Genetic Factors Study Among Congenital Heart Disease Children Using Multiplex Ligation Dependent Probe Amplification

Original Article

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ABSTRACT

Background: Congenital heart disease (CHD) is the most common disorder among live births with an incidence of 10/1000 newborns. It is also considered a major cause of morbidity and mortality. In most cases, the cause of CHD is multifactorial with a genetic background.

Aim of Study: The objective of this work was to improve the diagnostic outcome among children with CHD associated with other somatic anomalies or developmental delay by using Multiplex Ligation Dependent Probe Amplification (MLPA) technique.

Patients and Methods: Forty patients with CHD and extra cardiac manifestations were examined using conventional cytogenetic analysis and MLPA Microdeletion and Subtelomere kits. Chromosomal microarray (CMA) was carried out for three patients with normal MLPA results.

Results: MLPA analysis showed abnormalities in 5 patients (12.5%) in the form of Williams-Beuren, 22q11.2 microdeletion or DiGeorge (DS), Wolf -Hirschhorn and 2p25.3 microduplication syndromes. CMA showed an interstitial 2.27 Mb deletion of chromosome 2q22 including the entire *ZEB2* gene in one patient with characteristic facial features who was accordingly diagnosed as Mowat Wilson syndrome.

Conclusion: The present study markedly increased the diagnostic yield of patients with CHD associated with other somatic anomalies and detected two rare patients, one with atypical 2p25.3 microduplication and the other with Mowat Wilson syndrome. The conduction of larger analytical studies using different molecular cytogenomic techniques including CMA on a larger scale is recommended to provide better understandings of gene implication and improve the diagnostic and prevention strategies of CHD.

Key Words: CHD, Chromosomal anomalies, CNVs, Developmental delay, MLPA.

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INTRODUCTION

Congenital heart disease (CHD) is the most common disorder among live births with an incidence of 10/1,000 newborns (**Osoegawa *et al.*, 2014; Monteiro *et al.*, 2017**). It is considered a major cause of morbidity and mortality, especially when associated with extra cardiac malformations (**Van Karnebeek and Hennekam, 1999**). CHD in combination with other malformations occurs in about 25% of the cases, many of them being a part of recognizable genetic syndromes. In most cases, the cause of CHD is multifactorial (**Brent, 2004**).

Despite the strong genetic basis, a specific genetic etiology is identified in less than 20% of CHD cases. This reflects the low sensitivity of current routine cytogenetic testing in detecting causative genetic alterations. Multiple studies have shown that recurrent copy number variants (CNVs) may be found in 20% of patients with CHD (**Greenway *et al.*, 2009; Sørensen *et al.*, 2012**).

Multiplex Ligation-dependent Probe Amplification (MLPA) is an established technique for detection of known CNVs. The cost of MLPA is substantially less than that of whole genome molecular and cytogenenomic tools and the technique is relatively simple. Thus, MLPA assay specifically designed for screening of CHD patients could be used as a first-tier screening assay (**Sørensen *et al.*, 2012**).

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The aim of this work was to improve the diagnostic outcome of different genomic imbalances among children with CHD, associated with other somatic anomalies or developmental delay, by using Multiplex Ligation Dependent Probe Amplification (MLPA) technique.

PATIENTS AND METHODS:

This study included 40 patients with congenital heart desease (CHD) associated with other somatic abnormalities or developmental delay referred to the Multiple Congenital Anomalies (MCA) and CHD Clinic of the clinical Genetics Department, Medical Centre for Scientific Excellence, National Research Centre starting from October 2018 till end of 2019. An informed written consent was obtained from parents of the included patients. Approval of the Medical Research Ethics Committee of the National Research Centre was obtained before the start of the study. Patients up to 18 years old and of both sexes were included in this study. While, patients with isolated congenital heart disease and patients diagnosed with trisomy 21 were excluded from this study. Comprehensive medical history was taken stressing on the family history to construct a pedigree for three consecutive generations. Thorough clinical examination was performed. Chest X-ray, ECG, and echocardiogram were carried out for all patients.

Conventional Karyotyping About 5ml venous blood was collected from the included patients, half on heparin to be cultured and prepared using GTG-banding technique (**Seabright, 1971; Verma and Babu, 1995**). Karyotype description was done according to the International System for Human Cytogenomic Nomenclature recommendations (**ISCN, 2020**).

