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GeNeEvent - Fourth International Conference on Birth Defects (ICBD) & Fifth Annual National Conference of the Society for Indian Academy of Medical Genetics (SIAMGCON 2018)

The fourth International Conference on Birth Defects and Fifth Annual National Conference of the Society for Indian Academy of Medical Genetics was held in Christian Medical College, Vellore from 13th to 15th December, 2018. It was organized by CMC, Vellore and the Indo-UK Genetic Education Forum, under the aegis of SIAMG. The conference was followed by post-conference workshops on cancer genetics, cardiovascular genetics and genetic counselling and a CME on rare diseases. A number of distinguished international and Indian faculty attended the conference and shared their experience and expertise. The academic sessions included deliberations on various aspects related to the diagnosis and management of birth defects. The highlights of the meeting included the Dr SS Agarwal Oration by Dr Dhavendra Kumar from Cardiff University, UK; the Dr IC Verma Outstanding Researcher Award lecture by Dr Radha Rama Devi, Clinical Geneticist and Metabolic Disorders specialist from Hyderabad; and presentation of the Dr SS Agarwal Young Scientist Award to Dr Anju Shukla from Kasturba Medical College, Manipal, for identification of a novel causative gene *AIMP2* for neurodevelopmental disorder. There were a number of interesting free papers as well as posters presented by enthusiastic, budding medical geneticists. The conference and workshops were appreciated by all the attendees and SIAMG was lauded for its ongoing contributions towards the field of Medical Genetics in India.

Miles to go!

Editorial

As the year 2019 dawns, I take this opportunity to reflect on the evolvement of our society, the Indian Academy of Medical Genetics, which enters the eighth year and our quarterly publication, Genetic Clinics which completes eleven years.

Starting with small steps, Genetic Clinics has made its presence felt among the professionals. We see several readers eagerly waiting and responding to the most popular section PhotoQuiz. The editorial team believes most of the contents are educative to the vast majority of readers. The team is now working towards getting this publication indexed in databases in the year 2019.

Our society looks more vibrant now recovering from initial shaky, toddling steps. The success of its fifth national conference held last month at the Christian Medical College, Vellore corroborates the same. The galaxy of medical scientists and enthusiastic delegates affirms the imminent success for genomics in India. The society and editorial board congratulates Dr Sumita Danda and her team for the massive efforts (read GeneEvent in this issue) and wish all the best for the next meeting of the society at Hyderabad, to be led by Dr Prajnya Ranganath and Dr Ashwin Dalal.

The beginning of the new year is also a time to deliberate on what lies ahead. Though there is much to be done for genetics health care and research in India, we seem to have made a good start. To begin with, the society has come up with a position statement to voice against discrimination based on genomic information of an individual (see the position statement in this issue). This is just a drop in the ocean of the task that calls for more active participation from members and professionals, specifically in the area of clinical care, diagnostic facilities and genetic counselling. With immense resources and technological advances within our country, we just need to gear for a fast track, yet efficient handling of genomic healthcare.

Wish you all a very happy 2019.

Dr. Girisha KM
Assistant Editor, Genetic Clinics
1st January, 2019

Felicitation function organized for Prof. IC Verma at New Delhi

23rd December 2018

We salute your vision, up to date knowledge, infectious enthusiasm, communication, writing and editing skills and the spirit to go on! Your sense of humour, your simplicity, kind and child like heart are adorable. Your contributions in the field of Medical Genetics are outstanding which sowed the seeds of this specialty in India which is now blooming and flourishing. We all love you Sir!

In this special issue of Genetic Clinics, we are publishing five selected abstracts from the ones that were submitted for the 4th International Conference on Birth Defects (ICBD) and the 5th Annual National Conference of the Society for Indian Academy of Medical Genetics (SIAMCON 2018), held in Christian Medical College, Vellore, Tamil Nadu, on 13th – 15th December 2018. Of these, 2 won the prizes for the best oral paper presentation (first and second), 2 for the best poster presentation (first and second) and 1 was awarded a special prize.

ABSTRACT 01

I. Paper awarded the first prize for oral presentation:

Mitochondriopathies: Further delineation of clinical, radiological and genotypic spectrum

Ms. Parneet Kaur[1], Dr Malavika Hebbar[1], Dr A Shrikiran[2], Dr Ramesh Bhat Y[2], Dr Leslie Edward S Lewis[2], Dr Sheela Nampoothiri[3], Dr SJ Patil[4], Dr Suvasini Sharma[5], Dr KC Rakshith[6], Dr Nutan Kamath[7], Dr Ali Kumble[8], Dr Rajesh Shetty[9], Dr Katta M Girisha[1], Dr Anju Shukla[1]

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Aim: To define clinical, radiological and genotypic spectrum of mitochondriopathies.

Objectives:

1. Clinical, radiological and molecular characterization of mitochondriopathies in the Indian population
2. To identify novel phenotypes of mitochondriopathies and their underlying genetic mechanism

Methods: This case series is a part of a larger cohort of individuals with neurodevelopmental disorders. Clinical and radiological evaluation was performed for all families by a medical geneticist. This was followed by exome sequencing for index patients in families without definite clinical diagnosis and Sanger sequencing in families with definite clinical diagnosis. Validation of the identified pathogenic variant and bi-allelic segregation analysis was performed by Sanger sequencing.

