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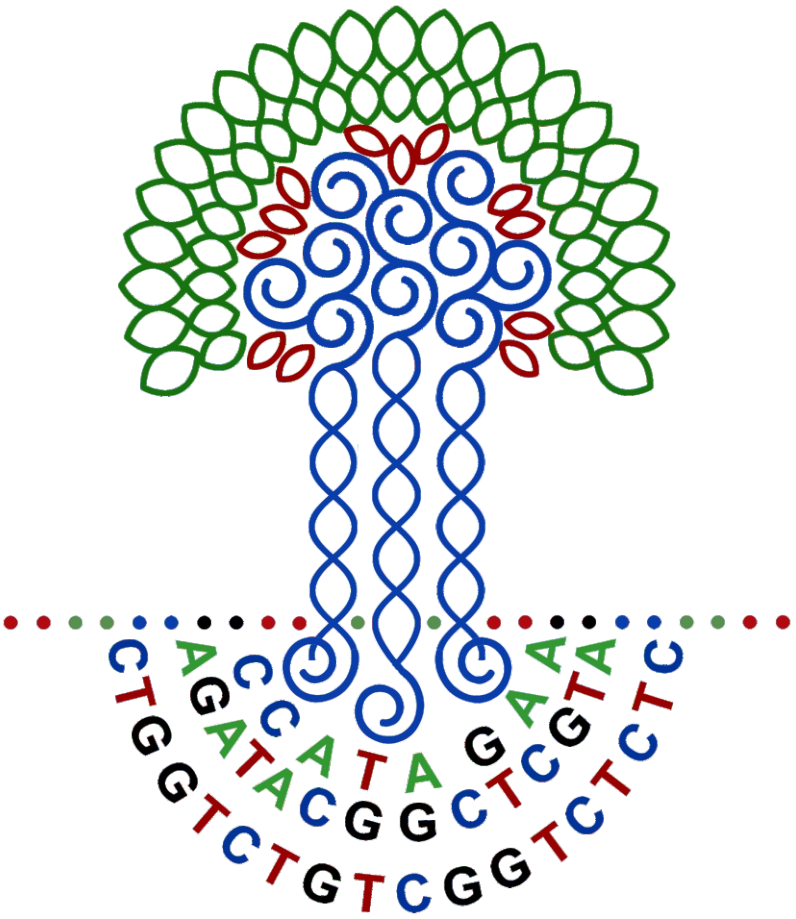

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PhotoQuiz 55

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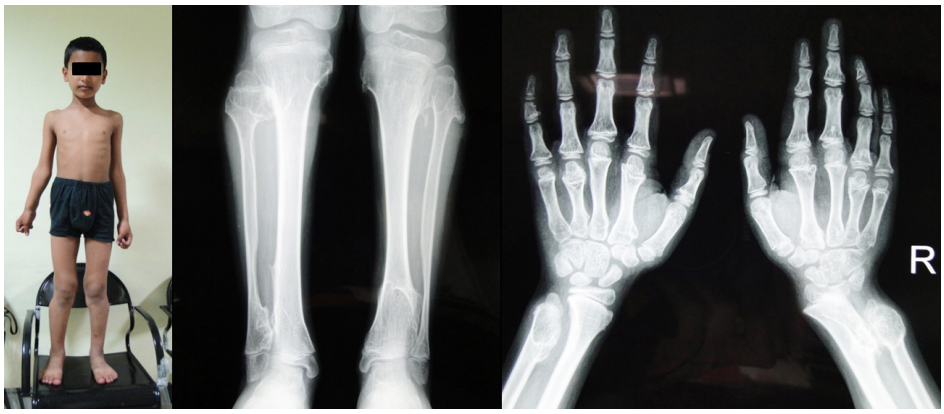
This 12-year-old male child, of normal height and intellect, was referred for evaluation of painless hard swellings on the limbs, especially near the joints. His skeletal radiographs are provided. Identify the condition.

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



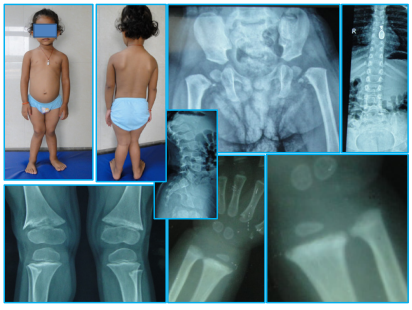
Answer to PhotoQuiz 54

Schmid-type metaphyseal chondrodysplasia (OMIM #156500)

Schmid-type metaphyseal chondrodysplasia (SMCD) is an autosomal dominant skeletal dysplasia, characterized by short stature that usually develops by around two years of age, short limbs, genu varum deformity, and a waddling gait. The radiographic features include metaphyseal changes at the ends of the long bones including splaying, flaring, and cupping; shortening of the tubular bones; and anterior cuppingand splaying of the ribs. Platyspondyly and vertebral end-plate irregularities are less commonly seen with SCMD. It is caused by heterozygous variants in the COL10A1 gene (OMIM*120110).

Correct responses were sent by:

1. Dr Aradhana Dwivedi, Army Hospital Research & Referral, New Delhi
2. Dr Mallikarjun R Patil, Bangalore
3. Dr Vinu N, Centre for Human Genetics, Bangalore



Completing the Human Genome Project: Filling in the gaps

Editorial

The Human Genome Project was declared to have been completed in 2003. Since then, we geneticists are using the data on a regular basis for genetic diagnosis. High throughput technology has made the diagnosis of monogenic disorders very easy, and the scope of exome sequencing and genome sequencing is becoming broader andmore universal. Now, the challenge is the roughly fifty percent of cases where exome sequencing and even genome sequencing do not provide the answers. The important reasons are causative variants in the region not covered and the sequence variants of types which cannot be detected by current analyzing techniques. As the technology for sequencing improves, the patient sequencing data and analysis pipelines are giving better results. Better reference genome and annotation of each nucleotide in the human genome needs more work.

Though the Human Genome Project was declared complete, about 10% of the genome was not sequenced. This includes telomeric regions, pericentromeric regions and centromeres. The work of filling the gaps of the genome is going on. The GenExpress in this issue talks about the 'Telomere to Telomere' consortium and completion of X chromosome sequencing. The long-read sequencing technologies are making this possible. The other aspect is representation of all populations in the reference genome so that the variants in normal populations are documented. Only 0.1% of our genome varies from individual to individual, but even 0.1% of 3 billion nucleotides amounts to a lot. The current human reference genome does not have representation of many populations. The Human PanGenome Consortium aims at removing the racial and ethnic biases in the human reference genome.It is working towards thedevelopment of a next-generation genome reference representation that can capture all human genome variation and support research on the full diversity of populations. With a complete pangenome reference sequence along with information of structural variants and epigenetic marks, novel genetic mechanisms for diseases may get identified and improve the diagnostic yield. As these gaps in the genome sequence are getting filled, the Society forIndian Academy of Medical Genetics (SIAMG) continues to fill the gap in your knowledge as we gain some. Also, there as gaps in our knowledge, gaps in communication with patients, gaps with contacts with referring physician, etc. There is a lot of work for 2022.

Wish you all a happy and healthy, corona-free new year.

Dr. Shubha Phadke
1st January 2022

Clinical Vignette

Recurrent Non-immune Hydrops and Epiphyseal Stippling in Fetuses Affected with Infantile Sialic Acid Storage Disease

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Abstract

This is the report of a woman with two pregnancies, subsequently terminated, for fetuses presenting with non-immune hydrops, and infantogram showing extensive bone stippling. Clinical exome sequencing was carried out in the DNA banked from one of the affected fetuses. This identified a homozygous pathogenic variant; c.110_111delinsGGA (p.Ser37TrpfsTer41) in the *SLC17A5* gene,revealing the diagnosis of infantile sialic acid storage disease (ISSD).Stippled epiphyses have been previously reported in-utero as well as in post-delivery radiographs in ISSD. These are the first cases of stippled epiphyses in fetuses affected with ISSD reported from India.

Keywords: Non-immune fetal hydrops; Epiphyseal stippling; Infantile sialic acid storage disease

Introduction

Non-immune hydrops in a fetus is a severe condition which results in excessive accumulation of fluid within the fetal extravascular compartments and body cavities and is the end-stage of a wide variety of disorders. The exact prevalence is unknown and various causes have been implicated such as congenital heart disease, chromosomal disorders, infections, and monogenic disorders; in some cases, it is idiopathic. Next-generation sequencing technology has enabled us to diagnose inborn errors of metabolism antenatally in fetal hydrops cases in the modern era. The prognosis of non-immune hydrops fetalis is generally poor. We describe here a lady where the cause of fetal hydrops was identified to be infantile sialic acid storage disease (ISSD), based on which accurate genetic counselling could be provided and definitive prenatal diagnosis for the subsequent pregnancy could be offered.

Clinical details

A 24-years old woman with history of two previous spontaneous abortions presented to us in her third pregnancy. She was consanguineously married (fourth-degree consanguinity) and had no other antenatal risk factors. Her anomaly scan, done at18 weeks of gestation, was normal. A follow-up ultrasound scan done at 29 weeks gestation showed moderate fetal ascites, shortlong bones and mild cardiomegaly. Scan findings revealed short long bones with femur length of 39.8 mm (Z score: -3), along with unilateral club foot, possible syndactyly of lower limbs and a bell shaped thorax. Stippling of calcaneum was not detected in the antenatal scan at 29 weeks.

