, *TBX1*, *JAG1*, *TFAP2B*, *PTPN11*, *NOTCH1*, and *HAND1/2* (Clark et al., 2006; McCulley and Black, 2012) have been implicated in sporadic CHDs. The correct formation of the heart is dependent on the correct differential expression, co-expression profile, and interaction of each of these genes involved in cardiogenesis at the right stage of the heart formation process. We performed an enrichment analysis using version 10.5 of STRING (Jensen et al., 2009; Szklarczyk et al., 2017) querying genes involved in fetal heart development to assess co-expression (Fig. 2).

Genes associated with CHD in humans have been supported by animal studies. Gene regulatory networks in zebrafish are increasing our understanding of heart development. Our enrichment analysis conducted is supported by data that elucidated that altered gene expression of transcription factors *TBX5* and *NKX2*-5 in zebrafish can lead to subfunctionalization (Hill et al., 2017; Rodius et al., 2016) with a dynamic interactome analysis. There is time-dependent expression of cardiac ontogeny and regulation in heart formation with any alteration leading to significant consequences for heart formation (Li et al., 2014). Differential expression of the transcription factors *TBX5* and *TBX20* has been demonstrated to affect cardiac development given evidence to the critical effects of cardiac gene expression and combinatorial regulatory interactions on the correct formation of the heart (Plageman and Yutzey, 2004).

Collectively, these data demonstrate clear differences in both the expression and function of transcription factors and suggest that the modulation of cardiac gene expression potentially plays a role in CHD. With this in mind, single nucleotide polymorphisms (SNPs) that may affect gene and protein profiles of cardiogenesis-associated genes may be detrimental to fetal heart development. Several studies conducted in other populations mostly of Caucasians and Asian decent have shown several SNPs in genes involved in cardiogenesis as potential etiologies to non-syndromic CHD (Table 3).

The causal genes have mostly been found to be factors that interact with each other during the formation of the heart and muscles. Some of these transcription factors like *NKX2-5* has been found to influence septation in heart differentiation and maturation and are responsible for maintenance of the atrioventricular node throughout one's lifetime. In most of these studies, it is observed that CHD phenotypic outcome is not singularly linked to a single SNP in a gene. Though SNPs may potentially affect heart morphogenesis, the genes involved in cardiogenesis may interact with each other and have various cardio-morphogenesis functions.

The complex network of gene–gene and protein–protein interactions involved in cardiogenesis could be a reason why there is so much phenotypic variation in CHD. An enrichment analysis was performed to show this complex interaction network using geneMANIA cytoscape plugin by determining the interactions of wild-type genes (Montojo et al., 2010) (Fig. 3).
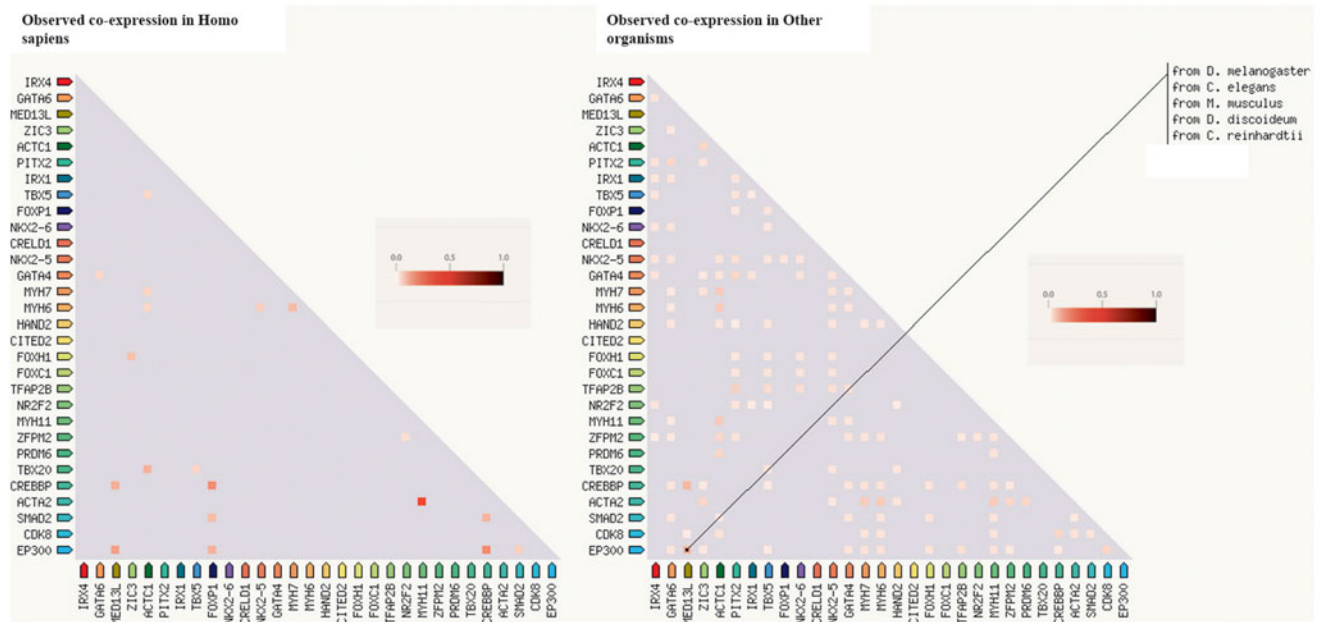
FIG. 2. Genes (Ligand receptors, transcriptional, structural) involved in cardiogenesis and their co-expression profiles in *Homo sapiens* and other organisms. Using the genes implicated in cardiogenesis as query, co-expression profiles were generated using *version 10.5 of STRING.*