Results: In the above-mentioned cohort eighteen families were diagnosed with mitochondriopathies. Six truncating and nine missense variants were identified in nuclear genes *NDUFAF6, NDUFV2, NDUFV1, SURF1, SDHB, MGME1, TYMP, PNPLA8, AUH, ACO2, CLPP,* and *GCDH*. Ten of these variants are novel. Among these families, disorders of the respiratory chain complexes (n=12), disorders of mtDNA maintenance (n=3), and disorders of phospholipid metabolism (n=1) were noted. Additionally, two novel disorders of the respiratory chain complexes were identified along with the causative genes, *ISCA1* and *NAXD*. Final diagnosis in these families with underlying genetic variants is given in table 1.

Discussion and Conclusion: Mitochondriopathies are a group of clinically and radiologically heterogenous conditions and have a complex underlying pathophysiology involving genetic variants in either the nuclear or mitochondrial genome. This implies that the inheritance patterns observed with these disorders are diverse too, including Mendelian and mitochondrial inheritance, the former being more commonly observed. We report 18 families with mitochondriopathies (Table 1) and their clinical, radiological and genotypic spectrum. Developmental delay, neuroregression, seizures, cardiac and eye abnormalities were noted to be common clinical features. Characteristic radiological findings were noted in majority of the families. Application of exome sequencing in this heterogenous cohort helped in identification of molecular cause in known mitochondriopathies and elucidation of novel phenotypes.

ABSTRACT 02

II. Paper awarded the second prize for oral presentation:

Genetic and Phenotypic Heterogeneity in Waardenburg Syndrome

Mr. Somashekar PH[1], Dr Sheela Nampoothiri[2], Dr Kalpana Gowrishankar[3], Dr Radha Rama Devi[4], Dr Neerja Gupta[5], Dr Dhanya Lakshmi Narayanan[6], Dr Anupriya Kaur[7], Dr Shruti Bajaj[8], Dr Sujatha Jagadeesh[9], Dr Leslie Lewis[10], Dr S Shailaja[11], Dr Girisha KM[1], Dr Anju Shukla[1]

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[11]*Department of Ophthalmology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India.*

Aim and Objective: Analysis of phenotypic and genetic diversity in Waardenburg syndrome (WS).

Materials and Methods: We investigated a cohort of 15 families (17 subjects). Fourteen of these families were clinically diagnosed with WS and one family with isolated non-syndromic hearing loss (NSHL). Genetics testing was done by Sanger sequencing or Whole Exome Sequencing (WES).

Results: We identified thirteen single nucleotide variants (SNV) and one copy number variation (CNV) in genes known to cause WS. Intra familial phenotypic variability and non-penetrance were observed in families diagnosed with WS1, WS2 and WS4 with pathogenic variants in *PAX3*, *MITF* and *EDNRB* respectively. We observed gonosomal mosaicism for a variant, c.256A>T in *PAX3* in an asymptomatic father of two affected siblings. Biallelic novel missense variant, c.1021C>G in *MITF* was identified in a patient with WS2. A variant, c.673G>A in *EDNRB* in homozygous state was identified in a patient diagnosed as WS2. Two pathogenic variants, c.166C>T in PAX3 and c.1047delC in *EDNRB* in heterozygous state were identified in subject diagnosed as WS1. Extended exome analysis for CNVs revealed 0.17 Mb heterozygous deletion encompassing *SOX10* in a patient diagnosed with WS 4. A homozygous known stop-gain variant, c.71G>A in *GJB2*, known to cause Deafness, autosomal recessive 1A was identified in a subject diagnosed as WS1. A novel stop-gain variant, c.1608C>G in *ADGRV1* and a known missense variant, c.575C>A in *TYR* known to cause Usher syndrome 2C and albinism respectively were identified in a subject diagnosed as WS2.

Discussion and Conclusion: Our cohort demonstrates intra and inter familial phenotypic variability and non-penetrance in families with WS. We report gonosomal mosaicism in WS1 and biallelic variants in *MITF* and *EDNRB* causing WS2. Blended phenotype of non-syndromic hearing loss and albinism mimicked WS. A phenocopy of WS1 was observed in a subject with a reported pathogenic variant in GJB2, known to cause isolated NSHL. These novel and infrequently reported observations exemplify the genetic heterogeneity and phenotypic diversity of WS.

(Funding: Science and Engineering Research Board, Government of India, India (YSS/2015/002009)).

ABSTRACT 03

III. Paper awarded the first prize for poster presentation:

Genetic analysis of clinically diagnosed Neurodegeneration with brain iron accumulation (NBIA cases) - Identification of common and rare subtypes

Rekha A[1], Sangeetha Yoganathan[2], Karthik Muthusamy[2], Sudhakar SV[3], Maya Thomas[2], Sumita Danda[1]

[1]*Departments of Medical Genetics,* [2]*Neurological Sciences,* [3]*Radiodiagnosis, Christian Medical College Vellore.*

Introduction: Neurodegeneration with brain iron accumulation is a heterogenous group of disorders characterised by the accumulation of iron in the basal ganglia that results in dystonia, spasticity, intellectual and motor decline, neuropsychiatric disabilities, and optic atrophy or retinal degeneration. Current diagnosis is facilitated by Brain MRI findings of "eye of tiger" sign in the typical form of NBIA. Genetic studies helps in confirming the diagnosis, delineating the subtype and genetic counselling. In India data on genetically de[FB01?]ned NBIA cases are limited and underdiagnosed. Hence we aim to identify the spectrum of pathogenic variants in patients diagnosed with NBIA.