Overall, a guarded prognosis was explained to the couple, and they were counselled regarding genetic evaluation of the fetus. As the lady had two previous spontaneous abortions and the scan in the ongoing pregnancy was abnormal, showing fetal hydrops and other anomalies, the couple was counselled keeping in mind the possibility of chromosomal anomalies. Single gene disorders causing hydrops were also considered. Differential diagnoses included skeletal dysplasias such as achondrogenesis, thanatophoric dysplasia or Jeune asphyxiating thoracic dysplasia and storage disorders such as Gaucher disease, mucopolysaccharidosis, or mucolipidosis. The couple were explained that genetic testing would help in determining the recurrence risk and subsequent planning of pregnancy.

The woman underwent percutaneous umbilical cord blood sampling (PUBS). Due to financial constraints, initially only a karyotype was done. Fetal DNA banking was done so that further evaluation such as exome sequencing could be planned if the karyotype turned out to be normal. Following this the pregnancy was terminated at 29 weeks gestation. A still born baby girl was delivered and an infantogram done showed calcific stippling. The couple, however, did not consent for fetal autopsy.

The fetal karyotype was normal. The parents were counselled, and clinical exome sequencing was planned in the banked fetal DNA. Possibility of chondrodysplasia punctata, both rhizomelic and non-rhizomelic type (Conradi-Hunermann syndrome), and other peroxisomal disorders such

as Zellweger syndrome were considered based on the family history of consanguinity, the USG findings, examination of the expelled fetus and the infantogram. Genetic counselling was provided with possibility of monogenic autosomal recessive disorders and clinical exome sequencing in the banked DNA was carried out for diagnostic purposes. This revealed a novel homozygous pathogenic variant c.110_111delinsGGA (p.Ser37TrpfsTer41) in exon 2 *ofSLC17A5* (ENST00000355773.5), which is associated with infantile sialic acid storage disease (ISSD). This variant results in frameshift and premature truncation of the protein 41 amino acids downstream to codon 37. This variant has not been reported in population databases such as gnomAD and 1000 Genomes. The in-silico prediction tool MutationTaster2, predicted this variant to be damaging. The reference region is conserved across mammals. No other clinically significant variants were identified. The parents were counselled about the recurrence risk of 25% in every pregnancy. Prenatal diagnosis in the first trimester was offered for subsequent pregnancies. They were counselled about other reproductive options such asin vitro fertilization (IVF) with preimplantation genetic testing (PGT) or use of donor gamete. Extended carrier screeningfor the family was also suggested.

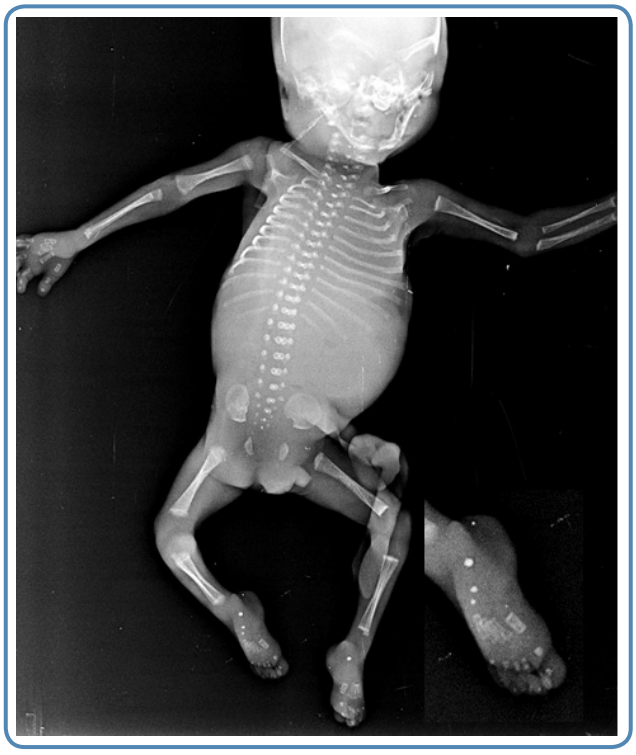

Figure 1 Infantogram showing stippling of hand bones and heels of the secondaffected fetus (calcaneal stippling highlighted in the inset)

In the subsequent pregnancy, the parents came in the first trimester seeking prenatal diagnosis. Targeted mutation analysis was done in the fetal DNA sample obtained by chorionic villus sampling. This showed an affected fetus due to the presence of the same variant in a homozygous state. The parents were counselled regarding the poor outcome and similar phenotypic manifestations of fetal hydrops; however, they decided to continue the pregnancy. Early anomaly scan, done at 16 weeks, revealed similar fetal phenotype of hydrops with long short bones, as before. In view of scan findings, the couple were offered termination of pregnancy.However, the couple opted for termination only at 20 weeks gestation, when the scan showed gross hydrops and repeat genetic counselling was done,where the poor prognosis was re-emphasized. Infantogram of the expelled fetus revealed epiphyseal stippling (**Figure 1**).

Discussion

We report here a novel homozygous pathogenic variant in the *SLC17A5* gene in two fetuses presenting as non-immune hydrops and short long bones. Infantograms of the terminated fetuses showed epiphyseal stippling. Biallelic pathogenic variants in the *SLC17A5* gene cause sialic acid storage disorders which can present as Salla disease (OMIM # 604369), which is mainly reported in the Finnish population, or as a more severe disease known as infantile sialic acid storage disease (OMIM# 269920) which is pan-ethnic. This is an autosomal recessive condition.

SLC17A5 gene codes for the product named sialin (Miyaji et al., 2008). The protein is a vesicular excitatory amino acid transporter (VEAT) which has two functions. In the synaptic vesicles of the central nervous system, sialin causes vesicular storage and subsequently exocytosis of aspartate and glutamate. Whereas in the lysosome, it acts as an H(+) coupled sialic acid exporter(Miyaji et al., 2008).

The founder variant p.Arg39Cys in homozygous state is associated with Salla disease which is characterized by very slowly progressive neurological deterioration. The same variant in compound heterozygous state with other pathogenic variants results in intermediate forms of ISSD. The other variant reported to cause the

intermediate type is homozygous p.Lys136Glu, while various other pathogenic variants cause the more severe ISSD phenotype. Allother variants reported till date lead tothe severe phenotype. Among the severe type-causing pathogenic variants, nonsense, missense, frameshift, splice-site and small deletions have been reported.

The infantograms of the terminated fetuses reported here showed calcific stippling; thishighlights the presence of stippled epiphyses with fetal ascites/hydrops as a prenatal and/or early neonatal presentation of severely affected cases of ISSD. This feature along with non-immune hydrops can be confused with other causes of skeletal dysplasia. Stippled epiphyses are seen in the infantogram commonly due to other genetic conditions involving peroxisomal biogenesis disorders such as rhizomelic chondrodyplasia punctata and Zellweger syndrome, or due to maternal factors such as maternal systemic lupus erythematosus (SLE),or warfarin embryopathy. The fetal, maternal, and teratogenic causes of epiphyseal stippling in the perinatal period, are listed in **Table 1** (Wainwright&Beighton, 2010; Alrukban & Chitayat, 2018).

Table 1 Summary of the fetal, maternal, and teratogenic causes of perinatal epiphyseal stippling

Etiology	Conditions
Fetal Factors	
Chromosome abnormalities	• Turner syndrome • Down syndrome • Trisomy 18, trisomy 9, trisomy 16
Peroxisomal disorders	• Infantile Refsum disease, • Neonatal adrenoleukodystrophy • Zellweger syndrome • Rhizomelic chondrodysplasia (RCDP1, 2, and 3)
Lysosomal storage disorders,	• Type II mucolipidosis • Type III mucopolysaccharidosis • GM1 gangliosidosis
Cholesterol synthesis defects	• Smith–Lemli–Opitz syndrome • Conradi–Hünermann syndrome • Greenberg dysplasia • Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD syndrome) • Lathosterolosis
Abnormal vitamin K metabolism	• ARSEgene-relatedX-linked recessive chondrodysplasia punctata
Teratogens	
Infections	• Rubella • Cytomegalovirus (CMV)
Drugs	• Warfarin
Maternal factors	
Severe malabsorption	
Vitamin K deficiency	
Maternal autoimmune diseases	• Systemic lupus erythematosus (SLE) • Mixed connective tissue disorder (MCTD) • Sjogren syndrome

Froissart and colleagues reported the clinical, morphological, and molecular aspects of the in-utero presentation of *SLC17A5*-associated ISSD (Froissart et al., 2005). They described the features of eight fetuses in-utero and four neonates, detailing the ultrasonography findings, autopsy findings and molecular testing of the targeted gene. Of the 12 prenatal and perinatal cases, stippled epiphyses were seen in two of the four neonatal cases and six of the eight prenatal cases with the severe ISSD type. Apart from ascites, other features noted in antenatal casesreported by the authors include hepatomegaly, ventriculomegaly, short limbs, short femur, and club feet. Placental hydrops was also found in some cases.