DNA Extraction The other half of the blood sample was collected on EDTA and underwent DNA extraction using the QIAamp® DNA Mini Kit, according to the manufacturer's instruction. The quality and quantity of the DNA samples were determined using a NanoDrop® spectrophotometer.

MLPA analysis was done for all studied patients using commercial kits SALSA MLPA probemixes, microdeletion syndrome probemix (P245) and subtelomere probemix (P070) according to the manufacturer's instruction (MRC-Holland).

Chromosomal microarray was carried out for three patients showing normal result by MLPA assay, using Affymetrix Genome-Wide Human SNP Array 6.0, Thermo Fisher Scientific, UK.

RESULTS

The present study included 40 patients with congenital heart defects associated with extracardiac malformations and/or developmental delay, their clinical features are shown in table (1). Their age ranged from 3 days to 15 years with a mean age of 28 months. The highest percentage (60%) was located in the age group ≤1st year. They were 26 boys and 14 girls, giving a male to female ratio of 1.8:1. Family history revealed that 20 patients (50%) had positive parental consanguinity, and 17 patients (42.5%) had a family member with reported congenital anomalies.

Table 1: Clinical picture of the studied patients (*n*=40):

Variable	Categories	N	٪
IQ	- Normal	22	55.0
	- ID	18	45.0
Congenital heart defects	- Septal	22	55.0
	- Valvular	7	17.5
	- Fallot	2	5.0
	- Cardiomyopathy	2	5.0
	- Combined septal & valvular	7	17.5
Facial dysmorphism	- Negative	1	2.5
	- Positive	39	79.5
Other congenital anomalies	- Negative	5	12.5
	- Positive	35	87.5
Abnormal growth	- Normal	24	60.0
	- Abnormal	16	40.0
Behavioral disorders	- Negative	38	95.0
	- Hyperactive	2	5.0
Convulsions	- Negative	23	57.5
	- Positive	17	42.5
Short stature	- Negative	29	72.5
	- Positive	11	27.5
Microcephaly	- Negative	26	65.0
	- Positive	14	35.0

All the 40 studied patients showed normal karyotype results. MLPA analysis using SALSA MLPA P245 Microdeletion syndromes probemix showed abnormalities in 4 patients (10%). Two of them (5%) showed 7q11.23 microdeletion causing Williams-Beuren syndrome, one patients (2.5%) showed 4p16.3 microdeletion causing Wolf-Hirschhorn syndrome and one patient (2.5%) showed 22q11.2 microdeletion causing 22q11.2 deletion syndrome. While, MLPA analysis using SALSA MLPA P070 Subtelomeres Mix probemix showed 2p25.3 subtelomeric duplication in one patient (2.5%) making the overall MLPA diagnostic yield is 12.5%

CMA showed an interstitial 2.27 Mb deletion of chromosome 2q22 in one patient including the entire *ZEB2* gene:

arr[hg19]2q22.2q22.3(143375948_145653287)x1. Other genes were also found to be deleted in this region including *HSR, VCRL2, TSE2, CMD1H, COPD, CHDS2, GTDC1, ARHGAP15* and *MAFD* (this case was previously presented in details: **Refaat *et al.*, 2021**).

Detailed data of MLPA-positive cases:

Patient 1: was a 9-year-old male presented with CHD, microcephaly and mild intellectual disability. There was no parental consanguinity and no family history of similar conditions. His weight and height were on mean standards for age and sex, his head circumference was 48 centimeter (cm) (-1.5 SD). Developmental history revealed delayed sitting and Low birth weight (LBW). The pregnancy history was uneventful with no history of maternal infection or drug intake. General examination revealed dysmorphic facial features in the form of upturned nostrils, long philtrum and cupped ears with a bilateral incomplete single transverse palmar crease. Echocardiography revealed patent foramen ovale, pulmonary stenosis, Tricuspid regurge, supravalvular Aortic stenosis, pulmonary hypertension and cardiomegaly. The patient was clinically diagnosed as Williams-Beuren syndrome. MLPA analysis using probemix P245 Microdeletion syndromes revealed a deletion in Williams-Beuren syndrome specific region at 7q11.23, (Figure 1).