Patients and methods: Nineteen patients with clinically diagnosed NBIA (2014-2018) were included in this analysis. These patients were referred from the department of Neurology and presented with any one or more of clinical features such as regression in milestones, dystonia, deterioration of vision and hearing, and spastic quadriparesis. Neuroimaging revealed iron deposition in the basal ganglia con[FB01?]rming NBIA. We have performed NGS based screening in 5 patients and targeted single gene analysis in 14 patients to identify the genetic variations causing NBIA.

Results: The mean age of patients was 8.4±4.4yrs and male to female ratio was 5:4.5. We have identified homozygous/compound heterozygous variants in 16 patients in which 10 were classified as novel variants. One patient was identified to have heterozygous variant and another patient was found to be negative for any mutations. Interestingly, one patient who was initially suspected to be NBIA based on MRI brain was found to be compound heterozygous for variants in *GLB1* gene confirming GM1 gangliosidosis on Clinical exome sequencing.

Molecular analysis helped us to stratify NBIA cases into 5 different subtypes. Seven patients were categorised into PLA2G6-Associated Neurodegeneration (PLAN) confirmed by genetic mutations. Six patients were subtyped into (PKAN) Pantothenate Kinase-Associated Neurodegeneration due to *PANK2* gene mutation. One patient was identified to have a rare form of FA2H; Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN) and the other patient with C19ORF12; Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN) mutation. One patient was genetically proven rare case of BPAN with *WDR45* gene mutation (Figure 1).

Conclusion: In conclusion, the proportion of patients with PLAN subtype was higher than reported in literature. Mutations in *PLA2G6* gene in exons 16 & 7 in four patients indicates that those exons can serve as hotspots for genetic testing. The hot spots in *PANK2* gene were found to be exons 1 and 2. Establishing molecular analysis (*PLAN* and *PKAN* genes) assisted us to genetically confirm the diagnosis of NBIA in 68% of cases and we could offer prenatal diagnosis for two families. The advancement in Next generation sequencing and Clinical exome analysis furnished better understanding of genotype-phenotype correlation including differential diagnosis of NBIA as GM1 gangliosidosis.

ABSTRACT 04

IV. Paper awarded the second prize for poster presentation:

Spondyloepiphyseal dysplasia congenita caused by biallelic c.3190C>T in *COL2A1*

Ms. Eram Fatima Amiri[1], Dr Gandham Bhavani[1], Dr Amita Moirangthem[2], Dr Nishimura G[3], Dr Mortier G[4], Dr Anju Shukla[1], Dr Katta M Girisha[1]

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[2]*Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Rd, Lucknow, India,*
[3]*Center for Intractable Diseases, Saitama Medical University Hospital, Saitama, Japan,*
[4]*Center of Medical Genetics, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium*

Aim and Objective: The aim of the study was to identify the genetic cause in a family with clinical features of spondyloepiphyseal dysplasia.

Patients/ Material and methods: We ascertained a consanguineous family with two affected siblings, a 7 years old male (proband 1) and 10 years old female (affected sibling) who presented with gait abnormalities. In proband 1 clinical features of exaggerated lumbar lordosis, scoliosis, lower limb length discrepancy and mild joint laxity were noted. Only exaggerated lumbar lordosis was noted for affected sibling. Both had radiographic features suggestive of mild platyspondyly with irregular end plates, epiphyseal dysplasia of femora with delayed carpal ossification. The parents were clinically unaffected.

Whole exome sequencing was done for the proband 1 followed by segregation analysis and validation of the variant in proband 1, his parents and proband 2 was done by Sanger sequencing.

Results: Analysis of exome data revealed a novel missense variant c.3190C>T p.(Arg1064Cys) in exon 47 in homozygous state in *COL2A1* gene in the proband 1. The variant was detected in homozygous state in proband 1 and affected sibling. The parents were heterozygotes for the variant.

Discussion: Heterozygous pathogenic variants in *COL2A1* are known to be implicated in the pathogenesis of several types of skeletal dysplasia collectively known as type II collagenopathies. In the recent literature, two families have been reported with homozygous pathogenic variants in COL2A1. The affected individuals reported had short stature, kyphoscoliosis, barrel-shaped chest, short neck, flat face, waddling gait, brachydactyly and myopia. The clinically unaffected parents were heterozygotes for the condition. However, our probands had milder phenotype in comparison to the previously reported individuals. Here we report an additional family with spondyloepiphyseal dysplasia congenita which further validates the pathogenicity of homozygous missense variants in COL2A1, leading to spondyloepiphyseal dysplasia congenita.