From the interaction network, it can be deduced that genetic variants share common pathways. This may explain the genetic heterogeneity of CHD (Reamon-Buettner and Borlak, 2004). Some previous studies have shown that the interaction of transcription factors *GATA4* and *NKX2-5* was critical during heart formation (Kinnunen et al., 2015; Slagle and Conlon, 2016). There is a lack of information on the genetic architecture (cardiogenesis genes) of CHD on the African continent even in countries with good economic standing. A case–control study in an Egyptian cohort showed a novel nonsynonymous sequence variation in *GATA4* (P193H) detected in 9.1% of the study population with septal defects (Shaker et al., 2017).

Epigenetics: a game changer in CHD?. During cell differentiation and embryonic morphogenesis, epigenetic modifications can arise leading to effects that play a critical role in gene regulation and expression affecting genomic functions. Epigenetics involves heritable changes in gene activity, regulation, and expression that can occur as a result of several factors without modification in the DNA sequence. Epigenetic mechanisms include DNA methylation, chromatin modification, and microRNAs (Saetrom et al., 2007). DNA methylation, one of the first epigenetic mechanisms to be studied is involved in a variety of biological processes such embryonic development, X-chromosome inactivation, and genomic imprinting (Bird, 2002).

DNA methylation changes in CHD have recently been found in myocardial biopsies obtained from patients with TOF and VSD. Two mechanisms were identified to be involved in TOF and VSD namely hypermethylation of distinct CpG islands in the promoter of *SCO2* leading to reduced gene expression and differential methylation influencing alteration and formation of alternate splicing that affect protein function in genes like *TNN1*, *MYL7*, *PDZ*, *PDLIM3*, and *TNNT2* (Grunert et al., 2016).

Another case–control study involving pediatric patients with sporadic or isolated TOF and healthy controls showed that in addition to two identified SNPs (*rs11582932T>G, rs11265385T>G*), two methylation changes in the promoter regions (B1-1 and B3) significantly decreased the *VANGL2* mRNA and protein levels in TOF patients (Yuan et al., 2014). *VANGL2* is a critical gene that regulates cell polarity and polarized cell movements (Wansleeben et al., 2010) and studies suggest that it plays a significant role in heart development (Ramsbottom et al., 2014; Yu et al., 2012).

DNA methylation is known to be catalyzed by DNA methyltransferases (*DNMT1, DNMT3A,* and *DNMT3B*) and methyl-CpG-binding domain protein 2 (MBD2). The expression profile of these methyltransferases and accompanying polymorphisms in the binding protein domains have a potential influence of biological process and corresponding clinical outcomes. A case–control study looking at the expression profile of *DNMTs*, *MBD2*, and long interspersed nuclear elements (*LINE-1*) methylation status in infants with TOF showed that lower levels of *LINE-1* methylation significantly caused aberrant *MBD2* mRNA levels with lower DNMT1 and DNMT3B likely playing a role in TOF pathogenesis in a process involving hypomethylation of genes, which is critical cardiogenesis (Sheng et al., 2013).