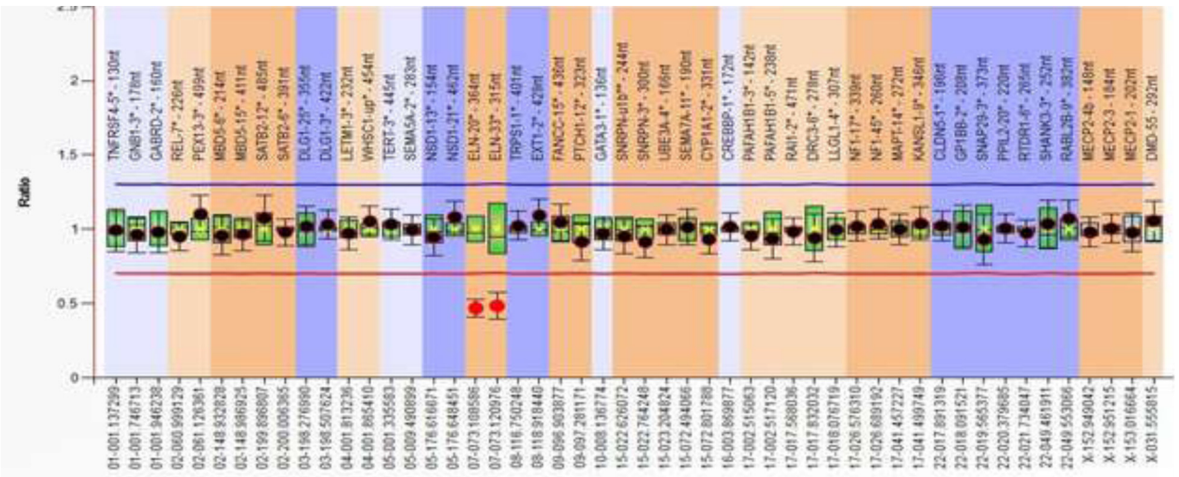

Figure 1: Ratio chart of patient (1) showing typical deletion in 7q11.23 region using SALSA MLPA probe mix P245 Microdeletion syndromes.

Patient 2: was a 9-month-old male presented with CHD and delayed speech. There was no parental consanguinity but there was a family history of intrauterine fetal death (IUFD). His weight, height and head circumference were on the mean standards for age and sex. The pregnancy history was uneventful apart from respiratory tract infection with antibiotic intake and vaginal bleeding. General examination revealed mild dysmorphic features in the form of asymmetric cupped ears, full cheeks, with an incomplete simian crease on left hand. Genital examination revealed bilateral retractile testes.

Echocardiography showed supravalvular aortic stenosis, mild left ventricular hypertrophy, cardiomegaly and patent ductus arteriosus. He was clinically diagnosed as Williams-Beuren syndrome. MLPA analysis using probemix P245 Microdeletion syndromes revealed a typical deletion in 7q11.23 Williams-Beuren syndrome region.

Patient 3: was an 8-month-old female presented with CHD and Intellectual disability (ID). There was no parental consanguinity and no family history of similar conditions. She was microcephalic, underweight and the length was less than -2 SD. Developmental history revealed low birth weight (LBW). General examination revealed dysmorphic facial features in the form of frontal bossing, hypertelorism, broad nose, highly arched eyebrows, epicanthal folds, short philtrum, micrognathia and dysplastic ears. Echocardiography showed Atrioventricular septal defects (AVSD). Neurological examination revealed hypertonic convulsions with brisk reflexes and agenesis of corpus callosum (ACC).

MLPA analysis using probemix P245 Microdeletion syndromes revealed typical deletion in 4p16.3 region causing Wolf-Hirschhorn syndrome, (Figure 2).

Patient 4: was a 6-month-old male presented with CHD and delayed milestones. There was a positive parental consanguinity and no family history of similar conditions. His weight was 5kg (-3.6SD), length was 63cm (-2.1SD) and his head circumference was 39cm (-2.8SD). Developmental history revealed poor suckling and delayed milestones. Delivery history revealed postnatal asphyxia and cyanosis. General examination revealed dysmorphic facial features in the form of low anterior hairline, ptosis, depressed nasal bridge, long nose and low set ears. Echocardiography showed VSD, ASD and pulmonary hypertension. Neurological examination showed hypotonia and hyporeflexia. MLPA analysis using probemix P245 revealed a typical deletion in 22q11.2 region extending between LCR (A) and LCR (D), establishing the diagnosis of DiGeorge syndrome, (Figure 3).