As electron microscopic findings show engorged lysosomes due to abnormal storage of sialic acid, ISSD is classified under the category of lysosomal storage disorders. There is similarity in clinical features namely hydrops, coarse face, and short bones, seen with other lysosomal storage disorders such as mucopolysaccharidosis and mucolipidosis. However, a case series and review of literature by Lemyre et al, mentioned that the features of dysostosis multiplex were mild and corneal clouding was absent(Lemyre et al., 1999).

There is no specific treatment for this condition. The infantile type has a shortened life span and Lemyre et al reported death in early infancy with a mean age of 13.1 months. (Lemyreet al., 1999). Genetic counselling remains an important aspect of management. Prenatal diagnosis remains the mainstay of management in couples with previously affected fetuses or children. This report highlights stippled epiphyses as an important feature of the in-utero presentation of infantile sialic acid storage disease.

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GeNeViSTA

An Overview of the Genetic Basis and Clinical Approach for Peroxisomal Disorders

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Abstract

Peroxisomal disorders are a rare heterogeneous group of inherited inborn errors of metabolism. Most of the peroxisomal disorders manifest in neonatal, infantile, and childhood periods. There are certain intricacies in diagnosing peroxisomal disorders due to overlapping phenotypes, complex biochemical tests, clinical and genetic heterogeneity. The diagnosis of milder and atypical phenotypes is even more complicated.This article describes the genetics of peroxisomal disorders and provides guidelines for the diagnosis of these disorders in routine clinical practice.

Keywords: Peroxisomal disorders; Clinical approach

Introduction

Peroxisomes are single membrane cytoplasmic organelles with diverse dynamic functions. The word 'peroxisome' was coined by Christian de Duve. Peroxisomes are involved in multiple metabolic functions in the body (**Figure1**). They do not have their own DNA like mitochondria. Membrane proteins, matrix proteins, and peroxins are peroxisomal proteins that are responsible for maintaining the structure of peroxisomes, for

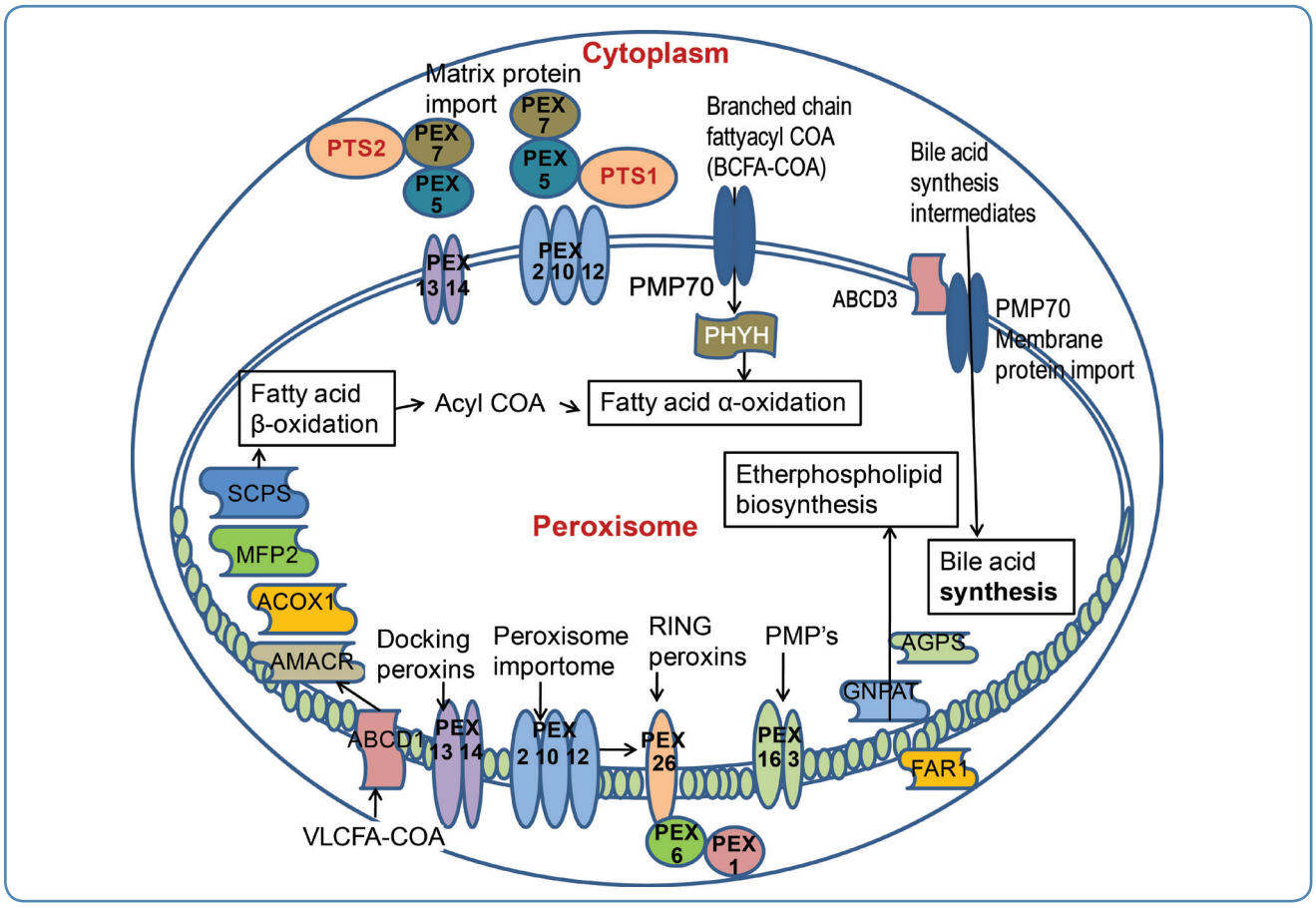

Figure 1 Functions of peroxisomes and the genes involved in peroxisomal disorders

peroxisomal division/assembly, and for performing various cellular biochemical functions.

The main functions of peroxisomes are α and β oxidation of fatty acids, synthesis of plasmalogen, cholesterol and bile acids, detoxification of glyoxylate and hydrogen peroxide, and catabolism of lysine.

Peroxisomal disorders are a broad spectrum of disorders with phenotypic and genotypic variability. Most of them present in the neonatal and pediatric age groups.They are classified into two subgroups. The first group is peroxisome biogenesis disorders (PBDs) which occur due to defective peroxisome assembly. The second group is peroxisomal dysfunction due to single peroxisome enzyme deficiencies.The most typical disorder under peroxisome biogenesis disorders is the 'classical' Zellweger syndrome, a severe form of the Zellweger spectrum disorders (ZSDs). The most common disorder of peroxisomal dysfunction is X-linked adrenoleukodystrophy (X-ALD).

Classification of peroxisomal disorders

The classification of peroxisomal disorders is outlined in **Tables 1 and 2** (Takashima et al., 2019; Wanders, 2017).

Genetics of peroxisomal disorders

Most of the peroxisomal disorders have an autosomal recessive pattern of inheritance, with few exceptions such as X-linked adrenoleukodystrophy. The phenotypic severity of the ZSDs is based on the type of pathogenic variants in PEX genes. Mutations in the PEX1 gene account for 60% and mutations in *PEX6* account for 10-15% of cases of ZSDs. As ZSDs are a rare group of disorders, the exact genotype and phenotype correlations have not been established but loss-of-function (LoF) variants like truncating variants have been found to lead to a more severe phenotype than missense variants. Biallelic pathogenic variants in the *PEX7* gene are known to cause severe rhizomelic chondrodysplasia punctata type 1, but some variants in *PEX7* can cause the less severe peroxisome biogenesis disorder 9B with absence of chondrodysplasia and rhizomelia, which includes the adult-onset Refsum disease phenotype of cataracts, retinitis pigmentosa, hearing loss, ataxia, neuropathy and ichthyosis, and the more recently described phenotype of cataract with neurodevelopmental disability (Masih et al., 2021).

Some of the peroxisomal disorders are now being identified to be autosomal dominant. *PEX6* is associated with autosomal recessive PBD 4A and

Table 1 Classification of peroxisomal biogenesis disorders

Disorder	Gene	Protein/function	Peroxisomes and their structure in IHC
i. Group A(Zellweger spectrum disorders)			
1. Severe phenotype	PEX1 PEX2 PEX 5 PEX 2,10,12, PEX 13,14 PEX 3,16,19 PEX 6,26	RING peroxins Peroxisome importome PTS1-linked signaling Peroxisome importome Docking peroxins Peroxisomal membrane proteins RING peroxins	Absent
2. Intermediate phenotype			Absent
3. Milder phenotype			Absent
ii. Group B			
1. Rhizomelic chondrodysplasia punctate type 1	*PEX7*	PTS2-linked signaling	Enlarged
2. Rhizomelic chondrodysplasia punctata type 5	*PEX5*	PTS1-linked signaling	NA

NA – Not available

Table 2 Disorders of peroxisome function (Single enzyme deficiency)