ABSTRACT 05

Analysis of Homozygosity Stretches Around Homozygous Pathogenic Variations for Autosomal Recessive Disorders in Indian Patients from Consanguineous and Non-Consanguineous Families

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We compared stretches of homozygosity around homozygous pathogenic / likely pathogenic sequence variations causing autosomal recessive disorders in consanguineous and non-consanguineous families. The exome data of the cases in whom the homozygous pathogenic / likely pathogenic sequence variations were identified was analysed. All 24 cases with AR disorders from consanguineous families were homozygous for the disease causing variations (12 out of 24 being novel variations) and had large (Average – 77.2 Mb,Range - 5 Mb to 271 Mb) stretches of homozygosity around the disease causing pathogenic or likely pathogenic variations. For AR disorders from non-consanguineous families, the disease causing variations were in homozygous form in 13 (9 being novel) out of 19 cases and 6 were compound heterozygous. In the cases with homozygous pathogenic variations from non-consanguineous families; there were stretches of homozygosity around the causative sequence variations (Average - 27.9 Mb, 0.6 Mb to 188 Mb).

We also reviewed our data of SNP microarray of cases from 50 consanguineous and 50 non-consanguineous families. In cases born to consanguineous parents the sizes of Regions of Homozygosity (ROH) regions were 28 Mb to 770 Mb. The average number of ROH more than 5 Mb were 11.59 (1 to 25). Amongst 50 cases from non-consanguineous families, 26 had at least 1 ROH more than 5 Mb (Average 2.33 of 26 cases). The sizes of runs of homozygosity regions varied from 3 Mb to 49 Mb (0.10 % to 1.7% of total genome; average 0.74%).

In India the custom of marriages amongst caste groups has been followed for ages. We have seen that for many rare autosomal recessive (AR) disorders, the affected individuals are homozygous for rare disease causing pathogenic variations, suggesting effects of inbreeding. Long stretches of homozygosity around homozygous rare pathogenic variants supports the notion that the system of marriages between closed groups (castes) has many founder mutations and using the strategy of homozygosity by descent even in non-consanguineous families can be fruitful in identifying novel pathogenic variations and novel genes.

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Genetic and Radiographic Profile of a Family with Osteopoikilosis

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Abstract

Osteopoikilosis is a rare condition of bones inherited in an autosomal dominant manner caused by mutations in *LEMD3*. It is characterized by sclerotic bone lesions in the epiphyses and metaphyses of long tubular bones, carpal bones, tarsal bones, pelvis, and scapulae (Serdaroglu et al., 2007). Individuals with osteopoikilosis are usually asymptomatic and often diagnosed incidentally through radiographs done for other medical conditions (fractures, joint dislocations, etc). Here we report the case of a 19 years old male with generalized back pain and radiographic evidence of multiple hyperostotic spots throughout the skeleton. The mother of the proband also had similar radiographic findings. A heterozygous pathogenic variant in *LEMD3* is identified to be the cause of osteopoikilosis in them.

Introduction

Osteopoikilosis (MIM #166770) is an autosomal dominant sclerosing bone dysplasia with multiple endostosis. Characteristic circular or ovoid shaped bone lesions in wrist, foot, pelvis, scapula and end of long bones are commonly seen (Ye et al., 2017). Individuals are usually asymptomatic and sometimes may also develop superficial skin lesions/ dermatofibrosis (Baasanjav et al., 2010). They are diagnosed by radiographs done incidentally for other medical conditions such as fractures or joint pain (Mahbouba et al., 2015). Heterozygous variations in *LEMD3* are known to be causative of the osteopoikilosis phenotype (Hellemans et al., 2004).

Case summary

A 19 years old male was referred with persistent lower back pain of one month. His birth and development was unremarkable. In childhood, he had history of recurrent fractures in the left leg on trivial trauma. On examination, the head circumference was 53 cm (-2 SD for age), height was 172 cm (normal for age) and weight was 47 Kg (-2 SD for age). No characteristic skin nodules were observed. His intellect was appropriate for age and he had no other co-morbid conditions. In radiographs, numerous symmetric, hyperostotic, well defined, ovoid spots more localized in the epiphyses and metaphyses of long bones, and in other bones like scapula, spine and pelvis were seen (Figure 1 A-C). The proband's mother was also asymptomatic and had similar radiographic findings. The typical hyperostotic spotted bone lesions were observed in her radiographs (Figure 2 A-B).

Informed consents were obtained and 3ml of peripheral blood was collected from the proband and parents. Genomic DNA was extracted and the coding exons and their flanking intronic regions of *LEMD3* (NM_001167614.1) were PCR amplified with the primers designed for the same. Sanger sequencing of the PCR amplicons and data analysis revealed C-to-T transition in exon 9 (c.2203C>T) in *LEMD3*. This pathogenic variant was predicted to change arginine amino acid to a stop codon (p.Arg753Ter). It is a known pathogenic stop gain variant and is predicted to cause premature termination of translation thus forming a truncated protein. This variant is not observed in population databases like 1000 Genomes Project, Exome Aggregation Consortium and our in-house data of 569 exomes. Multiple *in silico* analysis tools are consistent in predicting that the variant may damage the LEMD3 protein function. Bi-allelic segregation in his parents was performed. The same variant, c.2203C>T was found in his mother who also shared similar radiographic features with the proband and the variant was not observed in the father. Radiographic findings observed in the proband and his mother are in concordance with osteopoikilosis (Figure 3 A-B).