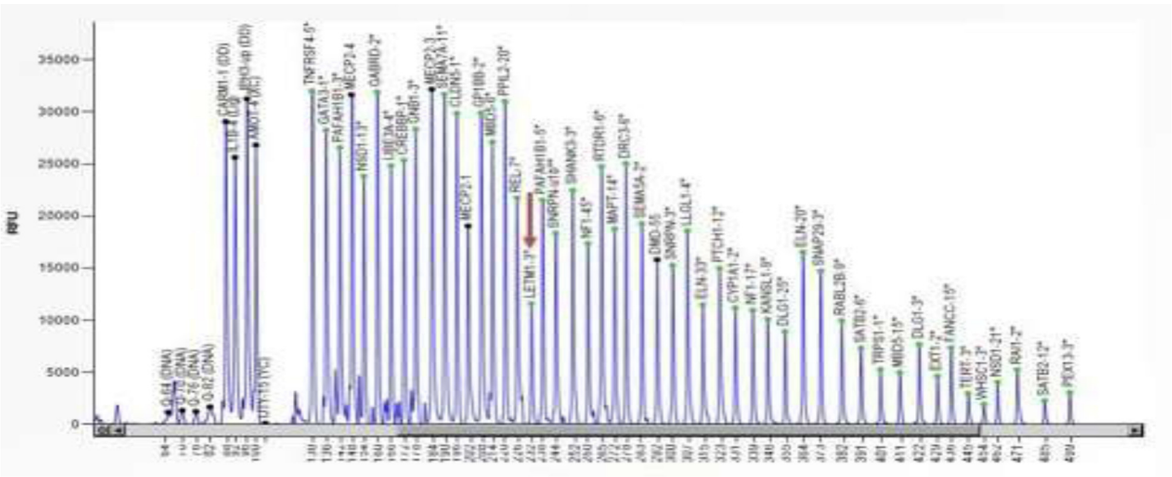

Figure 2: Electropherograms of patient (3) showing a typical deletion in 4p16.3 region using, SALSA MLPA probemix P245.

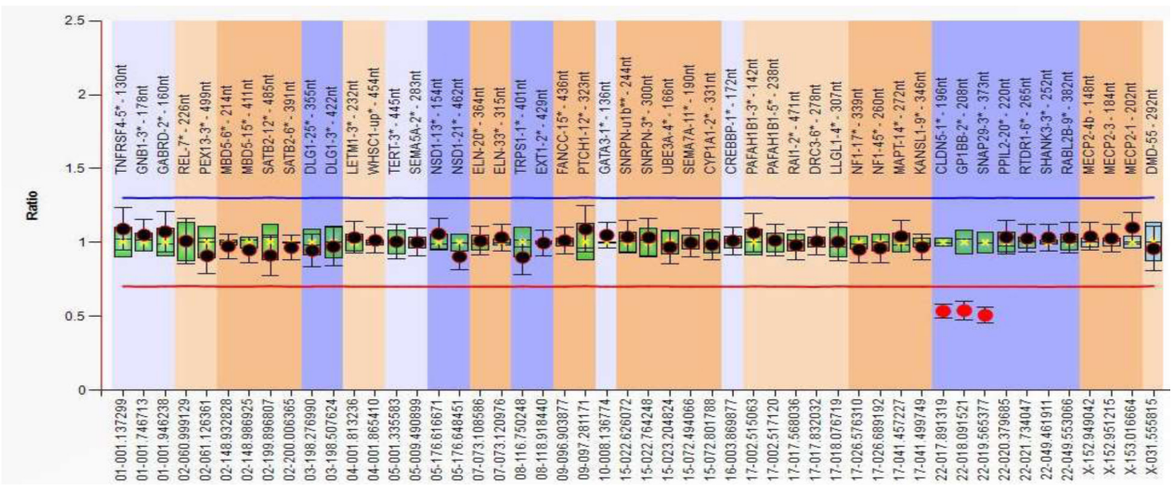

Figure 3: Patient (4) showing typical deletion in 22q11.2 region using SALSA MLPA probemix P245 Microdeletion syndromes.