Chromatin modification that involves remodeling and histone modification have significant roles in activating or silencing gene expression. The SWI/SNF complex is a family of ATP-dependent chromatin remodeling proteins that regulates transcription in the heart in tandem with co-activator and repressor complexes. This complex is made of Brahma (Brm) or Brg1 ATPase, which is critical to chromatin remodeling machinery for vertebrate heart formation (Lei et al.,

TABLE 3. SELECTED GENETIC POLYMORPHISMS IDENTIFIED IN GENES LINKED WITH HEART DEVELOPMENT AND ASSOCIATED WITH NON-SYNDROMIC CONGENITAL HEART DEFECTS

Gene	Nucleotide/Protein change	Effect	Phenotype	Population	Reference
IRX1	p.Gln240Glu p.Ser298Asn p.Ala381Glu	Non-synonymous	TrA, TGA	Asian (Chinese)	Guo et al. (2017)
PITX2	p.R91Q p.T129S	Loss-of-function mutation	TGA, VSD	Asian (Chinese)	Panepistēmio tēs Krētēs. et al. (2014)
HAND2	p.L47P	Loss-of-function mutation	TOF	Asian (Chinese)	Lu et al. (2016)
GATA4	c.431C4T p.Ala144Val	Possibly damaging	PA, ASD	Asian (Japanese)	Yoshida et al. (2016)
	c.1064C > G, T355S c.1129A > G, S377G c.1138G > A, V380 M c.1180C > A, P394T c.1273G > A, D425 N	Missense	ASD, VSD, PDA, DORV, TOF, PS	Asians (Indians)	Bose et al. (2017)
GATA6	c.788 C > G	Missense	VSD	Asian (Chinese)	Xiong et al. (2013)
	p.D404Y p.E460X	Decreased transactivation activity	TOF, VSD	Asian (Chinese)	Wang et al. (2012)
	c.151G>A/(E51K), c.551G>A/(S184 N) c.733G>C/(G245R),	Reduction in the transactivation capacity of downstream genes	TOF, TrA	Asian (Chinese)	Lin et al. (2010); Wang et al. (2014)
NR2F2	c.220_222dup/p.Gln75dup c.1022C>A/p.Ser341Tyr c.614A>T/p.Asn205Ile c.753G>C/p.Glu251Asp c.1234G>T/p.Ala412Ser c.509A>T/p.Asp170Val c.970p1G>A (14;15)(q23:q26.3)	Reductions in transcriptional activity	TOF, AVSD, CoA,	Caucasians	Al Turki et al. (2014)
PRDM6	c.1646G>A/p.Arg549Gln	Epigenetic regulation of ductus remodeling	PDA	Caucasians	Li et al. (2016a)
FOXC1	c.788G>C/p.Cys263Ser c.1385A>G/p.Gln462Arg Copy number variation		CoA	Caucasians	Sanchez-Castro et al. (2016)
TFAP2B	c.601+5G>A c.435_438delCCGG		PDA	Asian (Chinese)	Chen et al. (2011)
NKX2-5	c.1006 G > A 1433A>G	Affects septation during cardiac morphogenesis and maturation and maintenance of the atrioventricular node	TOF, PA, PDA TOF PLSVC, BAV	Asian (Chinese) Asian (Chinese) Caucasians	Xiong et al. (2013) Cao et al. (2015); Cao et al. (2016); Dargis et al. (2016)
	c.608A>G/p.E203G c.646C>T/p.R216C c.852G>A/p.N226D		VSD	Asian (Indians)	Dinesh et al. (2010)

(continued)

TABLE 3. (CONTINUED)