Disorder	Gene	Protein/function	Peroxisomes and their structure in IHC
i. Etherphospholipid biosynthesis			
1. Rhizomelic chondrodysplasia type2 (Dihydroxyacetonephosphate acyltransferase deficiency)	*GNPAT*	Plasmalogens synthesis	NA
2. Rhizomelic chondrodysplasia type 3 (Alkyldihydroxyacetone phosphate synthase deficiency)	*AGPS*		
3. Rhizomelic chondrodysplasia type 4 (Fatty acyl-CoA reductase 1 deficiency)	*FAR1*		
ii.Fatty acid β-oxidation			
1. X-linked adrenoleukodystrophy	*ABCD1*	VLCFA transporter	Normal
2. Acyl COA oxidase deficiency	*ACOX1*	Peroxisomal β-oxidation	Enlarged
3. D-Bifunctional protein deficiency	*HSD17B4*		Enlarged
4. Sterol carrier protein X deficiency	*SCP2*	Peroxisomal β-oxidation	NA
5. Alphamethylacyl COA racemase (AMACR) deficiency	*AMACR*		NA
iii.Fatty acid α-oxidation			
1.Refsum disease (Phytanoyl-CoA hydroxylase deficiency)	PHYH	Peroxisomal α-oxidation	NA
iv.Disorders of Glyoxylate cycle			
1.Hyperoxaluria type 1 (Alanine-glyoxylate aminotransferase deficiency)	*AGXT*	Peroxisomal glyoxylate cycle	Small
2.Glycolate oxidase deficiency	*HAO1*	Glyoxylate metabolism	NA
v. Bile acid synthesis			
1.Bile acid-CoA: amino acid N-acyltransferase deficiency	*BAAT*	Peroxisomal acyl-CoA acyltransferase	NA
2.Acyl-CoA oxidase 2 deficiency	*ACOX2*	Branched-chain acyl CoA oxidase	NA
3.PMP70 deficiency	*ABCD3*	Peroxisomal membrane protein	NA
vi. H2O2 Metabolism			
1.Acatalasemia (Catalase deficiency)	*CAT*	Antioxidant	Normal
vii. Lysine catabolism			
1.L-lysine oxidation		L-pipecolic acid degradation	NA

Abbreviations: IHC-Immunohistochemistry, NA-Not available

4B, but in a few patients with a heterozygous variant in the *PEX6* gene, allelic expression imbalance leading to an overrepresentation of a mutant allele and ZSD phenotype has been reported (Falkenberg et al., 2017). Likewise, biallelic pathogenic variants in the *FAR1* gene lead to the autosomal recessive peroxisomal fatty acyl-CoA reductase 1 disorder, which is characterized by severe psychomotor retardation during infancy followed by childhood spasticity, but a few patients with a heterozygous pathogenic variant in *FAR1* have been reported to have cataracts and spastic paraparesis.

Peroxisome biogenesis disorders also exhibit mosaicism in a few patients. In type 1 mosaicism, normal peroxisomal activity is revealed in fibroblasts with abnormal biochemical profiles. In type 2 mosaicism, with the same genotype,there is a difference in peroxisome morphology in different tissues.

Clinical features of peroxisomal disorders

1.Peroxisome biogenesis disorders (PBDs)

These are autosomal recessive genetic disorders with an incidence of approximately 1:30,000 to 1:50,000 newborns.The Zellweger spectrum of disorders and rhizomelic chondrodysplasia punctata (RCDP) spectrum are included under this category.

i. Zellweger spectrum of disorders (ZSDs)

The phenotype of ZSDs usually ranges from severe form to intermediate and milder forms with the typical presentation. Patients with atypical presentation lacking the classical signs and symptoms of ZSDs have also been described. Dysmorphic features in severe ZSDs include the high forehead, large anterior fontanelle, hypoplastic supraorbital ridges, epicanthal folds, corneal clouding, cataract, and broad nasal bridge (**Figure 2**). Prognosis is guarded with early neonatal or infantile death. Most of the intermediate forms of ZSDs have late childhood deaths. Clues to the diagnosis of Zellweger spectrum disorders in different age groups with the differential diagnosis are depicted in **Figure 3**. The neonatal phenotype of X-linked adrenoleukodystrophy due to contiguous deletion of the ABCD1 gene which mimics peroxisome biogenesis disorders has also been described.

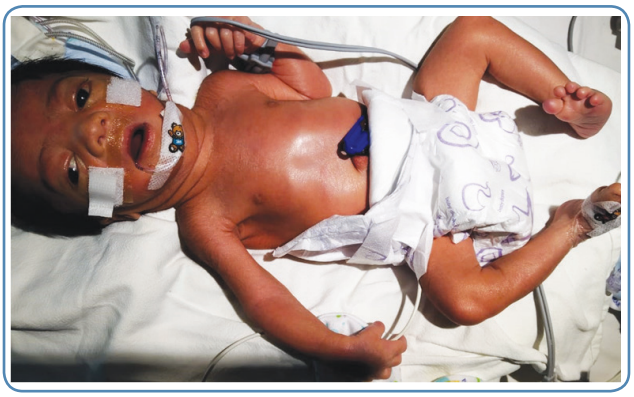

Figure 2 Dysmorphic features in a neonate with the severe Zellweger spectrum disorder

ii.Rhizomelic chondrodysplasia punctata spectrum (RCDP 1 and 5)

The phenotype of RCDP spectrum usually ranges from the severe form who present with midfacial hypoplasia, rhizomelic shortening at birth, to the intermediate form who present in childhood with joint contractures and spastic quadriparesis, and the milder forms who present with mild rhizomelic shortening. Severe phenotype can present either in the prenatal period or in the neonatal period.

2. Disorders of peroxisome function

i. Etherphospholipid biosynthesis disorders

RCDP types 2, 3, 4 are included under this category. The clinical features are similar to RCDP 1, 5 and they are differentiated by their genetic etiology. *FAR1*-related disorder is referred to as RCDP4 by some authors, but this disorder lacks the classical skeletal features of RCDP.

ii. Disorders with impaired fatty acid β-oxidation

X-linked adrenoleukodystrophy (X-ALD): X-ALD is an X-linked recessive disorder. It does not have any clinical features at birth. It can manifest with three different phenotypes. Different forms of X-ALD, their specific clinical features, and their age of presentation are depicted in **Figure 4**. Some female carriers can present with adrenomyeloneuropathy.

Alpha methylacyl-CoA racemase (AMACR) deficiency, acyl-CoA oxidase 1 (ACOX1) deficiency, D-bifunctional protein (DBP) deficiency, and sterol carrier protein X deficiency (SCPx) are the other disorders included under impaired fatty acid β-oxidation (Arora et al; 2020). SCPx deficiency has been described in one adult patient with

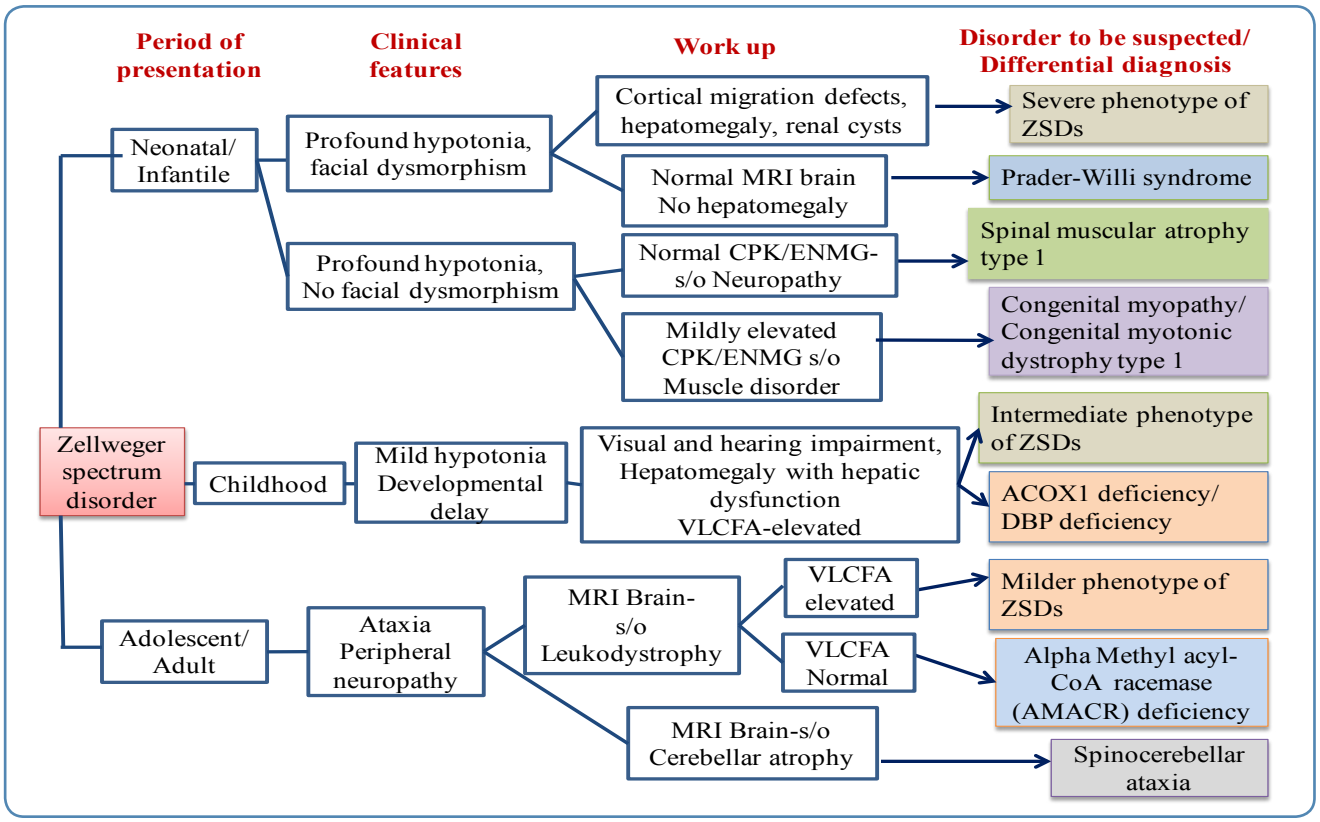

Figure 3 Clues to diagnosis of Zellweger spectrum disorders in different age groups with differential diagnosis

