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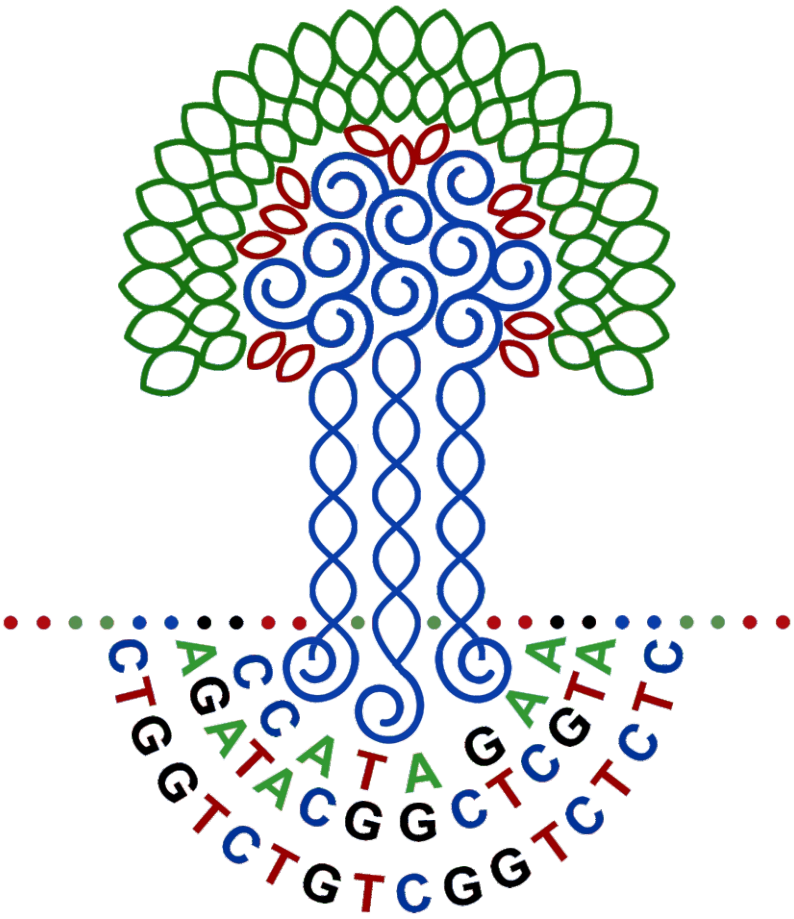

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PhotoQuiz 59

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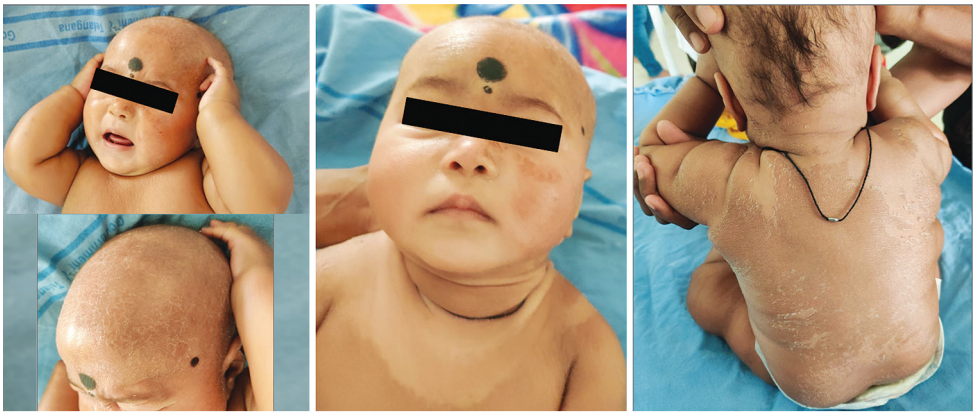
This infant was referred for evaluation of developmental delay and seizures. Significant improvement in symptoms was noted after starting specific metabolic therapy.

Please send your responses to editor@iamg.in
Or go to http://iamg.in/genetic_clinics/photoquiz_answers.php
to submit your answer



Answer to PhotoQuiz 58

Cornelia de Lange Syndrome

Cornelia de Lange syndrome is a monogenic disorder characterized by prenatal and postnatal growth restriction, distinctive craniofacial appearance, hypertrichosis, upper-limb reduction defects and global developmental delay. Facial features are characteristic and include microcephaly, synophrys, thick arched eyebrows, long eyelashes, anteverted nares, and long smooth philtrum. Cardiac anomalies, gastrointestinal dysfunction, and genitourinary abnormalities are frequent findings. Cornelia de Lange Syndrome is genetically heterogeneous and is caused by pathogenic variants in the *NIPBL, RAD21, SMC3, HDAC8* or *SMC1A* genes.

Correct responses to PhotoQuiz 58 are provided on page 3.

GeNeDit

Guest Editorial

Humanitarian Program for Gaucher Disease and Other Lysosomal Storage Disorders

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Lysosomal storage disorders (LSDs) comprise more than 50 diseases, each of which is individually rare, although collectively their prevalence is 1 in 5000 people (Verma et al., 2022). Majority of them occur due to mutations in specific enzymes that degrade the respective substrate that enters the lysosome through autophagy (van der Ploeg, 2022). The logical treatment is to make the enzyme and administer it to the patients. The challenge lies in the fact that the patients with each specific lysosomal storage disorder are very few, and pharmaceutical companies are not willing to take up the manufacture of these enzymes, because such a project would not be financially viable. Henry Termeer who pioneered the programs for enzyme replacement therapy (ERT) in 1990s for Gaucher disease and set the ball rolling for the manufacture of ERTs for other lysosomal disorders had recognized this downside of the high cost of manufacture of therapies for rare disorders. He knew that the introduction of enzyme replacement therapy (ERT) for Gaucher disease in 1991 would transform the life of patents with this disease. However, he recognized that due to the high cost of treatment it may remain unavailable to the vast majority of patients, especially in poor-resource countries. He stated right at the beginning that "any patient with Gaucher disease who needed to be treated with ERT, would have access to it, regardless of whether the cost could be paid" (Hawkins, 2019). This led to sowing the seeds of the humanitarian program for supply of ERT, and we must applaud his magnanimity in initiating this program.

International Gaucher Day (IGD) was launched in 2014 and is celebrated annually on 1st October to raise awareness of this disease. During the 2nd South Asia Gaucher Summit held on 1st October 2022, a presentation was made to describe the humanitarian program for this disease and the transformative impact it has had on the lives of patients. However, the program was not about simply distributing the enzyme, but involved building the support systems for it, and developing local expertise to manage these patients.

For ensuring success of the humanitarian program a number of principles were recognized and accepted (Verma et al., 2022): (1) A charitable foundation was set up, obtaining tax exemption for its activities, and ensuring that all products and services would be channelized through it. (2) Core elements of governance were identified such as engagement of senior executives / management of the manufacturing company and complete separation between humanitarian and commercial activities, with decision regarding allocation of ERT to be taken by the local experts' committee using detailed and consistent disease-specific medical criteria. (3) A number of committees were set up such as the management committee, cross-functional steering committee, and operation committee, to oversee the functioning, ensure program compliance at local, regional and country level, and establish the vision, mission, goals and objectives for the program.

Vital elements of the program were formulated: (1) Development of local healthcare systems to improve patient outcomes; (2) Provision of help where it was needed, and where treatment access was limited; (3) Planning for sustainable and long-term access; (4) Treatment based on recommendation by local doctors on consistent criteria, using best practices in disease management. This was necessary due to unique phenotypes and genotypes in developing countries that may differ from those in the West; (5) Operational excellence following all international and local regulations; (6) Establishing an infrastructure to support patient care, with local governments, physicians and non-government organizations; (7) Provision of same treatment and attention as is given to those patients who pay; (8) Entry to registries was made available; and (9) Compliance with ethical standards, institutional policies, and external governmental requirements, and continued efforts to meet strategic goals. These guiding principles were to be followed at all times striving for global standards.