Gene	Nucleotide/Protein change	Effect	Phenotype	Population	Reference
NKX2.6	1212G>T (3'UTR)	No transcriptional activity	BAV	Asian (Chinese)	Qu et al. (2014)
	p.K192X c.454A>C/p.K152Q	Reduced its transcriptional activating function	VSD	Asian (Chinese)	Li et al. (2016b)
TBX5	c.322C>A/p.Pro108Thr c.791G>A/p.Arg264Lys	Affect protein function	TrA VSD, PA	Asian (Japanese)	Yoshida et al. (2016)
TBX20	c.991A>G p.Thr331Ala	Possibly damaging	VSD	Asian (Japanese)	Yoshida et al. (2016)
CITED2	c.550G > A, Gly184Ser c.574A > G, Ser192Gly c.573–578del6, Ser192fs	Non-synonymous	MD, RAA, TOF AS AS, PVS, VSD, ASD	Asian (Chinese)	Xu et al. (2014)
	c.428 G>C p.Gly143Ala	Non-synonymous	PDA	Asian (Chinese Tibetan)	Liu et al. (2017)
	c.508_534del27 p.Ser170_Gly178del c.534_535ins27 p.Gly178_Ser179ins9 c.592_597delAGCGGC p.Ser198_Gly199del	Non-synonymous	VSD, ASD	Caucasians	Sperling et al. (2005)
	c.C418T, p. P140S c.C548T p. S183 L c.A586G p. S196G c.481–483delAGC p.Ser161delAGC c.574–579delAGCGGC p.Ser192_Gly193delAGCGGC	Non-synonymous	ASD, VSD	Asian (Chinese)	Liu et al. (2014)
FOXP1	c.1702C>T, p.Pro568Ser	Non-synonymous	AVSD	Caucasian	Chang et al. (2013)
MYH6	E501Stop, A230P IVS37-2A.G, R1116S, A1443D, R1865Q H252Q V700 M A1366D	Non-sense mutation, Splice site mutation, Missense mutations	TrA ASD TGA PFO AS	Caucasians	Granados-Riveron et al. (2010)
	c.50G>A, R17H c.1615T>C, C539R c.1628A>G, K543R	missense mutations	ASD	Caucasians	Posch et al. (2011)
ZFPM2/FOG2	p.V339I, p.A426 p.M703 L, p.T843 M	Non-synonymous	DORV TOF	Asian (Chinese)	Zhang et al., 2014); Qian et al. (2017)
	c. 972C>G, H324Q c. 3442G>A, E1148 K	Non-synonymous	TOF TOF/PFO	Asian (Chinese)	
ACTC1	c.251T>C, p.Met84Thr p.Glu101Lys p.Met125Val	Non-synonymous	ASD, VSD, PS,	Lebanese	Augiere et al. (2015)
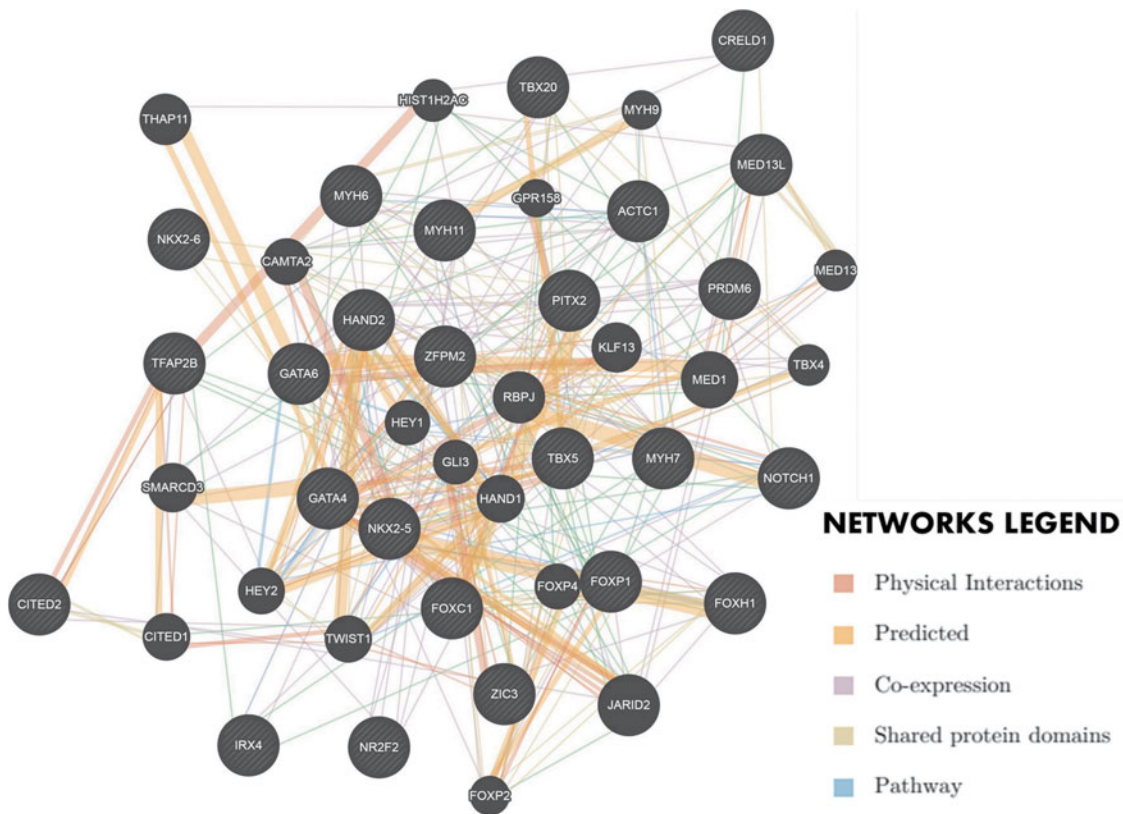
FIG. 3. Complex interactions of *genes involved in cardiogenesis.* (Network created using GeneMANIA Cytoscape plugin). Genes implicated in congenital heart defects were provided as query (*shaded gray* nodes) to see whether they have any direct interaction and a number of additional cardiogenesis genes were predicted to be related (*unshaded gray* nodes) in an enrichment analysis.