Patient 5: was a 5-month-old male presented with CHD and global developmental delay (GDD). There was a positive parental consanguinity and no family history of similar conditions. The patient's weight and length were below normal and he had microcephaly. Developmental history revealed global developmental delay and LBW. General examination revealed dysmorphic facial features in the form of sparse eyebrows, upward slanting of eyes, epicanthal folds, hypertelorism, long philtrum, micro-retrognathia and deformed ears. Abdominal and genital examination revealed congenital dermal melanocytosis on the back, inguinal and scrotal hernia. Upper and lower limbs examination showed arachnodactyly and broad big toes. Neurological examination revealed tonic convulsions. Echocardiography showed VSD, while MLPA analysis using MLPA probemix P245 Microdeletion syndromes revealed a normal result. By using MLPA Probemix P070 Subtelomeres Mix it showed 2p25.3 subtelomeric duplication, (Figure 4).

Patient 6: A 1-year-old boy presented with respiratory distress, and cyanosis. He had delayed motor and mental milestones and failure to gain weight. On clinical examination he had peculiar dysmorphic facies in the form of: long face, frontal bossing, sparse hair, microcephaly, scanty medially flared broad eyebrows, downward prominent columella with short philtrum, deep-set wide eyes, mild epicanthic fold, hypertelorism, low set ears with everted (uplifted) lobules, pointed chin, retromicrognathia, and short neck. Limb examination revealed a right clenched fist with overriding fingers. The patient also showed microcephaly (-3.2 SD).

Neurological examination revealed hypotonia with hyporeflexia. Brain MRI showed agenesis of the corpus callosum and white matter degeneration. Echocardiography confirmed VSD, ASD, and moderate valvular pulmonary stenosis.

Conventional karyotyping and MLPA analysis using Microdeletion and subtelomere probe revealed normal results. Chromosomal microarray (CMA) showed an interstitial 2.27 Mb deletion of chromosome 2q22 including the entire ZEB2 gene: arr[hg19] 2q22.2q22.3(143375948_145653287)x1.

This case was described in detail in **Refaat *et al.*, (2021)**.

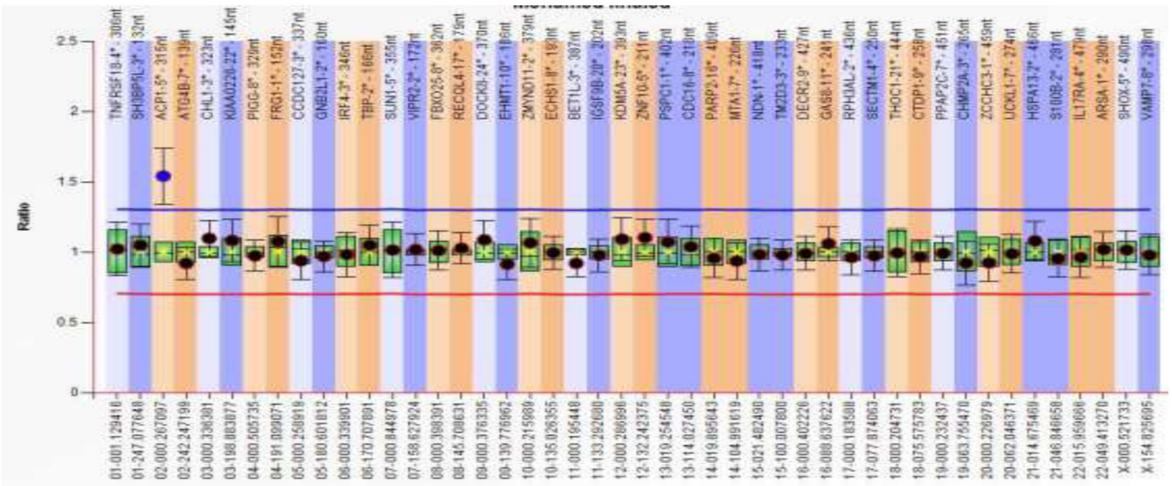

Figure 4: Ratio chart of patient (5) showing duplication in 2p25.3 region using SALSA MLPA probe P070 Subtelomeres Mix.