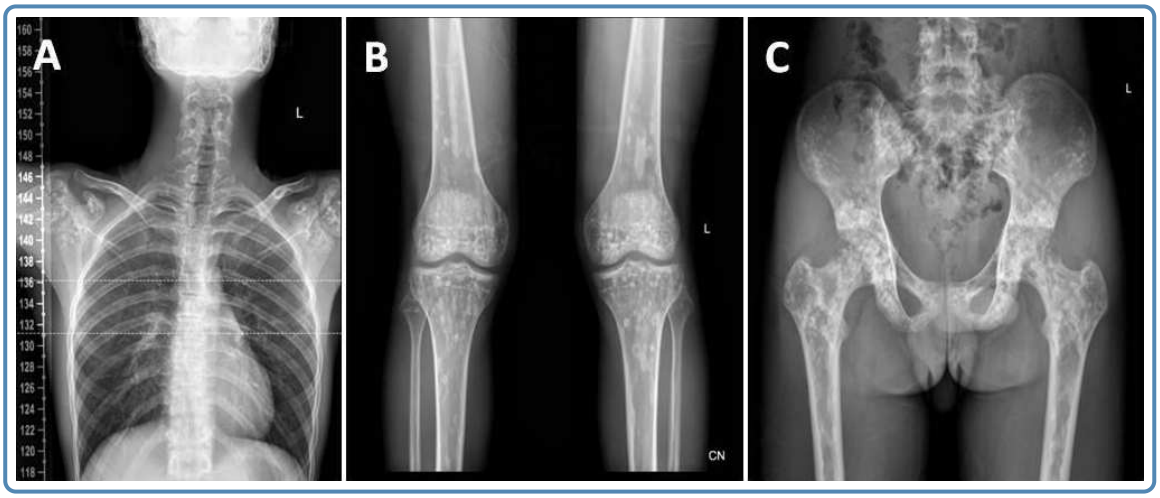

Figure 1 (A) Radiograph of the shoulder joint demonstrating multiple sclerotic foci involving the scapula, epiphysis and metaphysis of humerus in the proband, (B) Knee joint with small discrete sclerotic lesions involving the epiphyseal and metaphyseal regions of femur and tibia, (C) Hyperostotic lesions in pelvis, epiphyseal and metaphyseal regions of femur.

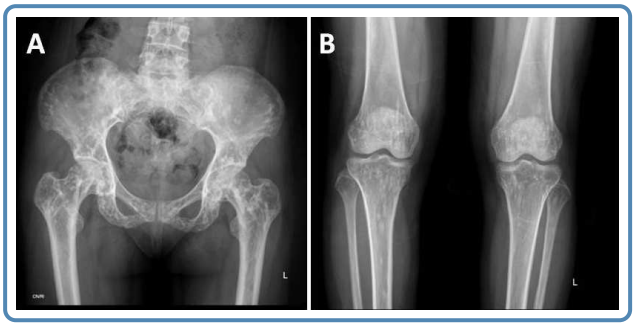

Figure 2 Radiographs of proband's mother shows – (A) Multiple sclerotic foci in pelvis, epiphyseal and metaphyseal regions of femur, (B) Knee joint with small discrete sclerotic lesions involving the epiphyseal and metaphyseal regions of femur and tibia.

Discussion

Osteopoikilosis, also called spotted bone disease, is a rare autosomal dominant bone dysplasia. The overall incidence of osteopoikilosis is 1 in every 50,000 subjects (Mohapatra et al., 2006). This condition is seen in both men and women and can become evident at any age. Both inherited and sporadic forms of this condition have been reported (Hellemans et al., 2004). Typically, the patients are asymptomatic, although as many as 20 % may have mild articular pain and joint effusion (Paraskevas et al., 2009).

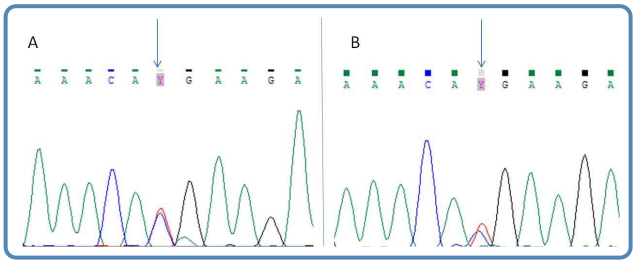

Figure 3 Sequence chromatograms of exon 9 in LEMD3 gene shows – (A) Proband with sequence variant c.2203C>T, in heterozygous state, (B) Mother with sequence variant c.2203C>T, in heterozygous state.

An epidemiological, clinical and radiological study has revealed that a predominance of lesions is seen in the phalanges of hand (100%) followed by carpal bones (97.4%), metacarpals (92.3%), foot phalanges (87.2%), metatarsals (84.4%), tarsal bones (84.6%), pelvis (74.4%), radius (66.7%), ulna (66.7%), sacrum (58.9%), humerus (28.2%), tibia (20.5%) and fibula (12.8%) (Benli et al., 1992). The primary cause of osteopoikilosis is heterozygous *LEMD3* mutations (Hellemans et al., 2004). The exact mechanism by which *LEMD3* mutation leads to bone lesions is not clear (Dheedene et al., 2009).