2012). Interactions between Brg1 ATPase and DNA-binding protein Parp1 with chromatin was shown to be involved in a prototypical shift in cardiac MHC isoform expression in pathological cardia hypertrophy.

It is also shown that α-*MHC* and *Serca2a* genes are highly expressed in healthy hearts whiles their expression is suppressed in heart hypertrophy. These suppression events are regulated by SWI/SNF containing *Brm/Brg1*-associated HDAC co-repressor complexes (Chang et al., 2011; El-Osta, 2011; Hang et al., 2010). These chromatin modeling complexes may play a critical regulatory role in CHD acquisition as their activities will affect expression or silencing of genes involved in heart formation, growth, and contractility throughout life.

The discovery of small non-coding RNAs known as microRNAs (miRNAs) of 20–22 nucleotides has evidentially shown to be crucial in post-translational mechanisms. miRNAs are classified as epigenetic markers with the specific biological processes of most miRNAs remaining unknown. However, several studies have shown how they control various physiological processes that can eventually have pathogenic roles in several diseases. Studies have shown that miRNAs operate by binding with specific sequences in the 3′UTR of target genes involved in development and physiology.

A functional analysis from a recent study in two Chinese Hans populations found out that *miR-9* and *miR-30a* down-regulated expression of *TBX5*, a vital transcription factor involved in cardiac development in a dosage-dependent

manner at the transcriptional and translational levels, respectively (Wang et al., 2017). These two miRNAs hybridized to the 3′UTR of the *TBX5* because of an SNP (rs6489956) that caused a change in binding affinity. Another recent study has shown that *miR-199a-5p*, *ATF6*, and *GRP78* 3′-UTR binding sites interact with the downregulation of *miR-199a-5p* having a favorable effect on myocardial unfolded protein response against hypoxia-induced ER stress in CHD leading to myocardial protection (Zhou et al., 2017).

It has recently been shown that altered expression levels of circulating miRNAs, *miR-421*, *miR-1233-3p*, and *miR-625-5p* in TOF patients with symptomatic right heart failure may play a critical role in diseases progression (Abu-Halima et al., 2017). The phenotypic manifestation of CHD can potentially be influenced by epigenetic mechanisms aside SNPs occurring in genes involved in cardiogenesis.

Copy number variation and CHD genetic paradox. Studies using chromosomal microarray have added many candidate genes to the list of potential etiologies for CHD (Soemedi et al., 2012). As previously mentioned, CHD does not follow classical Mendelian inheritance and the etiology of this complex disease remains unsolved for most cases. The phenomenon that results in sections of the genome being deleted or duplicated is known as copy number variation (CNV) and has become a key contributor to CHD (Lander and Ware, 2014). The role of CNVs in CHD occurs in

genomic regions responsible for cardiogenesis that affect heart formation.

Recently, Kim et al. (2016), highlighted the pathogenicity of CNVs of >300kb in size in non-syndromic CHD to be significantly associated with decreased transplant-free survival after surgery. Rare and or large CNVs present a greater burden in isolated CHD with an increased risk of death suggesting that CNV burden is an important modifier to CHD acquisition, phenotype, and survival (Kim et al., 2016). Different phenotypes including CoA (15q 11.2 dup), DORV (20p12.2 dup, 22q11 del), TOF (8p23.2 dup, 10p12.31 dup), TOF (22q11.22del), and TGA (Dup2 2q11) were associated with CNVs of children born with CHD who exhibited microdeletions and duplications (Campos et al., 2015; Mercer-Rosa et al., 2013).

CNVs potentially play a significant role in CHD influencing the phenotypic outcome in both simple and complex conditions. CNVs affect large chromosomal segments that involve millions of DNA base pairs and multiple contiguous genes that make the identification of a single causal gene for CHD and expressive phenotypes a major challenge. Also, finding CNVs across different segments of the chromosome and associating it to different phenotypes remains challenged due to expertise to analyze data that are generated.