DISCUSSION

Congenital heart disease (CHD) involves structural defects of the heart or large intrathoracic vessels and can be associated with other somatic anomalies or developmental delay in a large fraction of patients. In the present study an attempt has been aiming to diagnose children with congenital heart defect associated with extracardiac malformations and/or developmental delay or intellectual disability for proper genetic counseling and further management. The study included 26 males and 14 females with a male to female ratio of 1.8:1. Their age ranged from 3 days to 15 years with mean value of 28 months. CHD constitute the most common congenital anomalies at birth. Many patients require early intervention before they complete their first year of age. They are presented with a wide range of symptoms that can be confusing and may present with repeated pulmonary infections making them difficult to diagnose with marked mortality and morbidity (**Peña-Juárez *et al.*, 2020**).

Similar to our study male patients with CHD represented the larger group (55.5%) in the study conducted by **Çaylan *et al.*, (2023)** with male/female ratio 1.2/1.

Parental consanguinity was evident among our group of patients, reaching 50%. This finding is in agreement with the study conducted by **Shieh *et al.*, (2012)**, in which the prevalence of consanguinity reached over 50% and the risk for CHD was higher in the patients of consanguineous parents. **Yunis *et al.*, (2006)** showed that infants born to first cousin marriages had a 1.8 times higher risk of having CHDs compared to those born to non-consanguineous parents. This finding was also confirmed by **El Mouzan *et al.*, (2008)** who reported that congenital heart defects were present in 9.1 per 1000 patients of consanguineous parents versus 4.3 per 1000 non related parents.

Our findings, showing that family history of congenital anomalies (cardiac and extracardiac) was present among 42.5% of patients, which represents a clinical significance. Another study on 1634 pregnancies of women with familial history of CHD had reported a recurrence risk rate ranging from 3.5% to 7.5%, with exact concordance of CHD in 21.5% of cases and a partial concordance in nearly 20% of cases (**Fesslova *et al.*, 2011**).

Congenital heart defects reported in our study were mainly septal defects (55%), followed by valvular defects and combined septal and valvular (17.5%, each), whereas each of Fallot tetralogy and cardiomyopathy constituted 5%. This matches the results reported by **Iemini *et al.*, (2019)** in his study on infants suffering from congenital heart disease, in which VSD was the most commonly detected cardiac defects, followed by valvular defects. On the other hand, in his study conducted on patients suffering from Down, Turner, 22q11.2, Williams-Beuren, Alagille and Noonan syndrome **Ko, (2015)** reported septal, valvular and Fallot tetralogy as the most common cardiac defects.

Intellectual disability (ID) was present in 45% of our cases. Intellectual disability is a recurring finding in CHD syndromes in varying degrees, mainly ranging

from mild to moderate degrees. While Epilepsy and other neurological manifestations as hypertonic reflexes were present in 42.5%. Epilepsy is a very common findings in more than 20% of patients suffering from CHDs (**Desnous *et al.,* 2018; Ghosh *et al.,* 2020**). Brain anomalies were present in 17.5% of patients in the present study mainly in the form of agenesis of corpus callosum, brain atrophy and holoprosencephaly. Agenesis of corpus callosum (ACC) was reported in Mowat Wilson patients (**Garavelli *et al.,* 2017**) and in some patients suffering from other syndromes as 22q11.2 DS, Turner and Williams-Beuren syndromes (**Bearden *et al.,* 2004**)

Dysmorphism features were present in 97.5% of our cases with ear anomalies being the most common anomaly, (72.5%), mostly in the form of low-set ears. Low-set ears is a common finding in many syndromes with chromosomal imbalances, many of which are associated with congenital heart disease as in 22q11.2 DiGeorge syndrome, Noonan and Turner syndromes. Other associated dysmorphic features represent recurring features in multiple syndromes with CHD.

Limb anomalies also constitute an important feature in our study, encompassing 60% of the patients, mainly in the form of polydactyly, arachnodactyly, syndactyly, clinodactyly, fusiform broad fingers and joint laxity. Limb anomalies are common associations with congenital heart disease syndromes like (Down syndrome and Costello syndrome presenting with joint laxity, 22q11.2 microdeletion syndrome with polydactyly, Mowat Wilson syndrome with syndactyly and finger anomalies and Holt-Oram syndrome, characterized by upper-limb defects ranging from triphalangeal or absent thumb(s) to phocomelia (**Mowat *et al.,* 2003; McDermott *et al.,* 2019**).