At present there is no consensus on treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) are often used as an option for the treatment of pain. Analgesics such as acetaminophen and

opioids can also be used. Rare active lesions have been treated with bisphosphonate therapy, but the results are controversial (Woyciechowsky et al., 2012).

In our study, we are providing clinical, radiographic and genetic details of a familial case with osteopoikilosis.

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Dr S S Agarwal Young Scientist Award 2018

Dr S S Agarwal Young Scientist Award of SIAMG was won by Dr Anju Shukla, currently working as Associate Professor at Department of Medical Genetics, Kasturba Medical College, Manipal. Her paper describes two consanguineous families with two affected children each with microcephaly, refractory seizures, intellectual disability and spastic quadriparesis. This work is published in the Journal of Human Genetics and reports the first human disease associated with deleterious mutations in *AIMP2*. The condition is recently catalogued in Online Mendelian Inheritance in Man as Leukodystrophy, hypomyelinating, 17 (# 618006). Her focus of research is discovery of novel phenotypes and the underlying mechanisms of rare Mendelian neurodevelopmental disorders through application of genomic techniques. (Shukla A, Das Bhowmik A, Hebbar M, Rajagopal KV, Girisha KM, Gupta N, Dalal A. Homozygosity for a nonsense variant in *AIMP2* is associated with a progressive neurodevelopmental disorder with microcephaly, seizures, and spastic quadriparesis. J Hum Genet. 2018; 63:19-25. doi: 10.1038/s10038-017-0363-1)

GeNeXpreSS

Emerging Therapies for Rare Genetic Disorders

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Burosumab in X–linked hypophosphatemia (Carpenter et al., 2018)

X-linked hypophosphatemia, the most common heritable form of rickets, is caused due to loss-of-function mutations in the *PHEX* gene. It is characterized by increased secretion of fibroblast growth factor 23 (FGF-23) which leads to renal phosphate wasting, hypophosphatemia, rickets and osteomalacia, stunted growth, skeletal deformity, pain and limitation of daily activities. Conventional therapy with oral phosphate salts and vitamin D analogues is associated with poor compliance, incomplete healing of rickets, residual skeletal deformity, persistent short stature, gastrointestinal side effects and risks of hypercalciuria, nephrocalcinosis, and hyperparathyroidism. Burosumab is a recombinant human lgG1 monoclonal antibody that targets FGF-23. The authors have studied the effect of Burosumab in children aged 5-12 years. A total of 52 cases with active rickets and confirmed diagnosis of X-linked hypophosphatemia were taken. The authors concluded that 2 weekly regimen provided a sustained increase in the serum phosphorus level. There was substantial healing of rickets in all children with severe rickets with improvements in multiple related efficacy endpoints. However, effect on adult height is unknown which will take years to evaluate. Also, long term treatment is required for proper assessment of joint related complications and risk of nephrocalcinosis.

Intraventricular Cerliponase Alfa for CLN2 Disease (Schulz et al., 2018)

Neuronal ceroid lipofuscinosis type 2 is a rare neurodegenerative disorder characterized by seizures and rapid decline in vision, motor, language, and cognitive functions. It is an autosomal recessive condition caused due to deficiency of the lysosomal enzyme Tripeptidyl peptidase 1 (TPP1). Cerliponase alfa is a recombinant form of human TPP1 and can be used as an enzyme-replacement therapy in patients with CLN2. In this study, the authors have evaluated the role of Cerliponase alfa in children with CLN2. A total of 24 children between the ages of 3 to 16 years were enrolled and they received intraventricular infusions of 300 mg every 2 weekly for a total duration of 96 weeks. The authors have concluded that intraventricular infusion of cerliponase alfa is associated with less decline in motor and language function as compared to historical cohorts.

Prophylaxis for hereditary angioedema (Syed et al., 2018)

Hereditary angioedema is an autosomal dominant condition characterized by recurrent attacks of angioedema. It is caused due to mutation in the *SERPING1* gene encoding C1 inhibitor. There may be reduction in levels of C1INH (C1 esterase Inhibitor) or there may be reduced functional activity leading to uncontrolled activity of plasma kallikrein causing excessive bradykinin production and angioedema. Lanadelumab is a human monoclonal antibody that inhibits plasma kallikrein. This drug has been approved for prophylactic use by US FDA in patients aged more than 12 years. The drug is given subcutaneously and can be self – administered.

Vestronidase alfa for mucopolysaccharidosis VII (Harmatz et al., 2018)

Mucopolysaccharidosis type VII is a rare genetic disorder caused by deficiency of the lysosomal enzyme β-glucuronidase. The authors have used

blind start trial design due to the small number of patients. A total of 12 patients were divided into four groups. After 24 weeks of treatment with Vestronidase, there was a significant reduction in urinary glycosaminoglycan excretion. Ten patients had improvement in the overall clinical outcome scores.