Literature Analysis and Discussion

Innovative policy and next generation technology research: focusing on African populations

The global burden of congenital anomalies, of which CHDs are the most common, indicates that 5% of deaths in children under five are due to CHDs (Hoffman, 2013). Despite the first heart transplant occurring on the African continent many decades ago, we discuss the fact that Africa still has a long way to go in the following dialog.

The first challenge is related to obtaining proper clinical data on the spectrum of commonly occurring CHD in Africa. Birth incidence, population prevalence, and qualitative CHD descriptions have not been well characterized in Africa. Prevalence of CHD in most African countries have generally been extrapolated by using data from previous studies from other jurisdiction (mostly developed countries), which may indicate that the figure in the public domain may not be a true reflection. This extrapolation is mostly emphasized by certain factors such as limited diagnostic proficiencies, lack of effective health-related statistics, a comprehensive database on newborns including any abnormalities observed and diagnosed. Also, one of the most common sources of determining prevalence is using hospital-based information, which does not necessarily give accurate statistics compared to using population-based studies.

Most African countries appear to be having high prevalence of CHD due to supposed risk factors associated with CHD such as age of mother, exposure to different teratogens, maternal malnutrition, and infections exposed to during pregnancy. Despite these challenges, there has been several studies in some African countries that addresses the burden and phenotypic spectra of CHD in these countries (Table 2), thus representing a reasonable estimation or burden of CHD in these countries.

Second, clinical epidemiology in African populations present different dynamics as the available data indicate that many African countries are under resourced to deal with the burden of congenital anomalies in general and, and specifically CHD, with regards to available surgical options and postsurgery management; This calls for an urgent implementation of a database of commonly and rare occurring CHD across the African continent in the relevant health facilities that attend to such newborns with CHD, to plan health resources adequately. This will be beneficial in monitoring the SDG on child mortality and most importantly, allow for effective and quality research into CHD in Africa, leading to effective planning, monitoring, and management of children with CHD in Africa.

Third, the few available clinical reports indicate that mortality and morbidity associated CHD in Africa remains a huge challenge even as health services and infrastructure improve. However, cases of mortality related to CHD appears to be under reported due to inadequacies of available professional for proper diagnosis, and the health information system, which affect data acquisition to properly monitor the burden of CHD remarkable. The African continent is generally lagging compared to the remarkable improvement in CHD management globally over the last few decades. Investments in infrastructure and specialist training can improve the diagnosis and amenable treatment of so-called complicated lesions.

Nonetheless, CHD go beyond the clinical, phenotypic, and even the surgical corrections involved. Understanding the causes or triggers of CHD in African populations and improving diagnostic accuracy are paramount to using preventive approaches if any to address the epidemic. One of the most common tools for assessing chromosomal deletions or rearrangements is karyotyping and fluorescent *in situ* hybridization analysis, which remains one of the starting points for genetic assessment of CHD patients (Gohring et al., 2011). These tests continue to remain relevant for the diagnosis of syndromic conditions such as trisomy 21, trisomy 13, trisomy 18, and known microdeletions (22q11.2 deletion and 7q11 deletion), as evidenced by the few available studies on the African continent, from South Africa and Cameroon, notably.

For isolated CHDs without any associated syndromes, not much has been done on the African continent and it is increasingly becoming relevant to use techniques that can help identify single gene variants, epigenetic markers, and possible CNVs in genes involved in cardiogenesis.

Understanding the genetic architecture of CHD patients of African descent will help better understand some of the triggers that lead to especially sporadic or isolated incidents that will help build a reliable register for public health education especially at ante- and postnatal clinics. Genetic investigations of CHD have the potential to improve prognosis from valuable information generated and may serve as a tool for predicting recurrent risk, assess familial inheritance pattern, therapeutic options for CHD patients who have undergone successful surgery, and appraise the need for further family screening.

A candidate gene approach using Sanger sequencing can be performed on known genes to evaluate disease causing mutations and their frequencies. However, considering the complexity of CHD and its genetic heterogeneity, the use of advanced genomic platforms will provide more insights. Next generation technologies that can be used to sequence

whole genomes (WGS) and exomes (WES), perform CNV analysis, transcriptome analysis, and homozygosity mapping will be useful for broader understanding of the genetic architecture of CHD in African populations to influence policy formulation. The use of Next generation sequencing (NGS) employing targeted panel sequencing, whole exome and genome sequencing allows for evaluation of massive gene numbers in one run is urgently needed for clinical use and research in African population.