The first charitable program was started in USA in 1991, in China in 1999 and in India in 2007, followed by multiple regional initiatives rolled out, culminating in the first non-US collaboration with an NGO [the Gaucher Initiative/Project HOPE

(Health Opportunities for People Everywhere)]. In India the first therapy was provided in 1997, although the Indian humanitarian program was officially launched later in September 2007. It is managed by the India Medical Advisory Board (IMAB) comprising of 16 leading global and national consultants, who provide clinical support and coordinate treatment for all patients – all brought together by one common thread – HOPE!! The Indian experts prepared for a leadership role in the care for lysosomal storage disorders and developed operational protocols and published guidelines on management (Puri et al., 2018).

Prior to the initiation of the program, during the visits by the senior staff of the company (Genzyme), the local experts emphasized the need for early and correct diagnosis. They put forward the request for support of the local laboratory scientists for training in foreign diagnostic centers. Soon, diagnosis of lysosomal disorders on dried blood spots was established and provided free to all patients in India and neighbouring countries. The Biochemical Genetics Laboratory in Sir Ganga Ram Hospital was made the nodal laboratory for this exercise. From January 2016 to September 2022, 6,788 dried blood spots were assayed and 1504 (22.1 %) turned out to be positive. There were 2,503 samples for estimation of glucocerebrosidase, the enzyme for Gaucher Disease and 499 (19.9%) positive cases were identified (Verma et al., 2017; Unpublished data).

The interest generated in inborn errors of metabolism (IEMs) through the humanitarian program led to the formation of the parent support group called the Lysosomal Storage Disorders Support Society of India (LSDSS). It was formed in 2006 but got registered in 2010. It has played a critical role in creating awareness and organizing meetings for the benefit of the patients and their parents and advocating for the cause of the affected children.

More than 3,300 patients with four LSDs [Gaucher disease, Fabry disease, and mucopolysaccharidosis (MPS) I and II] have been enrolled in more than 100 countries in six continents, while some of these patients have received treatment for more than 20 years. Of these patients 63.7% had Gaucher disease. This care represents more than 50,000 patient-years of experience extending over 30 years. Since the introduction of the program in 1991, the number of patients with Gaucher disease served is 1,248, number of countries supported since inception is 75, the number of individuals receiving humanitarian treatment annually is 652, the number of countries supported today is 52, average number of new cases approved each year over past 5 years is 48, while the average time current individuals have received humanitarian treatment is 9.8 years. The number of patents of Gaucher disease getting treatment in India at present is 75.

The first boy provided ERT in India was in 1997. From a pot-bellied child he has now grown to be a handsome adult who has qualified as an engineer and works in an IT firm and is currently Regional Manager for South Asia for the International Gaucher Alliance (IGA). Similarly, there are other success stories of courage and hope, well described in the book 'Roar for Rare: The Unheard Voices' (Sanofi Genzyme, 2020). There are 10 stories of people with Gaucher disease, five with Pompe disease, five with Fabry disease and seven with MPS I: in this book.

Takeda also has a successful humanitarian program based on a similar operational model for three diseases –Gaucher disease, Fabry disease and MPS II. Takeda's humanitarian program is on a smaller scale, there being 36 patients with Gaucher disease (GD), 26 with MPS II, and 7 with Fabry disease. Majority of patients with GD have been enrolled for 4-5 years, while 95% of patients with GD are being followed up regularly.

In closing while one thanks the pharmaceutical companies for their generosity in supporting the humanitarian program, we must spare a thought for the many affected children who are not covered by this program. Many children whose parents are working in large corporate organizations in India such as the Employees' State Insurance Corporation (ESIC) of the Ministry of Labor and Employment, the Armed Forces, and Public Sector Undertakings (PSUs) are fortunately receiving ERT from these organizations. However, the other children have to cope with their disease and disability with despair, and a bleak future. Let us hope their prayers will be answered by understanding officials in the Ministry of Health and Family Welfare, Government of India, with additional help from different PSUs under their corporate social responsibility (CSR).

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Clinical Vignette

Early Onset Marfan Syndrome in a Neonate with a Novel Pathogenic Variant in the Non-Hotspot Region of the *FBN1* Gene

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Abstract

Early onset Marfan syndrome (eoMFS) is a rare form of classic Marfan syndrome. It is distinct from the classic Marfan syndrome in severity. The present case report is of a neonate with increased length, facial dysmorphism and arachnodactyly without any joint contractures. On transthoracic echocardiography (TTE) there was annulo-aortic ectasia. Exome sequencing revealed a de novo novel splice site pathogenic variant c.4336+2T>C in intron 35 of the *FBN1* gene. The child was started on beta blocker therapy. On follow up, the child developed progressive increment in aortic root dimension with new onset mild aortic regurgitation and mitral regurgitation. Beta blocker was stopped and angiotensin receptor blocker (ARB) was started. The child responded well with ARB and kept on medical follow up. The current case highlights that the identification of more novel variants in non-hotspot regions of the *FBN1* gene would help in understanding the genotype-phenotype correlations in eoMFS. This case also highlights the relevance of timely molecular diagnosis which helps in appropriate management and prognostication in such a scenario.

Keywords: Early onset Marfan syndrome, *FBN1* gene, Fibrillinopathy

Patient details

This term female neonate was the first offspring of a healthy non-consanguineous couple. Detailed fetal anomaly scan showed bilateral choroid plexus cysts. Polyhydramnios was noted from 28 weeks. The baby was born by Cesarean delivery with a birth weight of 3.3 kg. On examination at birth, the length was 52cm (90th centile), head circumference was 36cm (95th centile) and weight was 3.3kg (70th centile). Arm span to length ratio was 1.07 and upper segment to lower segment ratio was 1.6. There was relative macrocephaly, sparse hair over the frontal region, depressed nasal bridge, deep-set eyes, down slanting of palpebral fissures, malar hypoplasia, high arched palate, and prominent chin (**Figure 1a**). The neck and spine were normal. Chest showed slight pectus excavatum. Extremities were long with long fingers (**Figure 1b**), toes and pes planus (**Figure 1c**). There were no contractures/joint dislocations. Central nervous system and per abdominal examination was unremarkable. On auscultation, there was non-ejection click and 2/6 ejection systolic murmur. Transthoracic echocardiography (TTE) at birth showed annulo-aortic ectasia with aortic root Z score of +2.4 (**Figures 2a, 2b, 2c, 2d**). Ophthalmological examination and hearing evaluation were normal. Bilateral choroid plexus cysts were noted on neurosonogram. Infantogram, ultrasound abdomen and extended newborn screening were normal. There was no family history of tall stature, sudden cardiac deaths or loss of vision. Parents were normal on clinical examination. Marfan syndrome was suspected and whole exome sequencing was done.

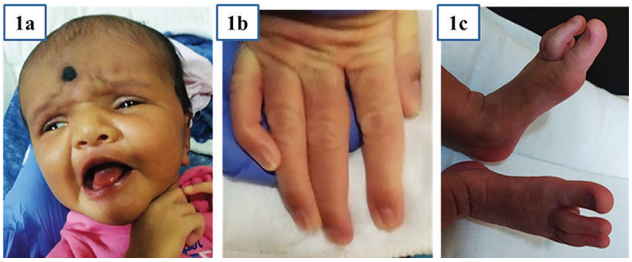

Figure 1 **Clinical features of the child**
1a. Craniofacial dysmorphism in the form of relative macrocephaly, sparse hair over the frontal region, depressed nasal bridge, deep-set small eyes with down slant of palpebral fissures, malar hypoplasia, and prominent chin
1b. Long fingers
1c. Pes planus with long toes

Whole exome sequencing of the child revealed a novel heterozygous pathogenic variant c.4336+2T>C (5' splice site) in intron 35 of the *FBN1* gene. The variant is not present in population databases. Classification of the variant is 'pathogenic' as per the American College of Medical Genetics and Genomics and the Association for Molecular

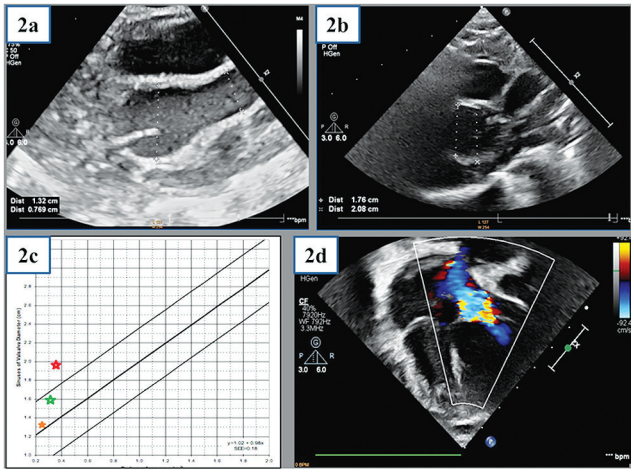

Figure 2 **2D Echocardiography findings**
2a. Transthoracic echocardiography (TTE) in the parasternal long axis (PLAX) view at birth showed aortic root dilatation of 13mm (Z score +2.4)
2b. TTE image in PLAX view at 7 months of age showed progressive aortic root dilatation of 20 mm(Z Score+7.2).
2c. Graph showing progressive dilatation of the sinus of Valsalva (aortic root) from birth till the age of 1.5 years.
2d. TTE image showing apical 4 chamber view with color integration at mitral valve showing moderate mitral valve regurgitation.