Emicizumab prophylaxis in Hemophilia A patients with or without FVIII inhibitors (Le Quellec et al., 2018)

Emicizumab is a recombinant monoclonal antibody that acts as a bridge between activated Factor IX and Factor X and thereby mimics the function of Factor VIII. In the phase 3 HAVEN1 trial conducted on 109 Hemophilia A patients, once weekly subcutaneous dosage regimen was found to maintain lowest factor levels to at least 10-15 IU/dl. It was also found that Emicizumab prophylaxis significantly reduced the bleeding episodes as compared to conventional episodic treatment with bypassing agents in case of patients with inhibitors against Factor VIII. There is increased risk of thrombotic events especially if the drug is used along with bypassing agents (BPAs) such as activated Prothrombin Complex Concentrates (aPCCs) and recombinant factor VIIa (rVIIa) during the episodes of breakthrough bleeding. There are concerns over use of this drug versus use of immune tolerance induction (ITI) therapy in children with inhibitors, as treatment with Factor VIII is more effective in comparison to BPAs in case of breakthrough bleeds. Also, as there is increased risk of thrombosis associated with BPAs, it has been proposed to start prophylaxis with Emicizumab along with ITI therapy in children with inhibitors.

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Equal Rights to Health Insurance and Employment: Prevention of Discrimination Based on Genetic Information Position Statement of the Society for Indian Academy of Medical Genetics (SIAMG)

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Background

Recent advances in genetics and genomic technologies have enabled prevention, diagnosis and improvements in health of general public. However currently all the health insurance providers exclude genetic conditions, birth defects, congenital disorders and congenital anomalies from the purview of coverage. The Society for Indian Academy of Medical Genetics strongly believes that an individual's genetic information should not be used for discrimination from health insurance coverage or discrimination in employment.

Present status

The Insurance Act, 1938, envisaged the establishment of the Insurance Regulatory Development Authority (IRDA) for regulating the insurance sector in India. The guidelines issued by IRDA on February 20, 2013, excluded conditions like pregnancy, infertility, congenital and genetic conditions, but did not define 'genetic' conditions (1). Following this, the insurance companies in India amended the terms of their policies and excluded 'genetic conditions' from insurance coverage. On July 29, 2016, IRDA issued a new guideline for standardization of insurance in health care in India, in which, 'genetic condition' is not mentioned and only 'congenital anomalies' are mentioned (2). On February 26, 2018, Delhi High court held that 'genetic disorder' is a vague term and should not be used to exclude insurance claims and directed the IRDA to re-look at their exclusionary clauses to prevent rejection of claims by insurance companies on the basis of genetic status of individuals (3). On March 19, 2018, IRDA issued a notification directing all insurance companies not to include 'genetic diseases' as one of their exclusion criteria in all health insurance policies (4). The Honorable Supreme Court of India has stayed the operation judgment of the Delhi High Court on August 27, 2018 (5).

The Universal Declaration of Human Rights (6), 1948 states, "Everyone has a right to a standard of living adequate for the health and well-being of himself and his family, including food, clothing, housing and medical care, and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age, or other lack of livelihood in circumstances beyond his control".

The European Convention on Human Rights & Biomedicine does not allow discrimination of any kind on the basis of genetic heritage and permits genetic testing for the purposes of health or for scientific research only and not for insurance purposes. Predictive genetic testing should not be done for insurance purposes (7). Many European countries like Austria, Belgium, Switzerland, Denmark and Portugal have made legislations for use and regulation of genetic data (3). Several countries across the world have enacted laws in respect of genetic discrimination by insurance corporations. The Genetic Non-discrimination Act, 2008, in United States of America, bars the use of genetic information in health, education and employment and prohibits charging of higher premium based on the genetic predisposition of an individual for developing a disease in the future (8).

Article 14 of the Constitution of India prohibits discrimination of any kind, which includes discrimination based on genetic heritage of an individual

(9). The Right to Health is a Fundamental Right, as an integral part of Article 21 (10) and Right to Healthcare is also a Fundamental Right and the right to avail an insurance is an integral part of Right to Healthcare. Hence it is unconstitutional to discriminate individuals based on their genetic status.

Position of the Society for Indian Academy of Medical Genetics (SIAMG) on discrimination against individuals with genetic conditions

Genetic and genomic information of an individual should not be used for discrimination against health insurance and employment. Any such discrimination would amount to misuse of such information.

Explanation:

1. Genetic and genomic information: This means history, clinical evaluation, imaging or medical tests that provide genetic information or reveal the genetic constitution of an individual. Genetic constitution of an individual is determined at the time of conception and well before birth of an individual. They can be revealed by several means: clinical evaluation, family history, analysis of pedigree, blood/urine or any other laboratory tests, imaging (CT scan, MRI, ultrasonography), genetic/genomic tests (Sanger sequencing, next generation sequencing or any other traditional or specialized genetic tests) and participation in genetic research. Genetic information of an individual aids healthcare of an individual.

2. Discrimination in health insurance: This includes levying additional premiums, asking for genetic/genomic information of an individual, refusing health insurance, refusing claims based on genetic and genomic information and refusing renewals

3. Discrimination in employment: Employers cannot discriminate in appointment, remuneration, promotion and provision of medical facilities based on genetic and genomic information.