Genital anomalies were recorded in the present study including hypoplastic labia minora (14.2% of females), undescended testis and hypospadias (15.3% of males). Some CHD syndromes present with Genitourinary tract abnormalities as hypospadias seen in Mowat Wilson syndrome and genital anomalies seen in leopard syndrome patients. Also Genitourinary tract anomalies are present in a large proportion of 22q11.2 DS including cryptorchidism and hypospadias, hydronephrosis and unilateral renal agenesis (**Van Batavia *et al.,* 2019**).

Short stature was documented in 27.5% of the patients of the present study and abnormal growth pattern was also detected in 35% of our patients mainly in the form of LBW, with delayed milestones as sitting and walking and also failure to thrive. Beside different syndromes with LBW and short stature, **Le Roy, (2019)** implied that children who have CHDs also suffer from malnutrition and nutritional deficiencies which may cause short stature on the long term.

Studies using standard Karyotyping, can only diagnose a minor subdivision of cases presenting with CHD, as conventional karyotyping is only efficient in detecting changes larger than 5-10 Mb, which represents nearly 9% of cases (**Richards and Garg, 2010**). The advances in microarrays technologies has increased the rate of detection of chromosomal aberrations in patients with CHD to nearly 16.6-30% (**Thienpont *et al.,* 2007; Hightower *et al.,* 2015**). This technique is useful to define the genetic etiology in patients that would have otherwise remained undiagnosed (**Delea *et al.,* 2022**). Nevertheless, the cost of array methodology is relatively high making its wide-scale usage in developing countries limited with a wider use of Multiplex Ligation-dependent Probe Amplification (MLPA) technique which is considered a good feasible alternative genetic screening test with a relatively good cost-benefit ratio for CHD patients (**Jehee *et al.,* 2011; Grassi *et al.,* 2022**).

In the current study, MLPA was performed for all patients, using SALSA MLPA probemix P245 Microdeletion syndromes and P070 Subtelomeres Mix. It revealed abnormalities in 5/40 patients (12.5%). Our finding is in agreement with the findings of **Sørensen *et al.,* (2012); Wang *et al.,* (2013) and Campos *et al.,* (2015)** whereas the chromosomal aberrations detected in patients with CHD using the MLPA assay ranged from 3.2-33.33%, which was highly related to the selection of patients and the type of MLPA probemixes used.

The MLPA results of our patients partially match with the results reported by **Monteiro *et al.,* (2017)** showing that 22q11.2 deletion syndrome, Williams-Beuren syndrome (deletion 7q11.23) were the most frequent abnormalities detected (2.5% and 5% of our patients respectively). Wolf-Hirschhorn syndrome was detected in a single patient in our study (2.5%), as well as in Monteiro and colleagues study.

William-Beuren syndrome patients (*patients 1 and 2*) suffered from supravalvular aortic stenosis, cardiomegaly, facial dysmorphism and patient number one suffered also from mild Intellectual disability (ID). Nearly 95% of William's patients show specific deletion covering 1.5-1.8 Mb, including 26-28 genes mapped in this region. *ELN, CLIP2, GTF2I, GTF2IRD1* and *LIMK1* are among the different reported contiguous genes, with *ELN* gene being the most relevant. *ELN* gene is mainly linked to cardiovascular and connective tissue abnormalities and point mutations in *ELN* were also connected with familial supravalvular aortic stenosis (**Li *et al.,* 1997; Adam and Schmaier, 2012; Collins, 2013; Kozel *et al.,* 2021**).

Patient 3 with confirmed diagnosis of Wolf-Hirschhorn syndrome presented with intellectual disability and CHD in the form of atrioventricular septal defects (AVSD)

associated with microcephaly, short stature, convulsions and dysmorphic facial features specific to this syndrome (**Paradowska-Stolarz *et al.,* 2013**). In Wolf-Hirschhorn syndrome, CHD typically includes atrial and ventricular septal defects, However, complex congenital heart disease may occur in few patients (**Von Elten *et al.,* 2013; Battaglia and Carey, 2021**).