Pathology (ACMG/AMP) variant classification guidelines. In-silico databases predicted the variant to be 'disease-causing' due to dysregulation of splicing. The residue at which the change occurred in the fibrillin protein is well conserved throughout evolution. Targeted testing of the couple revealed absence of the variant in them.

Initially the child was started on beta blocker therapy. As there was progressive dilatation of the aortic root (Z score +7.2) with new onset aortic and mitral valve regurgitation, beta blocker was stopped, and angiotensin receptor blocker (ARB) was started. Parents were counseled regarding future need of aortic and mitral valve surgery. At present, the child is 21 months old and is stable.

Discussion

Fibrillinopathies are a group of connective tissue disorders. Early onset Marfan syndrome (eoMFS), a fibrillinopathy, differs from classical Marfan syndrome in the clinical presentation and severity. EoMFS is more frequently sporadic (Hennekam et al., 2005). Modified Ghent criteria is used for diagnosis of early onset Marfan syndrome. These children present with senile facial appearance, ectopia lentis, arachnodactyly, scoliosis, joint contractures/dislocations, and cardiac involvement. Our patient did not have scoliosis or joint contractures/dislocations. Aortic root involvement is less common than valvular insufficiency and even if aortic dilatation occurs, dissection is quite rare (Stheneur et al., 2011). Aortic valvular insufficiency is less frequent but, in this child, aortic regurgitation was present. Those with valvular insufficiency had shorter life expectancy. The average age of death is reported as 16 months (Loeys et al., 2010).

Pathogenic variants in the *FBN1* gene can lead to mild to severe phenotype like mild skeletal abnormalities to the severe cardiac phenotype. Variants in early onset form of classic Marfan syndrome are located in exons 24-32 of the *FBN1* gene (hot spot region). Most of them are missense variants. This hot spot region encodes eight calcium-binding epidermal growth factor-like (cbEGF) domains with six conserved cysteine residues (Tiecke et al., 2001; Abdel-Massih et al., 2002). Substitutions of one of these cysteine residues disrupt the disulphide bond leading to misfolding of the domain, deleterious effects on the structure of fibrillin-1 protein, enhanced susceptibility of fibrillin for proteases, and interference with heparin binding which play a critical role in microfibril assembly (Haller et al., 2020; Matyas et al., 2007). Our case had a novel 5' splice site variant in intron 35 of the *FBN1* gene which is not in the hot spot region but is associated with a severe cardiac phenotype. This could be because of the effect of modifier genes (Faivre et al., 2009).

Neonatal Marfan syndrome (nMFS) is the differential diagnosis considered for this child. nMFS presents with cardiac failure in the early infantile period and they succumb by the age of 2 years. The average age of death in eoMFS is the adolescent period (Hennekam et al., 2005). Exact labeling of these patients would therefore help in appropriate counseling and more accurate prognostication.

Beta blockers are used to prevent and treat MFS patients including eoMFS. Recent studies have shown that ARBs are beneficial in patients with significant aortic root dilatation and mitral valve regurgitation (Strigl et al., 2007). Patients with congestive heart failure and severe aortic

regurgitation need aortic valve replacement, quadrivalve replacement or heart transplantation. Aortic root surgeries are recommended in cases with rapid progression of aortic diameter (>5mm/ year) or if aortic diameter is ≥ 45 mm (Takeda et al., 2016). Any surgical intervention in an infant is associated with significant morbidity and mortality. Early diagnosis and initiation of medical therapy helps in delaying the surgical intervention (Ardhanari et al., 2019). Treatment of early onset Marfan syndrome is still challenging even in patients with early diagnosis as there is no clear data on ideal medical management. In our case, the child was clinically stable on medical management at the age of 21 months.

Conclusion

This is the first reported patient of early onset Marfan syndrome with a pathogenic variant outside the non-hotspot region of the *FBN1* gene. Identification of new variants in non-hotspot regions and other genetic modifiers would help in clear understanding of the genotype–phenotype correlations of these patients.

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Clinical Vignette

Novel Findings in a Fetus with 4p Deletion Syndrome: Case Report and Review of Literature

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Abstract

The 4p deletion syndrome, also known as Wolf -Hirschhorn Syndrome (WHS), is caused by partial deletion of the short arm of chromosome 4. The syndrome is well known and extensively described in the pediatric age groups and young adults and about 83 prenatal cases have been described to date in world literature. But literature on the fetal phenotype and genotype of WHS is limited. We are reporting here the ultrasound features, fetal autopsy, and molecular diagnosis in a fetus with WHS, in whom the diagnosis was confirmed through chromosomal microarray of the amniotic fluid sample which revealed a genomic deletion of 17.3 Mb on cytoband 4p16.3p15.32 of chromosome 4.Dilated pulmonary artery and narrow aorta noted in this fetus are novel findings not reported earlier.

Keywords: 4p deletion; fetus; genotype-phenotype correlation

Introduction

Wolf-Hirschhorn Syndrome (WHS; OMIM # 194190), caused by chromosome 4p deletion, is a well-known microdeletion syndrome. It has an incidence of 1/20,000 - 1/50,000 with a female preponderance of 2:1 (Battaglia et al., 2008). The condition was recognized by Wolf and co-workers and Hirschhorn and his group independently (Wolf et al., 1965; Hirschhorn et al.,1965).

WHS syndrome is characterized by unique facial dysmorphism referred to as the 'Greek warrior helmet' appearance (which includes broad nasal bridge, high forehead, prominent glabella, hypertelorism), severe fetal growth restriction, multiple skeletal and cardiovascular anomalies, intellectual disability, seizures, eye defects, and urogenital defects (Battaglia et al., 2001).

WHS is a contiguous gene deletion syndrome. The syndrome is caused by partial loss of the short (p) arm of chromosome 4 (4p16.3). About 55% patients with WHS have a de novo simple deletion of 4p16.3 and 40%-45% of individuals with WHS have an unbalanced translocation. These unbalanced translocations may be de novo or inherited from a parent with a balanced rearrangement.

The phenotypic severity depends upon the size of the deletion; the larger the deletion, the more severe the manifestations (Zollino et al., 2000). The severity of WHS has been classified into three types depending upon the size of the deletion: mild- less than 3.5 Mb, moderate-5 to 18 Mb, and severe- more than 22 Mb (Zollino et al., 2000). Large deletions of 22 to 25 Mb or more are characterized by severe complex features, including typical facial appearance, severe intellectual disability, severe growth delay, severe seizures, neurological abnormalities, ophthalmic abnormalities, congenital heart malformations, skeletal and renal anomalies, cleft palate and hypospadias (Zollino et al., 2000).