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   (Ref: IRDAI/HLT/REG/CIR/046/03/2018)
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6. Universal Declaration of Human Rights, UN (December 10, 1948)
7. European Convention on Human Rights & Biomedicine, Oviedo (1997)
8. Genetic Non-discrimination Act of USA (2008)
9. Article 14 in The Constitution of India 1949
10. Article 21 in The Constitution of India 1949

The Executive Committee of the Society for Indian Academy of Medical Genetics approved this statement on 21 November 2018

PhotoQuiz - 43

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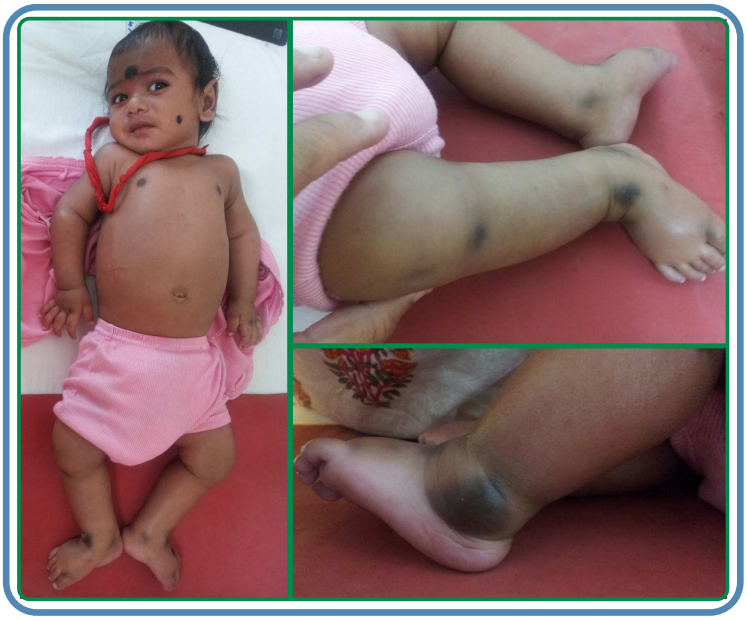
This 4.5 months-old male child, born to second degree consanguineous parents, was referred for evaluation of contractures of elbow, knee and ankle joints along with edema of the hand and feet and skin lesions on the lower limbs. He had excessive crying due to severe pain with movement. His elder male sibling had similar features and chronic diarrhoea with failure to thrive and had died at around 6 months of age. 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.

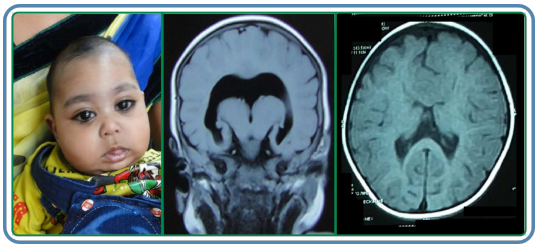


Answer to PhotoQuiz 42

The MRI shows holoprosecephaly. (Semilobar type).
Holoprosencephaly can be caused due to environmental or genetic causes.
Genetics causes could be due to chromosomal abnormalities or single gene disorders.
Craniofacial abnormalities like cleft lip/palate are seen in 80% of individuals with holoprosencephaly.

Correct Responses Were Given By:

1. Meenakshi Lallar,Rohtak
2. Ashka Prajapati, Ahmedabad
3. Jagadish Bhat, Goa
4. Lekshmi S Nair, Hyderabad
5. Jayaprakash KP, Kottayam



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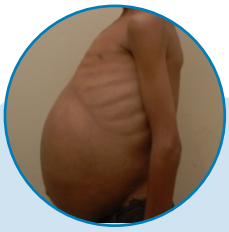
Patients with the following signs and symptoms may have a

Lysosomal Storage Disorder...



GAUCHER DISEASE

- Enlarged liver and spleen
- Delayed or stunted growth in children
- Easy bruising and bleeding
- Anemia and Thrombocytopenia
- Unexplained Bone pains
- Unexplained Avascular necrosis of femur

Cerezyme®# imiglucerase

POMPE DISEASE

- "Floppy" appearance in infants or young children
- Unexplained Cardiomyopathy
- Progressive respiratory muscle weakness or insufficiency
- Progressive Limb-girdle muscle weakness (in late-onset cases)

Myozyme®# (alglucosidase alfa)

MPS I DISEASE

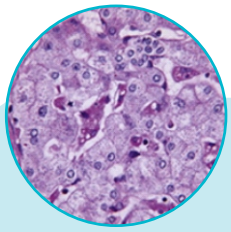
- Coarse facial features
- Early onset joint stiffness/ claw-hand deformities/ contractures
- Corneal clouding (leading to light sensitivity or impaired vision)
- Recurrent respiratory infections (including sinuses & ears)
- History of recurrent hernia repair in young age

ALDURAZYME®# (LARONIDASE)

FABRY DISEASE

- Severe burning pain in hands & feet
- Intolerance to heat & cold
- Inability (or decreased ability) to sweat
- Red, purple spots on skin (angiokeratomas)
- Evidence of early renal involvement (nephropathy)
- History of stroke in young age

Fabrazyme®# agalsidase beta



NIEMANN PICK - B DISEASE

- Enlarged liver & spleen
- Bleeding manifestations
- Skeletal abnormalities & Growth delays

Olipudase-α$

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