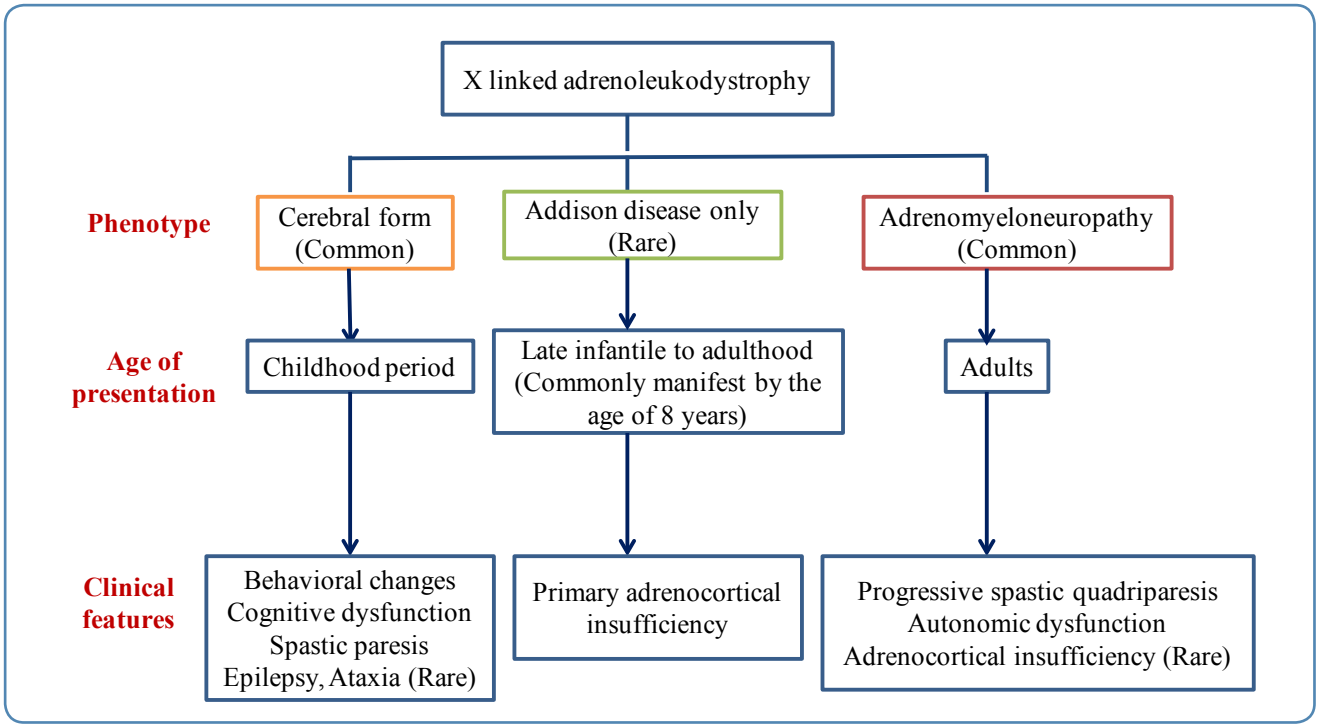

Figure 4 Different phenotypes, age of onset, and clinical features of X-linked adrenoleukodystrophy

dystonia, cerebellar signs, and motor neuropathy (Ferdinandusse et al., 2006).

iii. Disorders with impaired fatty acids α-oxidation

Refsum Disease (RD): RD is caused due to phytanoyl-CoA hydroxylase deficiency which is the first enzyme involved in the α-oxidation of fatty acids. Patients with RD usually present in late childhood. Clinical features of this disorder are represented in Figure-5. The entire spectrum of clinical manifestations is not seen in all cases.

iv. Disorders of the Glyoxylate cycle

Primary Hyperoxaluria type 1: Symptoms of this disorder manifest from infancy to adulthood but majority of them present in childhood or early adolescence. They present with recurrent nephrolithiasis due to deposition of calcium oxalate and nephrocalcinosis. Death in these cases is due to end-stage renal disease and renal failure.

v. Bile acid synthesis defects

Acyl-CoA oxidase 2 (ACOX2) deficiency, peroxisomal membrane protein 70 (ABCD3) deficiency, and bile acid-CoA: amino acid N-acyltransferase (BAAT) deficiency are included under this category. ACOX2 deficiency and ABCD3 deficiency present in childhood. Both these disorders have similar clinical features with predominant involvement of the liver (**Figure 5**). BAAT deficiency presents with itching and steatorrhea.

vi. H2O2 Metabolism

Acatalasemia/Hypocatalasemia: It is caused by either complete or partial loss of catalase activity in erythrocytes.This disorder is usually asymptomatic. In rare cases, it may be associated with oral ulcerations or gangrene, or diabetes mellitus.

The age of onset, clinical features, and features that should lead one to suspect the disorders of peroxisomal dysfunction are outlined in **Figure 5**.

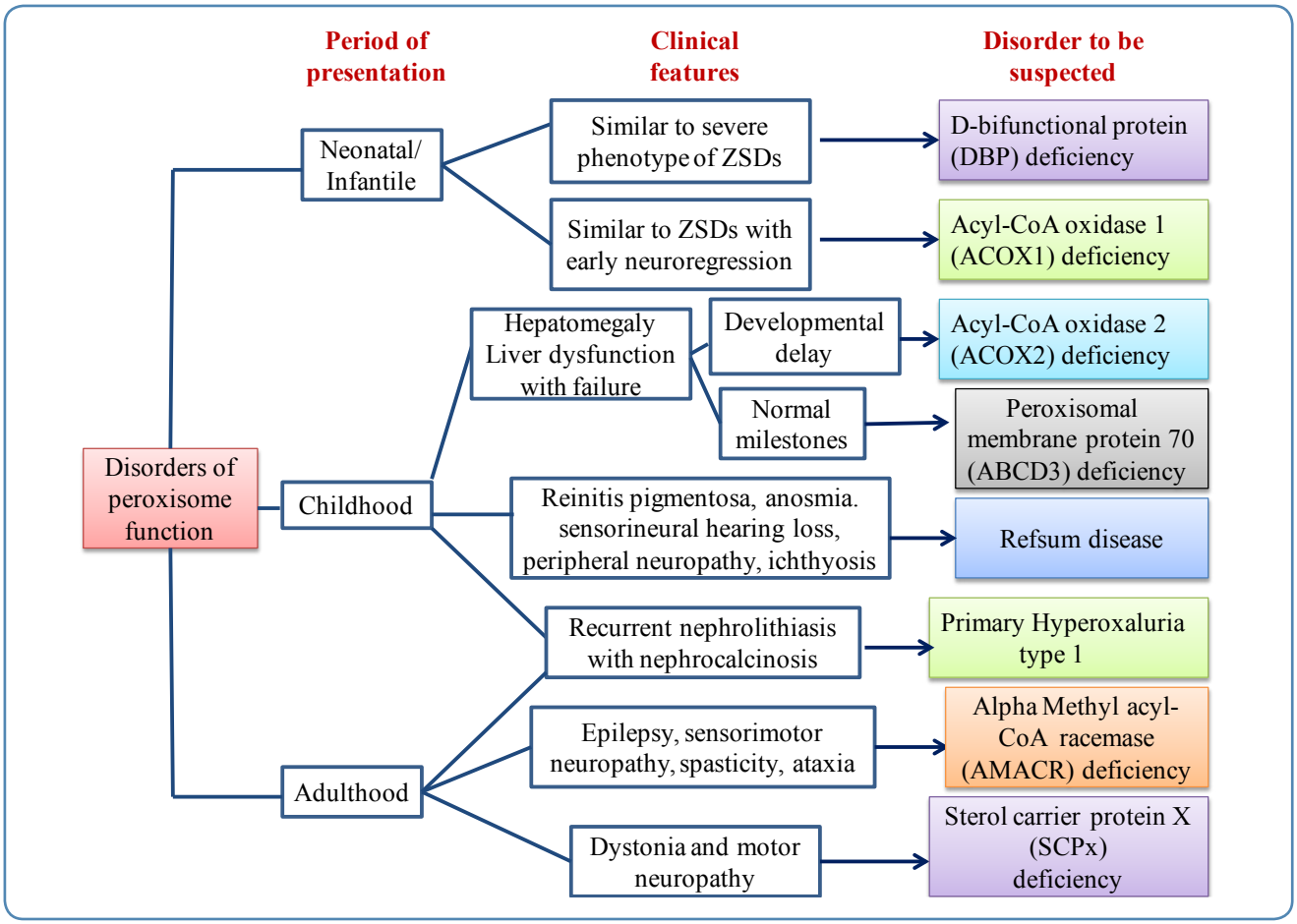

Figure 5 Flow chart showing clues to the diagnosis of disorders of peroxisomal function (single enzyme deficiency disorders)

Diagnosis of peroxisomal disorders

i. Biochemical workup

For most peroxisomal disorders, biochemical workup involves metabolite assay in plasma and/or red blood cells(RBCs). Very long-chain fatty acids (VLCFA), docosahexaenoic acid, phytanic acid, and plasmalogen are the biochemical parameters measured by gas chromatography/mass spectrometry (GCMS). VLCFAs are measured by analyzing the concentration of C26:0, the ratio of C24:0 to C22:0, and the ratio of C26:0 to C22:0. In ZSDs,VLCFA, phytanic acid, pristanic acid, docosahexaenoic acid, pipecolic acid, and bile acids are elevated in the plasma, and plasmalogens are decreased in the RBCs. An increase in phytanic acid with decreased pipecolic acid in plasma and decreased plasmalogen in RBC is suggestive of RCDP. In Refsum disease, phytanic acid levels are increased but plasmalogen and pipecolic acid levels are normal. In X-ALD, VLCFA is markedly elevated with normal levels of other biochemical substances (Wanders et al) 2018.