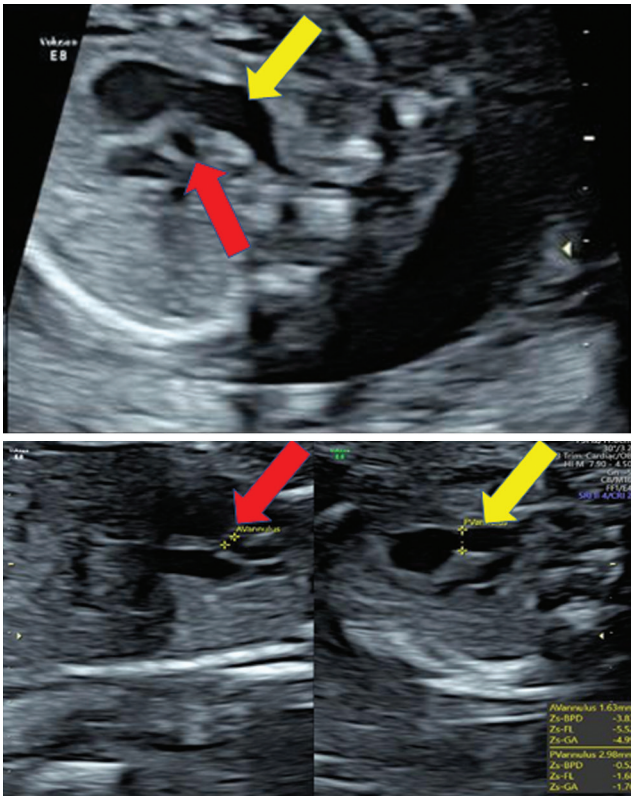
WHS critical region 1 and 2 (WHSCR1 and 2) have been identified as two critical regions for the disease. *WHSC1* and *WHSC2* genes are two candidate genes in the WHCR1 region. The *WHSC1* gene (OMIM * 602952) plays a major role in normal development and its deletion is likely to contribute to the WHS phenotype. The *WHSC2* gene (OMIM *606026) functions in mRNA processing and cell cycle. *LETM1* (OMIM 604407) is a candidate gene in WHSCR2 and is considered to be the major candidate gene for the seizure phenotype. (Zollino et al., 2008).

We report a male fetus of 20-21 weeks gestational age with 4p16.3 deletion syndrome, diagnosed by chromosomal microarray (CMA). The ultrasound and autopsy findings are described and the genotype-phenotype correlations in WHS are discussed.

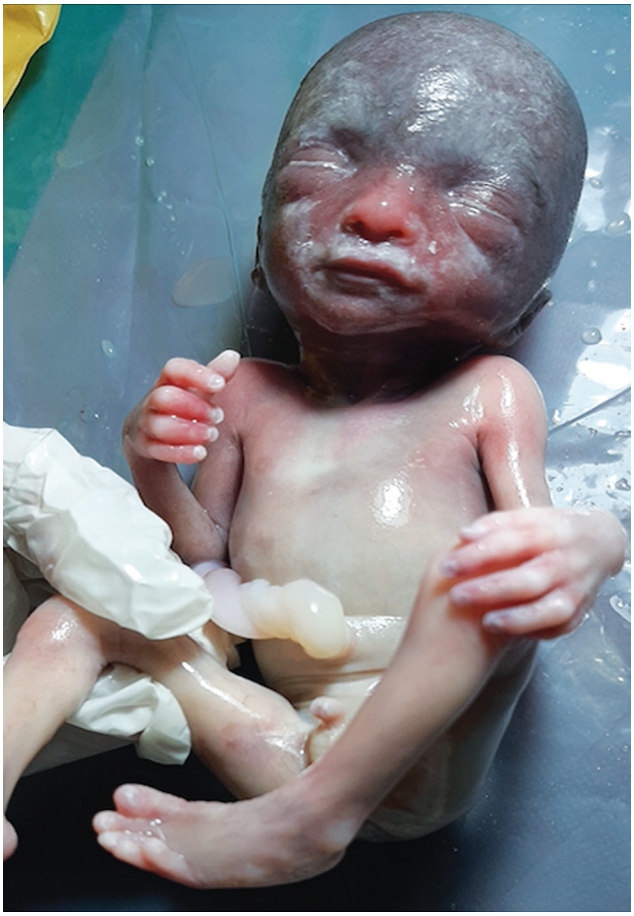
Patient details

A 33-year-old primigravida, with spontaneous conception, was referred at 19 weeks + 3 days of gestation, as her anomaly scan showed fetal growth restriction (estimated fetal weight was at 1st centile), narrow ascending aorta, and hypoplastic cerebellum (**Figure1a**). The transverse cerebellar diameter was 18 mm and was at 1st centile for

Figure 1



1a. Ultrasound of the fetus showing the narrow aorta (marked with red arrow) and dilated pulmonary artery (marked with yellow arrow)



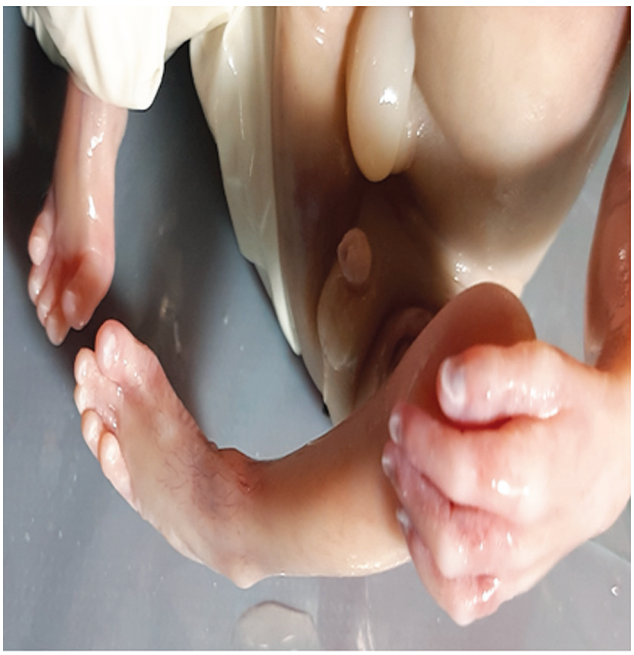
1b. Fetal autopsy showed broad nasal bridge and prominent glabella.

gestation. The aorta measured 1.63 mm at the aortic valve annulus (Z score- 4.99). The pulmonary valve annulus measured 2.98 mm (Z score -1.76) (**Figure 1a**) (Schneider et al., 2005). In addition, the dual marker test and NT (nuchal translucency) scan done earlier were normal. There was no family history of similar issues, and the couple was non-consanguineous. There was no history of fever or rash during pregnancy and no history of drug intake.

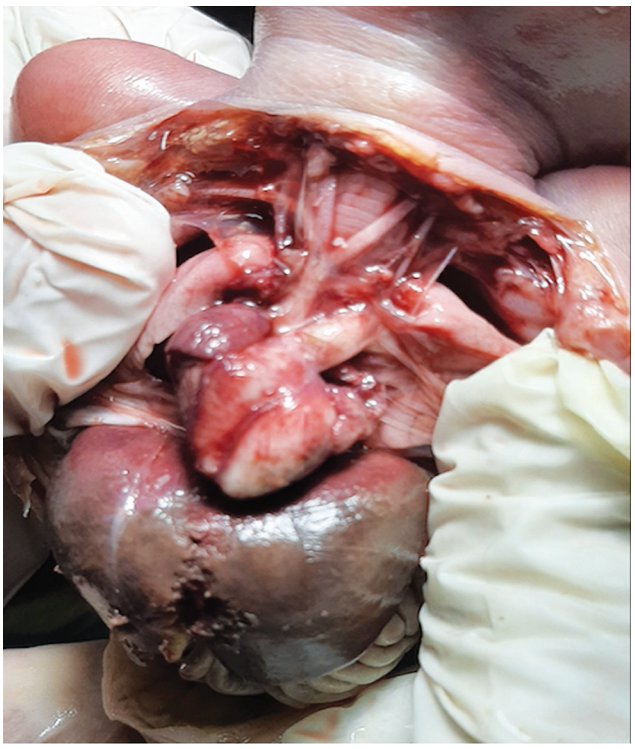
The patient was counselled about the guarded prognosis and associations with aneuploidy or copy number variation (CNV) and amniocentesis was done to check for the same. The fluorescence-in situ- hybridisation (FISH) report for five common aneuploidies (chromosomes 13, 18, 21 and sex chromosomes) in the amniotic fluid was normal.