RNASeq/Ampliseq that uses the NGS platform can be used to sequence cardiac transcripts from CHD patients from African populations who have undergone successful surgery to evaluate the transcriptomics of genes in cardiogenesis. ATAC-Seq (assay for transposase-accessible chromatin) and THS-seq (transposome hypersensitive sites sequencing) an innovative NGS platform can be used as a rapid and sensitive method for integrative epigenomic analysis (Buenrostro et al., 2013, 2015; Sos et al., 2016).

The use of chromosomal microarray analysis validated with NGS can be useful in identifying CNVs associated with NS-CHDs (Helm and Freeze, 2016; Zhu et al., 2016). With challenges in CNV data analysis, algorithms that use whole exome sequencing data such as CoNVex can be used to identify CNVs associated with non-syndromic congenital heart diseases (Sifrim et al., 2016). Molecular analysis coupled with multiplex ligation-dependent probe amplification (MLPA) technique is also useful in determining CNV in non-syndromic CHD (Campos et al., 2015).

With the goal of the Human Heredity and Health in Africa (H3Africa) Initiative to develop array chips with genes from African populations, biomarkers can be developed using sequencing and expression profile data of CHD patients in Africa, which will serve as a diagnostic and prognostic platform for management. This will translate to the incorporation of validated genetic data into clinical practice of CHD management including genetic counseling and pre/postnatal screening. The clinical utility of including genetic data in clinical practice can improve health outcomes of conditions through the use of genetic therapeutic dosing algorithms, diagnosis, and public health discourse (Dotson et al., 2016; McCormick and Calzone, 2016).

With the knowledge and understanding of epigenetics and environmental exposure including teratogens, which pregnant mothers are exposed to in certain parts of Africa during pregnancy, public health policies in African countries especially resource limited settings where getting access to surgical intervention is limited can be formulated as preventive measures to avert potential non-syndromic CHDs. Industrialization, which has been linked to epigenetic changes and pre- and postnatal care involving multivitamin supplementation should be linked with responsible innovative public health policies that seek to insulate pregnant women from exposures that may affect fetal development.

Outlook and key lessons for Africa

Research focusing on the genomics and epigenomics of non-syndromic CHD in African populations using next generation technologies can lead to biomarker development with improved diagnosis and prognosis. ''–Omics'' research is significant to the discovery and development of novel diagnostics for CHD in African populations. The current article has highlighted the lack of genomic and epigenomic research in Africa, which could be key to providing answers to unanswered questions on most especially non-syndromic CHD development and phenotyping. This therefore calls for much needed research to understand the genetic architecture of CHD in African populations to improve management of CHD.

Perspective on CHD epi**genomics** in Africa

Africa been touted as the cradle of mankind (Ozdemir et al., 2014) with a wide genetic diversity. Yet, the *epi***genetic** association of CHD in African populations seems to be overlooked by both researchers and policy makers. Over the past decades, most African countries have observed significant developments with corresponding industrialization. Industrialization affects biological circadian rhythms involving regulatory pathways resulting in rhythmic epigenetic modifications and the formation of epigenomes (Salavaty, 2015). DNA methylation and histone modifications serve to integrate environmental signals, nutrition, and xenobiotics for the cells to modulate the functional output of their genome. Most pregnant mothers in African countries are exposed to numerous environmental epigenetic risk factors that may affect their epigenome with corresponding effects on cardiogenes putting them at risk of having babies with CHDs.

Smoking, alcohol, consumption of herbal medicines, and exposure to environmental pollutants such as smokes from burning fire, car exhaust fumes, and inappropriate nutrition (malnutrition and eating of junk food) are becoming prevalent in Africa increasing incidence of noncommunicable diseases including CHDs (Hofman, 2014; Jenkins, 2003). Pregnant women are normally prescribed nutritional supplements like folate and iron to help with fetal development and prevent them from being anemic.

However, it is observed that at times these women do not adhere to their supplements as recommended, a common phenomenon in some African countries (Arega Sadore et al., 2015; Gebreamlak et al., 2017; Shewasinad and Negash, 2017) leading to anemia, which is not healthy for the growing foetus potentially influencing heart malformation (Feng et al., 2015; Linask and Huhta, 2010; Linask, 2013). Research evidence have shown how the *epi***genome** can influence malformation of the heart and lead to CHD phenotypes. An audit and research into the *epi***genetic** role of CHD being observed in African settings using available next generation technologies (''-omics'' research) and algorithms should be spearheaded especially looking at the influential risk industrialization and urbanization poses to the *epi***genome**.