Table 3 shows the list of various biochemical substances measured in blood and their levels in different peroxisomal disorders.

Table 3 Biochemical workup for suspected peroxisomal disorders

	In plasma						
	Zellweger Spectrum Disorders			**RCDP**	**X-ALD**	**RD**	**Fatty acid B-oxidation**
	Severe	**Intermediate**	**Mild**				
VLCFA (C26:0 & C26:1 Ratios of C24, C22 & C26/C22)	Markedly increased	Markedly increased	Increased	Normal	Markedly increased	Normal	Normal except increase in DBP deficiency & ACOX1 deficiency
Phytanic Acid	Markedly increased	Markedly increased	Increased	Markedly increased	Normal	Markedly increased	Normal except increase in DBP deficiency
Pristanic acid	Normal to increased	Normal to increased	Normal to increased	Normal	Normal	Normal	Normal except increase in AMACR & DBP deficiency
Pipecolic acid	Markedly increased	Markedly increased	Increased	Markedly increased	Normal	Normal	Normal
Bile acids	Markedly increased	Markedly increased	Increased	Normal	Normal	Normal	Normal except increase in AMACR & DBP deficiency
	In RBC						
Plasmalogen	Markedly decreased	Markedly decreased	Decreased	Markedly decreased	Normal	Normal	Normal

Abbreviations: DBP-D-Bifunctional protein, RCDP-Rhizomelic chondrodysplasia punctata, ALD-Adrenoleukodystrophy, RD-Refsum disease, VLCFA-Very long-chain fatty acids, AMACR-Alphamethyl acyl COA racemase deficiency

X-linked adrenoleukodystrophy is included in neonatal screening programs in several countries (Turk et al., 2020). Recently changes in phospholipid metabolites are found to be reliable biomarkers to indicate neuroinflammation in mice models and X-ALD patients. Further studies need to be done in a large cohort of X-ALD patients to use these metabolites as early biomarkers for neuroinflammation (Kettwig et al., 2021).

In primary hyperoxaluria type 1, the diagnosis is made by the presence of high urinary oxalate excretion and for glycolate oxidase deficiency the diagnosis is by documenting high urinary glycolate levels.

ii. Radiological features

Skeletal abnormalities

Chondrodysplasia punctata at the knee and/or ankle joints and along the vertebrae in early childhood and rhizomelic shortening are noted in skeletal radiographs in cases with RCDP and Zellweger syndrome (**Figure 6**). In addition, vertebral cleftsare seen on the skeletal survey in RCDP.

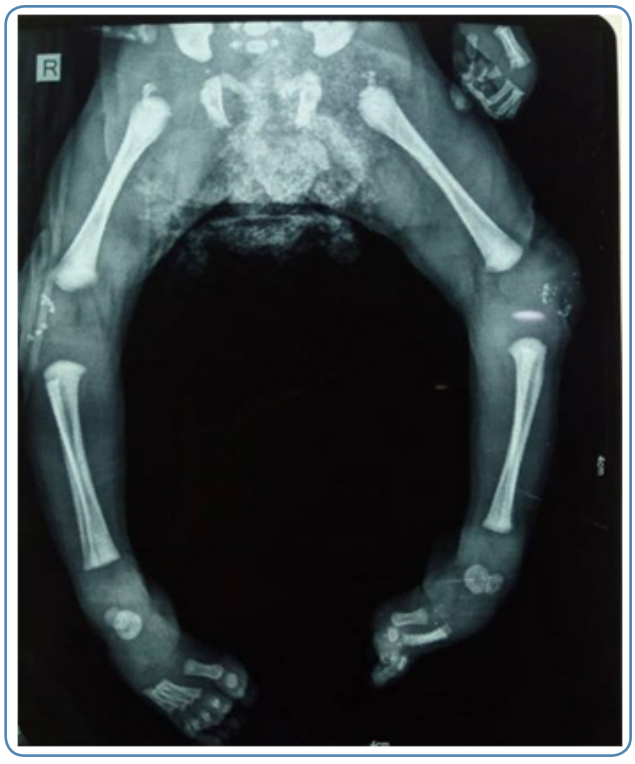

Figure 6 Skeletal radiograph showing chondrodysplasia punctata at the knee joint in a child with rhizomelic chondrodysplasia punctata

Neuroimaging findings

In peroxisomal disorders, specific findings in magnetic resonance imaging (MRI) of the brain are seen only in Zellweger syndrome (**Figure 7**) and X-ALD. In other peroxisomal disorders, MRI brain findings may provide clues to the diagnosis. MRI brain findings in peroxisomal disorders are listed in **Table 4**. Typical findings of the MRI brain may not be found in the initial stages of the disease in peroxisomal disorders as they evolve gradually during the disease course. In such a scenario biochemical workup and genetic evaluation would help in the diagnosis.

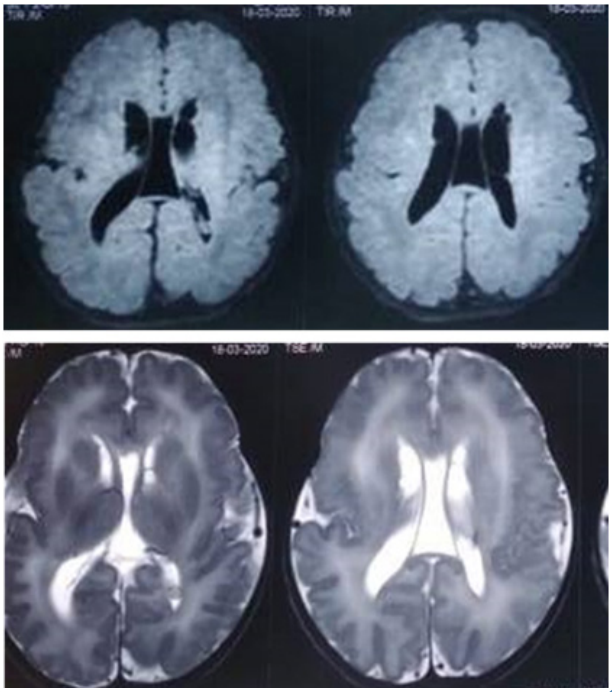

Figure 7 MRI brain findings in Zellweger syndrome
6A.T2 weighted MRI brain axial view showing germinolytic cysts
6B. T1 weighted MRI brain axial view showing diffuse polymicrogyria

Genetic evaluation

Peroxisomal disorders are rare inherited metabolic disorders. The diagnosis of a specific peroxisomal disorder can be made based on clinical features, biochemical workup, skeletal survey, MRI brain, and molecular genetic testing by whole/clinical-exome sequencing. Biochemical analysis is required to corroborate the genetic diagnosis in some cases especially in those with variants of uncertain significance.The genomics-first approach

Table 4 MRI brain findings in peroxisomal disorders

Peroxisomal disorder		Findings in MRI Brain
Zellweger Spectrum disorders (ZSDs)	Severe phenotype	Cortical migration abnormalities like perisylvian or diffuse polymicrogyria, germinolytic cysts (Figure 6) with or without myelination abnormality
	Intermediate and milder phenotype	Myelination abnormalities; demyelination initially starts in the cerebellum first and later on involves the entire cerebral region
Rhizomelic chondrodysplasia punctata (Severe type)		Ventriculomegaly, progressive cerebellar atrophy, delayed myelination of the supratentorial white matter, white matter signal abnormalities in the parieto-occipital region
Rhizomelic chondrodysplasia punctata (Milder type)		Normal
Cerebral type X-ALD		T2 weighted hyperintensities in parieto-occipital white matter; the frontal, parietal regions are involved rarely
Alpha Methylacyl-CoA racemase (AMACR) deficiency		Cerebral atrophy and T2-weighted hyperintensities are noted in the deep white matter of both hemispheres, thalami, midbrain, and pons.
Acyl CoA oxidase 1 deficiency and D-bifunctional protein deficiency		Cerebellar atrophy and periventricular white matter hyperintensities (Arora et al., 2020)
Sterol carrier protein X deficiency		Bilateral T2 weighted hyperintense signals in the thalamus and pons
Refsum disease		No specific MRI findings (Poll-The et al., 2012)

would be helpful in cases with milder and atypical phenotypes.