The couple decided to terminate the pregnancy. A male fetus of weight 284 gm was delivered vaginally after medical induction and referred for fetal autopsy. Fetal autopsy revealed a male fetus corresponding to 20-21 weeks gestation with dysmorphic facies: broad nasal bridge, prominent glabella, and abnormal shape of the feet (**Figures 1b and 1c**). Internal dissection showed narrow ascending aorta compared to the pulmonary artery and hypoplastic cerebellum (**Figure1d**).

Chromosomal microarray (4x180K; Agilent Array CGH, Agilent Technologies, California, United States) of cultured amniocytes revealed a significant deletion of 17.3Mb on cytoband 4p16.3p15.32(72447_17462172)x1.



1c. Abnormal shape of the feet noted.



1d. Fetal cardiac dissection showed narrow ascending aorta and dilated pulmonary artery.

Table 1 shows various features reported on antenatal ultrasound in literature in comparison to the features we observed in this fetus (Xing et al., 2018; Zhen et al., 2018; Chen et al., 2020).

Discussion

WHS, chromosome 4p monosomy, is a contiguous gene deletion syndrome. The unique features of 4p deletion syndrome include growth retardation, 'Greek warrior helmet' facial dysmorphism, intellectual disability, facial clefts, cardiac septal defects, corpus callosum agenesis, kidney abnormalities, feet malformations, congenital diaphragmatic hernia, increased nuchal fold thickening, and cystic hygroma.

The fetus in this study presented with mild fetal growth restriction (FGR), aortic atresia, pulmonary artery dilatation, and cerebellar hypoplasia on ultrasound. Fetal autopsy findings confirmed the same. Facial features were subtle, like prominent glabella and hypertelorism. In addition, both feet had an abnormal shape. Narrow aorta and dilated pulmonary artery are novel findings not reported in both the prenatal and postnatal series reported earlier. Xing et al. reviewed 37 cases of WHS reported in the literature along with their ten cases and reported that the standard sonographic features of WHS include intrauterine growth retardation (IUGR) (97.7%), typical facial appearance (82.9%), renal hypoplasia (36.2%), cardiac malformation (29.8%), cleft lip and palate (25.5%), cerebral abnormalities (25.5%), skeletal anomalies (21.3%) and increased nuchal translucency/nuchal fold thickness (19%) (Xing et al., 2018). In **Table 1**, we have compared about 83 fetuses reported in world literature (Simonini et al., 2022). The two most common features are FGR (fetal growth restriction) (81.92%) and typical facial anomalies (69.87%). (Xing et al., 2018; Zhen et al., 2018; Chen et al., 2020; Simonini et al.,2022). In the fetus we report, growth was less than 1st centile, however, typical facial features were not picked up on the ultrasound and we feel that it is difficult to detect subtle facial features of this syndrome by ultrasound without high index of clinical suspicion of this syndrome.

Cardiac malformations in WHS cases have been reported with a breakpoint between 4p15.2 and 4p16.3. Only three prenatal cases with larger 4p deletions have been reported. Verloes et al. reported a fetus with 4p14 deletion with atrial septal defect (ASD), tricuspid valve hypoplasia, pulmonic valve atresia, right ventricular hypoplasia,

and aneurysmal dilation of the ascending aorta (Verloes et al.,1995). von Elten et al. reported a fetus with hypoplastic left heart syndrome (HLHS) (von Elten et al., 2013). The fetus reported by Xing et al. had a 23.4 Mb deletion at 4p15.2 and had a complex heart malformation including interruption of the aortic arch, ventricular septal defect (VSD), and pulmonary hypertension (Xing et al., 2018). Postnatal studies mainly discuss genotype- phenotype in the context of facial features, seizures, and growth delay and not based on cardiac anomalies.

In our case study, the fetus had a 17.3 Mb deletion at 4p16.3. It is a moderate size deletion, and maximum cases of this syndrome reported in literature have moderate size deletions. Patients with deletion <5 Mb cannot be picked up on routine karyotype. Chromosomal microarray has higher resolution compared to the karyotype and can detect sub-microscopic deletions upto 20 kb, and hence should be offered in all cases of fetal ultrasound anomalies and FGR.

Deletion of *WHSC1*, (abbreviated later as *NSD2* gene) (OMIM *602952), can disrupt the regulation of several genes resulting in WHS features (Meckkawy et al., 2021) De novo loss-of-function variants in *NSD2* gene were recently reported in patients with atypical WHS and in developmental delay, congenital cardiac defects and autism (Bockzeck et al., 2018). Nimura et al. hypothesized that *NSD2* gene might play a role in modulating the cardiac transcriptional network through collaboration with *NKX2.5* gene (Nimura et al., 2009).

The recurrence risk is negligible in de novo/ sporadic cases. However, in cases where WHS is due to balanced translocation in parents, recurrence risk could be 30-40% and in such cases prenatal diagnosis can be done by chorionic villus sampling or amniocentesis during pregnancy.

Conclusions

Our report highlights novel findings like narrow ascending aorta and dilated pulmonary artery associated with fetal WHS, and further such studies may provide insight into correlation between the genotype and cardiac phenotype of WHS.

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Table 1 **Summary of phenotypic features in fetuses with Wolf-Hirschhorn syndrome**
(Xing et al., 2018; Zhen et al., 2018; Chen et al., 2020; Siminino et al., 2022)

Clinical feature	Number (%) out of 83 fetuses	Fetus in this report
Fetal growth restriction	68/83 (81.92%)	+
Facial anomalies	58/83(69.87%)	+
Microcephaly	16/83(19.27%)	-
Abdominal anomalies	10/83 (12.04%)	-
Cardiac anomalies	25/83 (30.12%)	+
Skeletal anomalies	17/83 (20.48%)	+
Cerebral anomalies	19/83 (22.89%)	-
Pulmonary malformation	12/83 (14.45%)	-
Cystic hygroma	8/83 (9.63%)	-
Increased nuchal translucency or nuchal fold thickness	18/83(21.68%)	-

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Handbook of Clinical Adult Genetics and Genomics - A Practice-Based Approach

Editors: Shweta Dhar, Sandesh Sreenath Nagamani, Tanya Eble. Department of Molecular & Human Genetics, Baylor College of Medicine (BCM), Houston, and Department of Internal Medicine, Baylor College of Medicine, Houston, Texas, United States. Published by Elsevier, Academic Press. 2020. pp 504.

This book written by physicians at the Baylor College of Medicine, who have been running an adult genetic clinic for many years, fills a void. It is written keeping in mind usefulness in practice and has four sections – the first provides information on basic genetics, genetic testing, and counseling, the second covers common genetic disorders that occur in various organ systems, the third informs about access to genetic services, billing, and reimbursement, and the fourth deals with new developments such as precision medicine and gene therapy. Adult-onset monogenic disorders and those with a genetic basis such as cancers, connective tissue disorders, neurological disorders and endocrine disorders are extensively covered. The section on tele-genetics and video consults would be useful in pandemic situations like COVID 19. A glimpse of the ethical,legal, and social implications of genetics is given. The sections on precision medicine and pharmacogenomics will be useful to the modern physicians. Vignettes add to the value of the book. Overall, the book is strongly recommended for all those interested in adult genetics. A minor criticism which the authors may fulfill in future editions is to provide more photographs of the clinical disorders.

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GeNeViSTA

Genetic Counselling and its Challenges in Leber Hereditary Optic Neuropathy: Two Illustrative Clinical Scenarios from India

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Abstract

Leber hereditary optic neuropathy (LHON) is a genetic disorder caused due to variations in the mitochondrial genome. Individuals with this condition present in the second/third decade with progressive central painless vision loss. Common pathogenic variants, m.3460G>A in *MT-ND1*, and m.11778G>A, and m.14484T>C in *MT-ND6,* are reported in around 95% of patients. Multiple studies with descriptions of phenotype, molecular basis, and prognosis are reported, however, only a few studies illustrate the importance of genetic counselling. This is a retrospective study. Here we aim to address and describe the challenges faced in the process of genetic counselling of two patients diagnosed with LHON and explain how these could be overcome. We highlight the importance of information on genotype-phenotype correlation, and cascade-screening in LHON and elaborate on the significance of psychosocial counselling.