Key lessons: Responsible innovative policies

Despite the need and effort to refine the real toll of CHD, the few available data indicate that CHD are a burden in Africa with significant populations having no access to proper diagnosis, medical care, and interventions such as corrective surgery and family support. Though mostly diagnosed in infants, there are asymptomatic adults living with CHD. One of the challenges to the early detection and management of CHD in Africa is the lack of policy direction for monitoring and screening newborns.

Basic screening such as pulse oximetry is available in most African health facilities, however, mostly physical

examination has become the norm for determining the wellness of newborns. In addition, for most African populations, there is not much data on the genetic predisposition to CHD, despite, the identifiable preventable causes that can be translated into prevention strategies. Apart from screening strategies, ''-omics'' research such as genomics and epigenomics is critical in African research and diagnostics as it will produce knowledge-based innovation that remains fundamental to understanding the precipitants, pathophysiology, prevention, and management of CHD. This calls for a holistic public health approach looking at risks assessment and diagnostic strategies (clinical and genomics) being put into effect.

In other jurisdictions like Canada, United States of America, United Kingdom, and New Zealand, innovative public health strategies such as cardiovascular genetic research and newborn screening strategies for critical CHD have been implemented to improve the clinical management of CHD (Cloete et al., 2017; Lancet, 2012; National Collaborating Centre for and Children's, 2008; Oster et al., 2013; Riehle-Colarusso et al., 2016). Policy innovations such as the following for African countries can lead to effective tracking, monitoring, and management of CHD incidences and epidemiology.

(1) Public health strategies and education should be intensified on CHD as it is observed that aside the common communicable and noncommunicable diseases that occur in most African populations, little is known of CHD to which parents and at times physicians miss the signs of, which lead to an increase in CHD-related mortality. Pulse oximetry screening in addition to physical examination should be made a routine in screening of newborns for CHD. Early detection will increase the survival rate and proper management of CHD patients.

(2) Interventional strategies for preventable risk factors associated with CHD such as nutritional deficiency in pregnant mothers, diabetes, and smoking should be implemented. CHD screening and interventional measures should be incorporated into health insurance coverage policies to reduce the financial limitations of CHD management.

(3) Investigating possible environmental exposures, medications, herbal concoctions, and consistent antenatal monitoring will help identify CHD babies early to effectively strategize intervention measures.

(4) Enhancement of birth surveillance, postnatal visits, and improved tracking of research to identify potential causes and long-term outcomes. As part of the policy framework, a centralized database is required to link access to health records across health facilities in African countries to allow continuity of management and follow-up.

(5) Support for public health, clinical and genetic research to outline the precipitants of CHD of diverse African populations will inform effective genetic counseling and future decisions for parents with CHD-children and CHD-adults.

(6) Responsible next generation technology policy research that will lay innovation frameworks for biomarker development for improved CHD diagnosis and prognosis. As part of responsible next generation technology policy research, biobanks and related infrastructure, where samples of CHD patients are stored for research purposes, should be established with proper management structures to ensure confidentiality and protection of patients' identity and samples.

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The authors declare there are no conflicts of interest.

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Abbreviations Used

22qDS = 22q11.2 deletion syndrome
AS = aortic stenosis
ASD = atrial septal defect
AVCD = atrioventricular conduction defect
AVCDD = A-V canal disturbance defect
AVD = aortic valve disease
AVSD = atrioventricular septal defects
CHD = congenital heart defect
CNV = copy number variation
CoA = coarctation of the aorta
DCMP = dilated cardiomyopathy
DORV = double-outlet right ventricle
EMF = endomyocardial fibrosis
HDC = hypokinetic dilated cardiomyopathy

HTN HD = hypertensive heart disease
IHD = ischemic heart disease
LVOTO = left-ventricular outflow tract obstructions
MD = mirror dextrocardia
MTHFR = methylene tetrahydrofolate reductase
ND = not determined
NGS = next generation sequencing
NR = not reported
NS-CHD = non-syndromic congenital heart defects
PA = pulmonary atresia
PAVSD = pulmonary atresia with ventricular septum defect
PDA = patent ductus arteriosus
PFO = patent foramen ovale
PMM = polymorphic microsatellite markers
PT = pericardial tamponade
PVS = pulmonary valve stenosis
RAA = right aortic arch
RHD = rheumatic heart disease
SDG = sustainable development goals
SNP = single nucleotide polymorphism
TA = tricuspid atresia
TGA = transposition of the great arteries
TOF = tetralogy of fallot
TrA = truncus arteriosus
VSD = ventricular septal defect
WES = whole exome sequencing
WGS = whole genome sequencing