Patient 4 was suffering from CHDs (VSD, ASD and pulmonary hypertension), delayed milestones (poor suckling and delayed sitting), microcephaly and dysmorphic facial features characteristic of 22q11.2 deletion syndrome, MLPA analysis confirmed the diagnosis with typical deletion in 22q11.2 region extending between LCR (A) and LCR (D) encompassing the *TBX1* gene seen in 22q11.2 deletion syndrome. Nearly 90% of patients with 22q11.2 deletion syndrome have similar deletion (3.0 Mb) with the *TBX1* gene being the main cause of congenital heart diseases (**Baldini, 2005; Morrow *et al.,* 2018**). Congenital heart defects are the leading mortality cause in 22q11.2 deletion syndrome. However, the use of CMA and MLPA has dramatically increased the diagnostic yield of 22q11.2 DS (**Sooknanan *et al.,* 2023; Szczawińska-Popłonyk *et al.,* 2023**).

Patient 5 presented with VSD and global developmental and speech delay (GDD). His general examination revealed dysmorphic facial features in the form of sparse eyebrows, upward slanting of eyes, epicanthal folds, hypertelorism, long philtrum, microretrognathia and deformed ears. MLPA showed 2p25.3 subtelomere duplication using MLPA Probemix P070 Subtelomeres Mix. Similar to our results, **De Rocker *et al.,* (2015)** reported six patients, including 3 members of the same family, showing 2p25.3 duplications ranging from 170 to 377 kb in size. They had mild to moderate intellectual disability with speech delay and behavioral problems. 2p25.3 Microduplications involving the *MYT1L* gene have been described in patients with isolated childhood-onset schizophrenia (**Lee *et al.,* 2012**). However, the phenotype is still not well characterized. **Bouassida *et al.,* (2023)** reported variable clinical features of 2p25.3 microduplications in the form of developmental and speech delays (33%), autism spectrum disorder (23%), mild-to-moderate ID (21%), schizophrenia (23%), and behavioral disorders (16%) associated with incomplete penetrance and variable expressivity. Our patient's specific dysmorphic features and CHD were not reported in isolated 2p25.3 so far. However other associated genetic background may have been interfered with the diagnosed genetic defect. Nevertheless, our patient represents a rare 2p25.3 microduplication presentation who adds to the small number in the literature and expands the reported phenotypes.

Patient 6 suffered from respiratory distress, cyanosis, CHDs (VSD, ASD, PS), delayed motor and mental milestones. His clinical examination revealed microcephaly, dysmorphic features with hypotonia and hyporeflexia. Brain MRI showed agenesis of the corpus callosum and white matter degeneration. He was selected for chromosomal microarray (CMA) as he had peculiar dysmorphic features suggestive of a chromosomal abnormality but showed normal results by conventional karyotyping and by both MLPA kits. CMA revealed an interstitial 2.27 Mb deletion of chromosome 2q22 including the entire *ZEB2* gene and he was diagnosed as Mowat Wilson syndrome (**Mowat *et al.,* 2003; Ghoumid *et al.,* 2013**). This patient was previously published (**Refaat *et al.,* 2021**)

Chromosome microarray analysis (CMA) is superior in detecting chromosomal microdeletions and microduplications all over the genome in patients suffering from congenital anomalies with early developmental defect. It has a high resolution, generally greater than 1kb (**Moeschler and Shevel, 2014**). Many studies suggest the need of CMA as a routine diagnostic test for unexplained developmental delay/intellectual disability (**Wang *et al.,* 2019; Akkus and Cubuk, 2024**). This coordinate with our study, where a well selected case out of three was diagnosed by CMA as Mowat-Wilson syndrome.

CONCLUSION

The etiology of most CHDs is still largely unknown but is highly believed to be multifactorial. Conventional karyotyping is only efficient in detecting changes larger than 5-10 Mb, which is present in nearly 9% of the CHD cases. The advances in molecular cytogenetic technologies increased the rate of detection of chromosomal aberrations in patients with CHD. However, the chromosomal microarray methodology is a relatively high cost technology. The introduction of MLPA technique was considered a good feasible alternative genetic screening test with a relatively good cost-benefit ratio for CHD patients. The incorporation of both technologies in Larger studies can help us more in the field of the genetic pathophysiology of CHD and improve diagnostic strategies, allowing early efficient intervention, targeted therapeutic procedures, and appropriate family counseling.

CONFLICT OF INTEREST

There are no conflicts of interest.

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