Keywords: Leber hereditary optic neuropathy, reduced penetrance, cascade screening, genotype-phenotype correlation, genetic counselling.

Introduction

Leber hereditary optic neuropathy (LHON) is a mitochondrial disorder where affected individuals present in the second/third decade of life with progressive painless central vision loss (Yu-Wai-Man & Chinnery, 2000). The diagnosis of LHON is established by mitochondrial DNA sequencing. Around 95% of individuals diagnosed with LHON are observed to carry one of the three common variations including m.11778G>A and m.14484T>C in *MT-ND6* or m.3460G>A in *MT-ND1* (Yu-Wai-Man & Chinnery, 2000). Reduced penetrance can be observed in this condition which is the result of mitochondrial mutation load and its interaction with environmental factors. Additionally, it is also sex and age dependent. Penetrance in males is reported to be as high as 50-60% whereas in females it is 10-20% (Puomila et al., 2007). Further, the peak of onset of symptoms is in the second/third decade of life and the chances of developing vision impairment reduce drastically thereafter (Yu-Wai-Man & Chinnery, 2000). The prognosis of the condition has also been reported to depend on the type of variation causative of LHON, that is, the individuals harbouring the m.14484T>C variant are observed to have a better visual prognosis with a partial recovery rate of 37-58% (Theodorou-Kanakari et al., 2018). LHON is one of the first mitochondrial conditions for which approved treatment is currently available. In 2011, a randomized placebo-controlled trial showed that treatment through Idebenone had significant improvements in visual acuity in patients with LHON (Klopstock et al., 2011). Idebenone was approved in 2015 by the European Medical Agency for the treatment of LHON (Carelli et al., 2017).

Here, we aim to address and describe the challenges faced in the process of genetic counselling with the help of illustrative clinical scenarios of two patients who were diagnosed to have LHON and how these could be overcome.

Clinical Scenarios

Patient 1

A 37-year-old male individual [Proband 1 (**Figure 1**; II.2)], first-born of a non-consanguineous couple was referred to the genetics clinic by an ophthalmologist. He presented with complaints of progressively diminishing, painless central vision loss. He started noticing these symptoms in the last two years, with an intermittent blurring of vision. His peripheral vision is comparatively preserved. There is no significant family history. His medical records were reviewed. The visual evoked potential testing showed mildly prolonged P100 latencies on the right side. Magnetic resonance imaging (MRI) of the brain and orbits were normal. Fundus examination reported bilateral peripapillary telangiectasias. Genetic testing by mitochondrial genome sequencing was already performed for him, which revealed the presence of the m.14484T>C variant in *MT-ND6*, confirming the diagnosis of LHON.

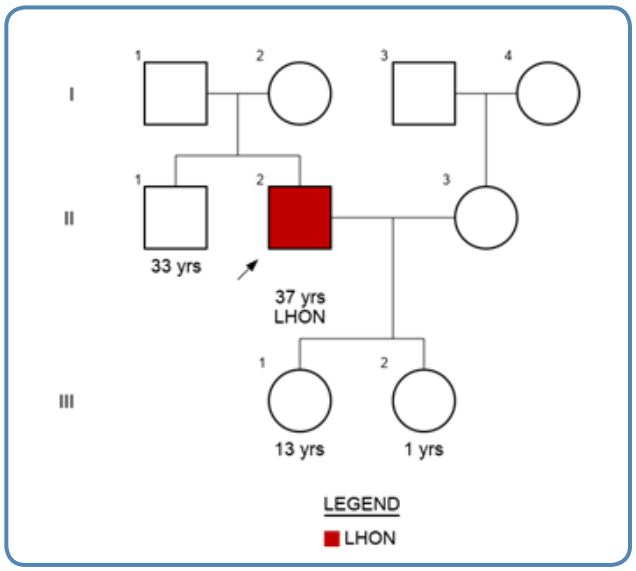

Figure 1 Three-generation pedigree showing Proband 1 at II.2

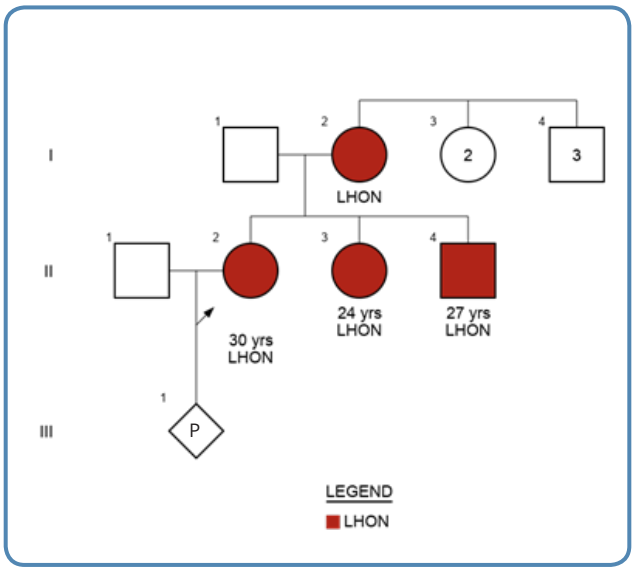

Figure 2 Three-generation pedigree with Proband 2 at II.2., her affected siblings at II.3., II.4., and affected mother at I.2.

The proband came for a genetic counselling session as he was unable to decipher the significance and long-term implications of his diagnosis. He is a ground engineer at the aviation services department and was anxious about losing his job as a result of the disease diagnosis.

Patient 2

A 30-year-old female [Proband 2 (**Figure 2**; II.2)], first-born to a non-consanguineous couple was referred to the genetics clinic by her gynaecologist. She presented with a history of visual impairment in herself and other family members. She first noted the onset of symptoms at 15 years of age with a mild blurring of peripheral vision, the symptoms progressed over the years and currently, there is a complete loss of vision. Upon taking a detailed family history, the proband revealed that her younger sister (in **Figure 2**; II.3) and brother (in **Figure 2**; II.4) also had similar complaints and currently both of them have blurred peripheral vision and no central vision. Proband's mother (in **Figure 2**.; I.2) had complaints of central vision blurring, onset in the third decade of life, and the symptoms progressed after the birth of her youngest offspring. Currently, she has diminished central vision with preserved peripheral vision. MRI (brain and orbit) of the proband was suggestive of thinned-out optic nerves (right>left). Genetic testing by mitochondrial genome sequencing was ordered by her ophthalmologist which revealed the presence of m.11778G>A in *MT-ND6*, confirming the diagnosis of LHON.

The proband is a primigravida (gestational age of 23 weeks) and wanted to understand the risk of occurrence of a similar condition in her ongoing pregnancy.

Discussion

Innumerable complexities of mitochondrial genetics contribute to challenges faced during genetic counselling of individuals with LHON as well as for the family members who want to understand the risk of occurrence of a similar condition. Some of these features include:

1. Progressive nature of vision loss
2. Adult/adolescent onset of the condition
3. Maternal inheritance
4. Sex and age-dependent penetrance
5. Discrepancies in the practice of the prenatal diagnosis

Taking the above two family case scenarios, we discuss the specific challenges faced during the post-test genetic counselling session.

Genetic counselling in India

Specialist facilities of clinical geneticists and genetic counsellors are still not available in every hospital and people still have to travel to tertiary care centres to access these services. Thereby,

genetic counselling services are mostly provided by either non-genetic medical practitioners or other health professionals with training in genetics.

With the increasing affordability and availability of genetic testing in India, physicians can now order a genetic test, and this is mostly without appropriate genetic counselling. A similar situation was faced in the above two families, where the genetic testing was advised without pre-test genetic counselling due to the non-availability of genetic counsellors in the hospital. The missed pre-test counselling sessions left the patients clueless about the expected results and implications of the disorder at hand. This challenge is observed within other specialties, for instance, neurology, cardiology, oncology, etc.