A diagnostic flowchart that can be used for peroxisomal disorders is given in **Figure 8**.

Management

Surveillance of most of the peroxisomal disorders is by regular monitoring of liver functions, renal and adrenal functions, and annual hearing and ophthalmologic evaluation. In addition, MRI brain is recommended in suspected cases of ZSDs, X-ALD, and also in ACOX1, AMACR, and DBP deficiency.

There is no complete cure available for peroxisomal disorders at present. Supportive therapies like adequate nutrition, physiotherapy, and occupational therapy are to be given. Symptomatic management includes antiepileptic therapy for seizures, and gastrostomy tube feeding for those with feeding difficulty.

Dietary restriction of phytanic acid helps to some extent in patients with Refsum disease. Pyridoxine supplementation has been tried in hyperoxaluria type 1 but has limited success. Good hydration, lithotripsy, and surgical intervention would be helpful to some extent in hyperoxaluria type 1 but there is a high chance of recurrence of renal stones. In cases with adrenocortical insufficiency, corticosteroid replacement therapy is recommended. In X-linked ALD, Lorenzo's oil has been tried but has limited success as it does not prevent the progression of neurological symptoms. If done in the early stages, allogeneic hematopoietic stem cell transplantation (HSCT) is shown to either prevent progression or reverse demyelination. Lenti-D gene therapy tried for patients in the early stages of cerebral type of X-ALD showed beneficial results in phase III clinical trial (Eichler et al., 2017). In 2018, Lenti-D™ was heralded as a breakthrough therapy by the United States Food and Drug Administration (US FDA) for treating the cerebral type of X-ALD, as it is found to

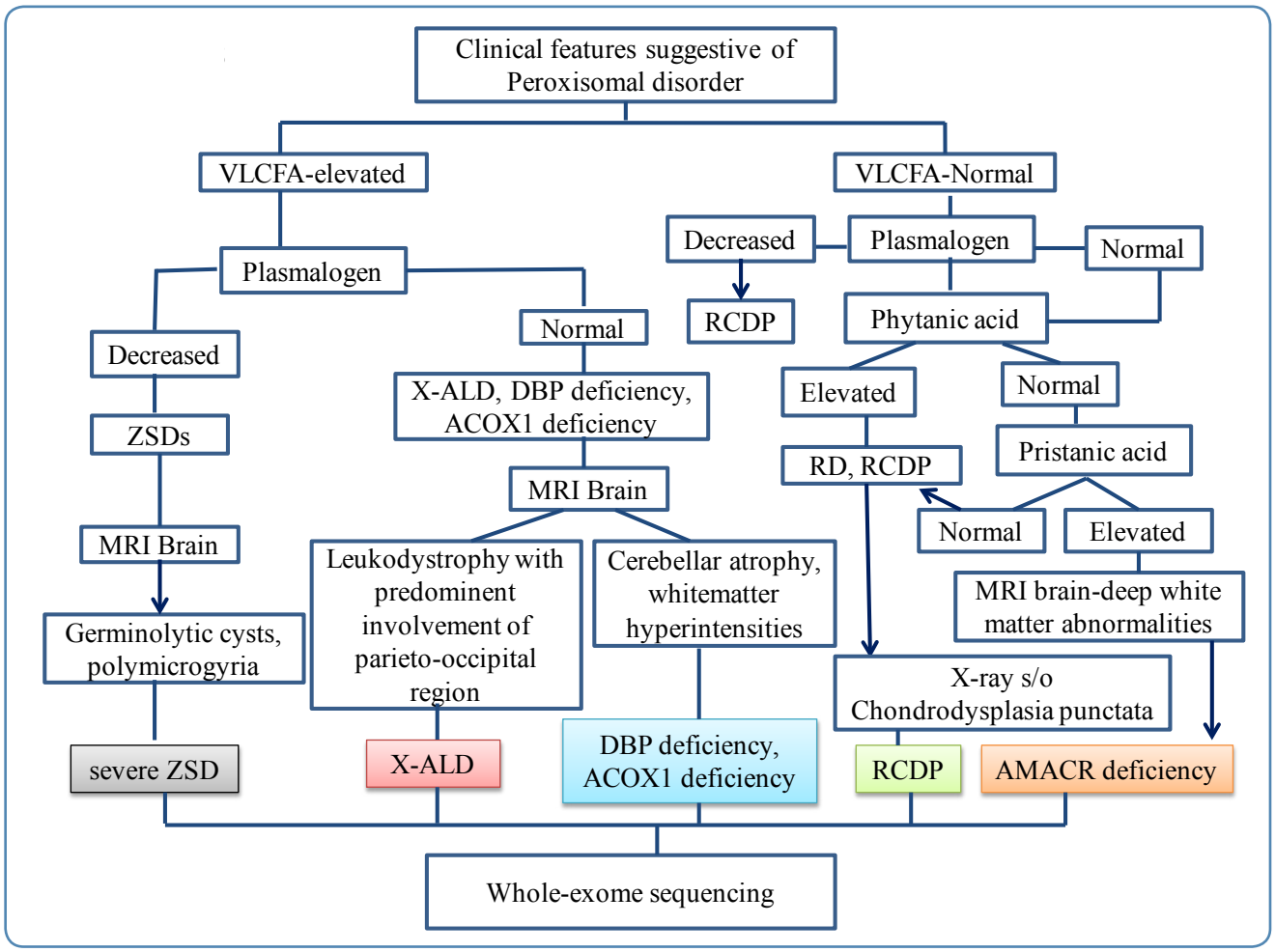

Figure 8 Diagnostic flow chart for peroxisomal disorders

provide significant improvement when compared to other available therapies.

Conclusion

Though most of the peroxisomal disorders can be recognized based on specific clinical clues and diagnostic workup, the milder and atypical phenotypes need a structured clinical and diagnostic approach to establish the exact diagnosis. There is no complete cure for these disorders except for supportive treatment and symptomatic management by a multidisciplinary team. Exact molecular diagnosis, therefore, helps in appropriate genetic counseling and definitive prenatal testing, and also helps the couples to make informed reproductive choices.

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GeNeXpress

A New and Exciting Era of Genomics: No Region is Beyond Reach

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Publication of initial drafts of the human genome by Celera Genomics and the International Human Genome Sequencing Consortium in 2001 revolutionized the field of genetics. Still, the current Genome Reference Consortium assembly (GRCh38.p13) contains several unsolvable gaps which include segmental duplications, ribosomal rRNA gene arrays, and satellite arrays. Inability to resolve these gaps was largely due to shortcomings of the existing short read sequencing technologies. Complete telomere-to-telomere reference genome assemblies are necessary to enhance our understanding of the chromosome function, human disease and genomic variation. With availability of low cost, high throughput long read sequencing technologies, the dream of creating complete and gapless human genome assemblies from diploid human genomes was undertaken by scientists from the Telomere-to-Telomereconsortium, an international collaboration of around 30 institutions from all over the world.

Telomere to telomere assembly of a complete human X chromosome (Miga et al., 2020)

To circumvent the complexity of assembling both haplotypes of a diploid genome, an effectively haploid CHM13hTERT cell line (complete hydatiform mole with 46,XX karyotype) which are uniformly homozygous for one set of alleles, was used for sequencing. The X chromosome was first selected for manual finishing and validation, owing to its high continuity in the initial assembly, distinctive and well characterized centromeric alpha satellite array, and disproportionate involvement in Mendelian disease. The high coverage, ultra-long-read nanopore sequencing of CHM13 genome was utilized along with complementary technologies for quality improvement and validation. The centromeric satellite DNA array of size 3.1Mb was reconstructed and 29 unresolved gaps in the current reference were fully resolved, including new sequences from the human pseudoautosomal region. The methylation patterns across complex tandem repeats and satellite arrays were also mapped with the help of ultra-long nanopore data. This manually finished X-chromosome assembly was estimated to be 99.9% accurate except across the largest repeats like DXZ1 satellite array (99.3% accuracy).

Segmental duplications and their variation in a complete human genome (Vollger et al., 2021)

Segmental duplications (SD), the most recent and highly identical sequences, play an important role in disease and evolution. Their length (frequently >100kbp), sequence identity, and extensive structural diversity among human haplotypes hampered the ability to characterize these regions at a genomic level. An analysis was performed in 266 human genomes using long read sequencing technologies. This study showed that 91% of the new T2T-CHM13 SD sequence (68.3Mbp) better represented the human copy number. It was also identified that SDs showed increased single-nucleotide variation diversity when compared to unique regions. Based on methylation signatures, transcription of duplicate genes and 182 novel protein-coding gene candidates were discovered. It was also found that 63% (35.11/55.7Mbp) of acrocentric SDs are distinct from rDNA and satellite sequences. These acrocentric SDs are 1.75-fold longer than other SDs, and are heteromorphic among human chromosomes. The T2T-CHM13 genome was also used to systematically reconstruct the evolution and structural haplotype diversity of biomedically relevant *(LPA,SMN)* and duplicated genes *(TBC1D3,SRGAP2C,ARHGAP11B)* important in the expansion of the human frontal cortex.

Few challenges faced were inability to fully sequence resolve all human haplotypes corresponding to specific duplicated regions using existing technology and accurate representation of these complex forms of human genetic variation, including its functional annotation.