Presymptomatic genetic testing is performed for asymptomatic individuals with a family history of an adult / late childhood onset autosomal dominant disorder. The a priori risk of disease is usually 50% based on the pedigree. Targeted testing of the familial pathogenic variant is performed after appropriate genetic counselling. The test, performed before the onset of symptoms, requires counselling by an experienced geneticist, ophthalmologist and genetic counsellor. For a mitochondrial disorder such as LHON, there are unique challenges related to presymptomatic testing. A pathogenic variant in an asymptomatic individual is not predictive of disease. Specific LHON-causing pathogenic variants have variable penetrance based on the sex of the patient. The risk of developing the disease, the extent of the phenotypic manifestations and disease progression are specific for the mutation.It is imperative to refer to published data for the specific familial variant for presymptomatic genetic counselling ((Yu-Wai-Man & Chinnery, 2000).

Financial and economic insecurities in progressive disabling conditions

Non-lethal adult/adolescent genetic conditions can leave patients with life-modifying disabilities. LHON is a progressive condition that can lead to permanent visual impairment (Yu-Wai-Man & Chinnery, 2000). Although the prognosis of individuals with m.14484T>C in *MT-ND6* is better, with better visual acuity, other variations of this condition can have a poor prognosis (Carelli et al., 2017).

Proband 1 who was a ground engineer at an airport, feared losing his job on receiving the diagnosis of LHON. He expressed his distress and worry with regards to the possible challenging financial situations as a sole earning member. Appropriate post-test genetic counselling and guidance of alternative employment options enabled him to communicate to his employer for reinstating him from a ground job to a desk job. Proband 2 was a homemaker and did not express concerns related to financial/economic insecurity.

Occurrence and recurrence in mitochondrial inheritance

Mitochondrial disorders pose challenges in reproductive counselling which includes explaining the occurrence and risk of recurrence of the disorder. In the process of providing information and educating, patients may end up feeling overwhelmed. Genetic counselling helped in conveying this information to the proband by using simple terms, visual aids, and appropriate counselling tools to simplify complex information that helped the affected person to understand and to effectively communicate the risks with other at-risk family members. Additionally, it facilitated informed decision-making and searching the reproductive options for subsequent pregnancies as in Proband 2.

Unavailability of condition-specific support groups

Awareness about genetic conditions is still emerging in developing countries like India. There are now well-established patient support groups and non-government organizations (NGOs) for a few common genetic conditions such as Down Syndrome, beta-thalassemia, fragile X syndrome, spinal muscular atrophy, etc. However, for rare conditions like LHON, unavailability still persists. This aggravates feelings of being lonely and helpless.

We were able to connect both the families to LHON-specific online support groups based in Canada and the United Kingdom. They were given information regarding patient groups on various social media platforms. Moreover, they were connected to a rare disease NGO in India that helped Proband 1 to receive Idebenone on a compassionate basis. Further, information regarding government policies for the visually impaired including employment transition, travel requirements, and allowances were provided.

Limitations of prenatal diagnosis for mitochondrial disorders

In case one, the proband (Proband 1) had completed his family. The mode of transmission of mitochondrial DNA is cytoplasmic. Since sperms do

not transmit cytoplasm during fertilisation, there is no risk of transmitting the mitochondrial mutation and hence prenatal diagnosis is not indicated in this case if the couple plans a subsequent pregnancy in the future.

In case two, there was an ongoing pregnancy at the time of diagnosis confirmation. The pregnancy was advanced till diagnosis was made and the counselling was challenging for prenatal testing as the family was unaware of the limitations of prenatal diagnosis for LHON.

Homoplasmic mutations are reported to be the most common disease mechanism in LHON however, in 10-15% of cases heteroplasmy is also reported (Yu-Wai-Man & Chinnery, 2000). For instance, in a study, individuals with an m.11778G>A pathogenic variant load of less than 75% in their leukocytes were unaffected (Smith, 1993). Moreover, the penetrance of LHON is sex-dependent as discussed above but gender selection is a punishable felony in India under the Pre-conception & Pre-natal Diagnostics Techniques (PC-PNDT) act (Bhaktwani, 2012). Therefore, Proband 2 was told about various reproductive options she could consider such as egg donor or adoption for the subsequent pregnancies.

Further, the female sibling of the proband was advised genetic counselling regarding the risk of recurrence of the similar condition and to discuss reproductive options to avoid the same. The male sibling of the proband was explained the negligible risk of transmission of this condition in his offspring.

Mitochondrial replacement therapy with three parent babies is an option for a couple to prevent transmission of a mitochondrial mutation. The oocyte nucleus of the mother with mitochondrial disease and the enucleated oocyte of the donor with normal mitochondria is utilized for fertilization. This can be by male and female pronulear transfer from the at-risk zygote to the enucleated donor zygote. The second option is of maternal spindle transfer in metaphase II and transfer to the enucleated disease-free donor (Yu-Wai-Man & Chinnery, 2000).

Practices for improving lifestyle

Due to the progressive nature of the disease observed in Proband 1, a few lifestyle modifications were suggested to help him cope better with the condition. For instance, he was advised to avoid driving so as to prevent any mishappenings. As his current employment necessitates the use of a computer he was introduced to various online applications/websites and assistive technologies such as Zoom Text, Job Access with Speech which provides text magnification and voice-over settings. Additionally, he was advised to discontinue alcohol and tobacco consumption as this could exacerbate visual impairment.

Conclusion

In previous times, the information about genetic tests, their availability and high costs limited their uptake. In the present times genetic tests are commonly used by all clinicians in practice and this has posed major challenges to appropriate patient counselling. It is crucial to achieve genetic literacy, enhance awareness of relevance of pre and post-test genetic counselling and understand the need of appropriate training for care of patients with genetic disorders.

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GeNeXpress

Lysosomal Storage Disorders: New Therapies in the Horizon

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Chemically modified recombinant human sulfamidase (SOBI003) in MPS IIIA patients (Harmatz et al., 2022)

This phase 1/2 clinical trial studied the effects of a chemically modified (glycan modification) variant of recombinant human sulfamidase (SOBI003), which was previously shown to cross the blood-brain barrier (BBB) and achieve good CSF levels in mice. The study evaluated the safety, efficacy, pharmacodynamics, and pharmacokinetics of this drug in six patients with MPS IIIA when used upto 104 weeks. Six children with developmental age more than or equal to 12 months were given 3 mg/kg or 10 mg/kg weekly intravenous injections. Serum and CSF concentrations of the drug increased with the dose, and 79% reduction in levels of heparan sulphate (HS) in the CSF was noted. Stabilisation of cognition was observed, and the drug was well tolerated; however,there was no significant benefit noted in the quality of life and sleep pattern.

Intravenous 2– hydroxypropyl–beta–cyclodextrin demonstrates biological activity and impacts cholesterol metabolism in the central nervous system and peripheral tissues in adult subjects with Niemann–Pick disease type C1 (Hastings et al., 2022)

This phase 1 trial involving intravenous 2-hydroxypropyl-beta-cyclodextrin (HPßCD; Trappsol® Cyclo™) was conducted following positive results in preclinical studies. Patients above 18 years with Niemann-Pick disease type C, with systemic manifestations including hepatosplenomegaly and central nervous system (CNS) involvement/ neurodegeneration, were included in the study. Thirteen patients were enrolled, of whom ten patients completed the study; six patients received 1500 mg/kg and four received 2500 mg/kg intravenous dose every 2 weeks for 14 weeks. The drug HPßCD was found to clear cholesterol from the liver and to improve peripheral markers of cholesterol homeostasis. A reduction of between 19-42% was noted in the CSF total Tau levels. HPßCD was detected in the CSF suggesting that it crosses the blood-brain barrier even with intravenous administration.

Venglustat, an orally administered glucosylceramide synthase inhibitor: Assessment over 3 years in adult males with classic Fabry disease in an open label phase 2 study and its extension study (Deegan et al., 2022)

Venglustat inhibits the conversion of ceramide to glucosylceramide and acts as a substrate-reducing agent for synthesis of complex glycosphingolipids. This study was a multicentric, open-label, single arm, phase 2a uncontrolled 3-year study to assess the safety, efficacy, pharmacodynamics, and pharmacokinetics of venglustat given once orally (15 mg dose) in treatment-naive adult male patients with classic Fabry disease. Nine of the 11 enrolled patients completed the 26-week initial clinical study followed by a 130-week extension study. Reduction in lysosomal GL-3 in skin biopsy by light microscopy was noted only at the end of 156 weeks, but plasma GL-1 and GL-3 levels decreased rapidly and significantly. Overall, the data from the study is promising.

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Seventh Annual Conference of SIAMG - SIAMGCON 2022

After 2 years of online meetings and webinars, the 7th Annual conference of SIAMG -SIAMGCON 2022 - organised in Lucknow, was a sweet reminder of the privilege and joy of meeting and collaborating with colleagues that we had previously taken for granted. The theme for this year's conference: 'Genomic data for precision medicine: Global perspective on the role of genomics in health care' was aptly chosen as with the availability of large amount of genomic and clinical data there is an urgent need of establishing databases and systems for patient care in India.

The two-day conference was preceded by a hands-on workshop on interpretation of genomic variants conducted successfully by Dr Madhuri Hegde, Dr Sharon Plon, Dr Avni Santani and Dr Stepahnie Bielas.

Delegates from various parts of the country enjoyed spectacular talks by the national and international faculty. Dr Abhay Karandikar, Director of IIT-Kanpur, was the Chief Guest for the inaugural function. The Dr SS Agarwal oration was presented by Dr Andrea Superti Furga, Professor and Head, Division of Genetic Medicine, Lausanne, Switzerland. Dr Girish Katta received the prestigious Dr IC Verma Outstanding Researcher award. Dr Neethukrishna Kaustubham was awarded the Dr SS Agarwal Young Scientist award.

A thought-provoking symposium on prenatal, perinatal, and neonatal genetics: 'From the Womb to the Cradle' was organized for pediatricians and obstetricians on 11th December 2022.

Table The following are the prize winners of the oral paper and poster presentations:

	Paper presentation	Poster presentation
1st prize	Shruti Pande, KMC Manipal	Mounika Endrakanti, AIIMS, New Delhi
2st prize	Prajna Udupa,KMC Manipal	Anupriya Kaur, PGI, Chandigarh
3st prize	Neha Quadri,KMC Manipal	Namanpreet Kaur, KMC Manipal
Consolation prize	Sudisha Dubey, SGRH, New Delhi Aman Kumar Suryan,CSIR-CCMB, Hyderabad	Sarah Bailur, Rainbow Children's Hospital Saurabh Vaish,SGPGIMS, Lucknow Suranjana Banik, AIIMS, Bhubaneshwar

Inaugural function

National and international faculty for SIAMGCON 2022

Pre-conference workshop held on 8th December 2022

Dr SS Agarwal Oration - 2022

The Dr Shyam S Agarwal Oration of the Society for Indian Academy of Medical Genetics (SIAMG) for the year 2022 was awarded to Dr Andrea Superti-Furga, Head of the Division of Genetic Medicine at the Lausanne University Hospital and Professor at the Faculty of Medicine and Biology of the University of Lausanne in Switzerland. Dr Superti-Furga is a world-renowned expert in the field of medical genetics. His clinical and research contributions in the areas of skeletal dysplasias, inherited disorders of connective tissue, inborn errors of metabolism and neurodevelopmental disorders have helped provide significant insights into the pathophysiology, diagnosis and management of these conditions and have led to the identification of many novel monogenic syndromes.

Dr I C Verma Outstanding Researcher Award - 2022

The Dr I C Verma Outstanding Researcher Award for 2022 was awarded to Dr Girisha KM, Professor of Genetics at the Sultan Qaboos University, Muscat, and Professor of Medical Genetics at the Kasturba Medical College, Manipal Academy of Higher Education, Manipal. He was conferred the award in recognition of his valuable research contributions to the field of medical genetics in India, especially in the area of skeletal dysplasias

Launch of the GeneTOP Module at SIAMGCON 2022

Winners of the oral paper and poster presentations

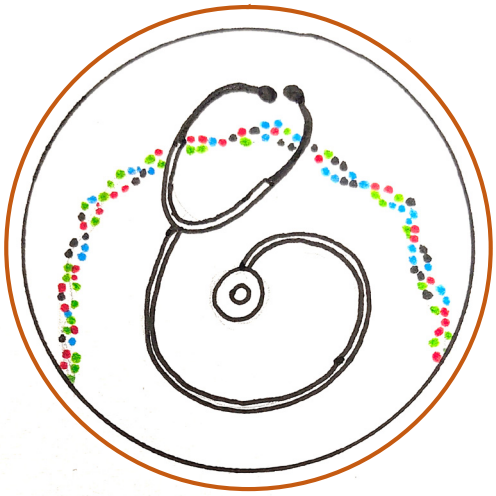
The online training course developed by SIAMG called 'GeneTOP: Genetics & Genomics Training and Orientation Program' was launched by Professor I C Verma at SIAMGCON 2022. GeneTOP is a free online resource available for medical doctors.

It will provide an opportunity to medical practitioners to get basic training in clinical genetics at their convenience from home. It can also be used by medical teachers for the training of their MBBS, MD and DM students. It will serve as the long-awaited online training program in medical genetics for all medical fraternity at various stages of their careers and belonging to any medical speciality.

Dr SS Agarwal Young Scientist Award

The Dr SS Agarwal Young Scientist Award was presented to Dr Neethukrishna Kausthubham from the Department of Medical Genetics, Kasturba Medical College, Manipal Academy of Higher Education, for her paper titled 'A data set of variants derived from 1455 clinical and research exomes is efficient in variant prioritization for early-onset monogenic disorders in Indians' published in the journal Human Mutation (Hum Mutat. 2021;42(4):e15-e61) under the guidance of Dr Girisha KM.

GeneTOP



– an Online Training Course in Medical Genetics

Medical genetics is playing an increasingly important role in the diagnosis and treatment of a number of diseases / disorders. Keeping in mind the rapidly increasing knowledge in the field as well as its growing importance for medical practitioners as well as students, the Society for Indian Academy of Medical Genetics (SIAMG) has developed an **Online Training Course *'GeneTOP: Genetics & Genomics Training and Orientation Program'*.** This course covers many clinically relevant topics and is aimed at improving the knowledge and understanding of medical practitioners and students alike.

The course consists of 57 topics covered under 4 modules, namely:

- Basic Genetics and Genomics
- Clinical Genetics
- Role of Genetics in Personalized, Predictive and Preventive Medicine
- Advances in Therapeutics for Genetic Disorders

A team of 16 expert faculty from across the country has contributed to this course. Each topic has a video of around 30 minutes and an optional set of 5 multiple choice questions (MCQs) to ensure that the important take-home messages are understood. Presentations have been kept lucid and crisp so as to appeal to diverse audience with an interest in medical genetics and will prove extremely useful to medical practitioners across specialties as well as students.

The course faculty are as follows:

Dr Shubha Phadke, SGPGIMS, Lucknow
Dr Ratna Puri, SGRH, New Delhi
Dr Girisha KM, KMC, Manipal
Dr Sankar VH, SAT Hospital, Trivandrum
Dr Prajnya Ranganath, NIMS, Hyderabad
Dr Meenal Agarwal,KEM, Pune
Dr Koumudi Godbole, DMHRC, Pune
Dr Dhanyalakshmi N, KMC, Manipal
Dr Madhulika Kabra, AIIMS, New Delhi
Dr Neerja Gupta, AIIMS, New Delhi
Dr Ashwin Dalal, CDFD, Hyderabad
Dr Kausik Mandal, SGPGIMS, Lucknow
Dr Shagun Aggarwal, NIMS, Hyderabad
Dr Anju Shukla, KMC, Manipal
Dr Chaitanya Datar, SMGTEF, Pune
Dr Amita Moirangthem, SGPGIMS, Lucknow

SIAMG is pleased to offer GeneTOP FREE OF COST.

For more details and registration, please visit: http://www.iamg.in/geneotp.html

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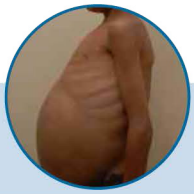

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