The complete sequence of a human genome (Nurk et al., 2021)

The unfinished or erroneously placed 8% of the human genome primarily comprised the heterochromatin and many other complex regions. These functionally important regions were explored using the single haplotype, denovo strategy using CHM13 cell lines. This cell line essentially being almost homozygous was used to overcome the limitations of the previous GRC's mosaic BAC-based legacy. This group also shifted to a new strategy that leveraged the complementary aspects of PacBio HiFi (20kbp read length with median accuracy of 99.9%) and Oxford ultra-long read sequencing (more than 1 Mbp read length with error rate of 15%) to remove the 20 year old barrier that had hidden 8% of the human genome from sequence based analysis. Targeted validation was done for all these complex regions using various complementary technologies. This new T2T-CHM13 reference included gapless assemblies of all 22 autosomes plus X chromosome, corrected numerous errors of previous assemblies and introduced nearly 200 million bp of novel sequence containing 2,226 paralogous gene copies, 115 of which are predicted to be protein coding. The newly completed regions include all centromeric satellite arrays and the short arms of all five acrocentric chromosomes.

Epigenetic Patterns in a Complete Human Genome (Gershman et al., 2021)

Existing epigenetic studies omitted unassembled and unmappable genomic regions like centromeres, pericentromeres, acrocentric chromosome arms, subtelomeres, segmental duplications and tandem repeats. The new T2T-CHM13 assembly enabled the exploration of full epigenome and enrichment of epigenetic marks was performed using k-mer assisted mapping methods. Base level maps were generated using nanopore sequencing data. A distinctive dip in centromere methylation was observed and was consistent with active sites of kinetochore assembly. Allele specific, long range epigenetic patterns in complex macro-satellite arrays like those involved in X chromosome inactivation were also interrogated using long read sequencing. Single molecular measurements by long reads enabled the clustering of reads based on methylation status alone, which in turn helped in distinguishing epigenetically heterogeneous and homogenous areas. Exploring the epigenome in a larger and more diverse sample set remains a significant challenge owing to difficulty in optimal sequence alignment.

The future of the Human genome – Beginning of the end

To overcome the limitation of CHM13 cell line which lacks a Y chromosome, sequencing and assembly of a heterochromatic and a highly repetitive Y chromosome from HG002 cell line is underway. Telomere-to-telomere assembly of heterozygous diploid genomes is an arduous task that lies ahead. With continued improvement of sequencing and assembly technologies, this is not far from reach. As one genome cannot represent all humanity, the human pan-genome reference will be a key step forward for biomedical research and personalized medicine. With availability of long read sequencing technologies, a new project, the UCSC Human Pangenome Center is underway to create 350 human genomes broadly representative of humanity.

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GeneFocus

The Emergence of Clinical Genomics and Genomic Medicine Across India: The Role of the UK-India Genomic Medicine Alliance

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Abstract

Genomic applications in precision medicine and healthcare are now globally recognised with huge public and private investments. The United Kingdom (UK)-India Genomic Medicine Alliance **(UKIGMA)** offers a unique opportunity for clinicians and scientists from UK and India, to work together and develop comprehensive genomic medicine and healthcare programmes through a series of genomic education and training courses, raising awareness on genomic applications for health and supporting the necessary infrastructure build-up for the benefit of the vastly heterogeneous people of India and South Asia.

Introduction

Genetic and genomic applications in healthcare are now globally acknowledged and considered as one of the most powerful and pertinent developments in the history of medicine. The practice of medicine is now for the first time, truly personalized, precise and evidence-based. India has made significant progress in this field and is one of the established leaders in South Asia. Education and training in all formats are the key for successful implementation. The successful movement for genetics-led medical education steered by the ***Indo-UK Genetic Education Forum,*** has generated much needed enthusiasm and direction across India and neighbouring regions. This forum has set its vision for genomic education and training aimed at medical and healthcare practitioners.

There are several unknown and undiagnosed rare diseases prevalent across India that are awaiting genomics input for precision diagnosis, novel therapeutic inventions, and precision prevention. It is extremely important that India takes the lead and develops a coordinated and comprehensive genomic medicine and healthcare programme.The Genomic Medicine Foundation (UK), offers a unique opportunity for the UK and Indian clinicians and scientists to work together and develop the genomic medicine and healthcare programme through a series of genomic education and training courses, raising awareness on genomic applications for health and supporting the necessary infrastructure build up for the benefit of vastly heterogeneous peoples of India. This is appropriately named the **'UK-India Genomic Medicine Alliance'** referred to as **'UKIGMA'.**

Aim of the UKIGMA

"To organise and lead a professional group of like-minded clinicians and healthcare professionals for promoting and supporting the genomic applications and translations in medicine and healthcare in India and across the Indian subcontinent"

Objectives of the UKIGMA

- Identify and enrol organisations andinstitutions engaged in scientific and applied research in genomics relevant to medicine and healthcare
- Encourage collaboration with individual genetic/ genomic clinicians andscientists, and other professionals in anthropology, population genetics, bioethics, social sciences and bio-economics
- Develop a programme for training and skills development through series of structured courses, workshops, and webinars in the key areas of applied and translational genomic medicine
- Plan and carry out specific audit on the outcomes of investments in institutions and laboratories as part of the current strategy for capital and infrastructure scientific developments for genomic medicine and healthcare
- Develop and steer through individual or group research projects related to utilization and the delivery of genomics-led medical and healthcare, specifically in laboratory genomics, functional

genomics, metabolomics, and computational genomics.
- Encourage dedicated genomics-led research programme for new drug discovery and development through clinical trials in specific genetically distinct ethnic population groups
- Identify disease-associated founder genome variants in different population groups for developing community based genomic healthcare

Some of the education driven activities are already included in the current ***Indo-UK Genetic Education Forum*** that continues within the objectives of UKIGMA. Since 2010, many academic institutions and hospitals across India and Sri Lanka have participated in this programme. The forum continues and would remain an integral part of the UKIGMA that plans to focus on a number of areas for working together and develop clinical, educational and applied research projects through mutual collaboration **(Table 1)**.

Professional and Scientific links

The alliance plans to work closely with related international organisations, specifically the Global Genomic Medicine Collaboration (G2MC) and Genomic Alliance for Global Health (GA4GH). The alliance expects to establish close working links with the Indian Government's genomic medicine initiatives led by the CSIR Institute of Genomics and Integrative Biology (IGIB), Department of Biotechnology (DBT) and the Indian Council of Medical Research (ICMR). It is anticipated that this major joint activity will have active input by members of the Indian Society of Human Genetics (ISHG) and the Society forIndian Academy of Medical Genetics (SIAMG). Some of the Indian genetic and genomic scientists are internationally renowned experts in Indian population genetics and genomic variation. The alliance welcomes genetic and genomic organisations, units, institutions, academic units, and laboratories to join and strengthen India's regional genomic leadership. It could be in the form of an informal 'expression of interest'or through a formal *'Memorandum of Understanding'* **(Figure 1)**.

Table 1 Selected work streams of the UK India Genomic Medicine Alliance

1. Genetic and Genomic Education
2. Birth defects (congenital anomalies)
3. Rare genetic diseases including inherited metabolic diseases
4. Cancer genetics and genomics
5. Cardiovascular genetics and genomics
6. Neurological and psychiatric genetics and genomics
7. Genetic and genomic eye diseases
8. Genetic and genomic kidney diseases
9. Infectious diseases (tuberculosis, malaria, dengue, human immunodeficiency virus (HIV) infection, COVID-19, and others)
10. Adult metabolic diseases (obesity, hyperlipidemia, diabetes mellitus)
11. Genome laboratory technologies (chromosomal microarray analysis; next-generation sequencing; whole-exome/genome sequencing; bioinformatics)
12. Ethical, legal and social issues (ELSI) in genomic medicine and healthcare

UK INDIA GENOMIC MEDICINE ALLIANCE

UK INDIA GENOMIC MEDICINE ALLIANCE "To organise and lead a professional group of genetic and genomic scientists, clinicians and healthcare professionals for promoting and supporting the genomic applications and translations in medicine and healthcare in India and across the Indian subcontinent"

Figure 1 Join UKIGMA.

Table 2 Institutes and organizations associated with UKIGMA'

Department of Cardiovascular Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh.
Department of Cardiology, All India Institute of Medical Sciences, New Delhi, Delhi.
The Centre for Precision Medicine, King George's Medical University, Lucknow, Uttar Pradesh.
Department of Biochemistry and Medical Genetics, JSS Higher Academy of Education and Research, Mysore, Karnataka.
Department of Clinical Genetics and Cardiology, Christian Medical College, Vellore, Tamil Nadu.
Department of Human Genetics, The University of Colombo, Sri Lanka.
The alliance is guided and supervised by an independent International Advisory Board. Other interested genetic and genomic clinicians, specialist genetic and genomic units and governmental and non-governmental organizations/ institutions are encouraged to join the alliance. For all enquiries please contact- d.kumar@qmul.ac.uk md@genomicmedicine.org genomicmedicineuk@gmail.com

GeneArt

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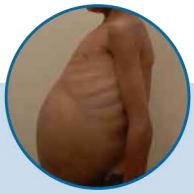

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- History of recurrent hernia repair in young age

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