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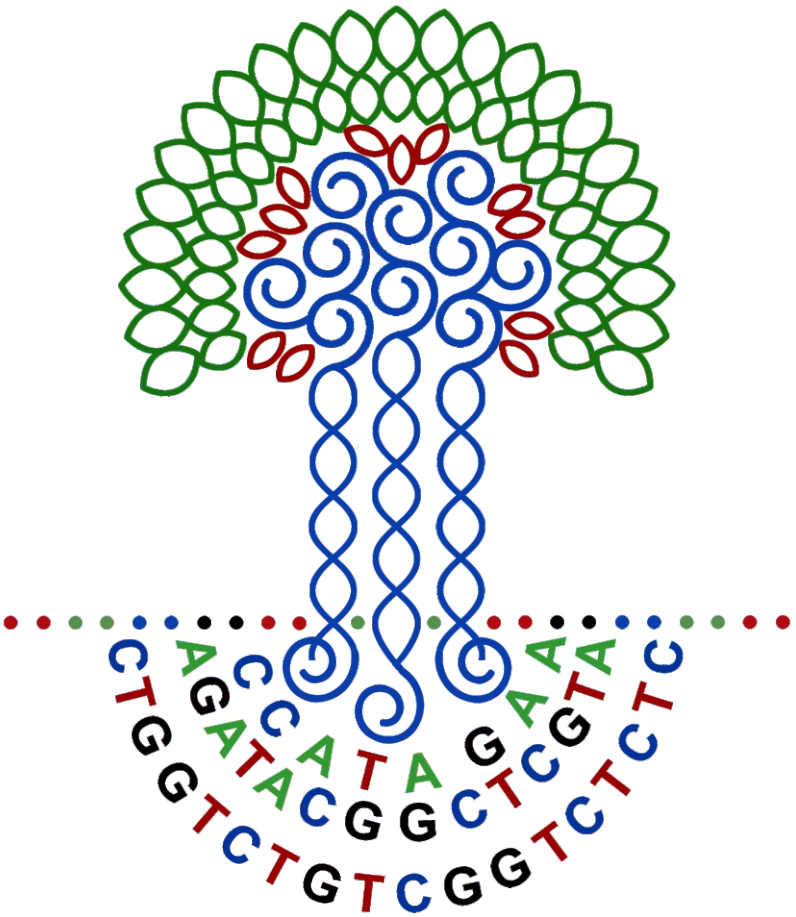
Table of Contents



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PhotoQuiz - 63

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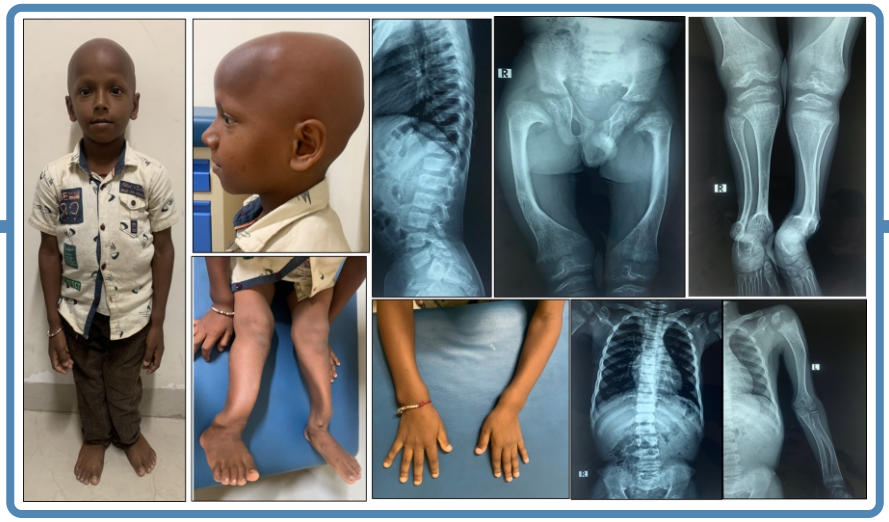
This 9-year-old boy was referred for evaluation of short stature and bony deformities. Identify the condition.

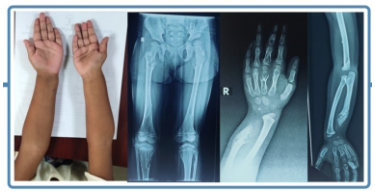
Please send your responses to editor@iamg.in
Or go to http://iamg.in/genetic_clinics/photoquiz_answers.php
to submit your answer.



Answer to PhotoQuiz 62

Multiple Enchondromatosis/ Ollier Disease

Ollier disease is a rare disorder characterized by multiple enchondromas, which are usually asymmetrically distributed and mostly involve the appendicular skeleton. It usually presents with painless bony masses, with the most frequently affected sites being the hands (phalanges and metacarpals) and the metaphyses and diaphyses of long bones. Genu valgus and cubitus varus deformity, limitation of joint mobility, leg-length discrepancy, pathological fractures, and facial asymmetry may also be seen. There is an increased risk of malignancies especially chondrosarcoma. Somatic mosaicism for variants in *IDH1*, *IDH2* or *PTH1R* have been found to be associated with this disorder.



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Medical Genetics in India: Coming of Age

Editorial

The Society for Indian Academy of Medical Genetics (SIAMG) was formed in 2012 and is now more than a decade old. Last month the eighth conference of SIAMG (IAMG 2023) was held successfully in New Delhi. The scientific program was excellent and reflected the current areas of research. The posters and oral presentations reflected the plethora of work being done in India. The number of participants has become sizable and was representative of the work being done in various areas. The increased number of participants means more patients are being catered to. The burden of rare diseases in India is huge due to the large population.

In addition to the work on diagnostics, there were many talks on the therapeutic aspects. Success stories of gene therapies are showing promise for many more disorders. The presentation of research work in sickle cell disease and Duchenne muscular dystrophy being done in India gave confidence that the 'Make in India' policy will make the latest therapies available to Indian patients at an affordable cost. The funding agencies in India are also focusing on the space of therapeutics of rare diseases. Products made by Indian pharmaceutical companies for Wilson disease, tyrosinemia, hereditary angioneurotic edema, etc. have become available in India. The central government's rare disease policy is being implemented in a practical way. The panel discussion on the policy gave some facts and discussed the way ahead. The beginning has been done but the road ahead appears bumpy. Research proposals on therapies for spinal muscular atrophy and Gaucher disease are being presented in the task force of funding agencies and show the talent and capabilities of Indian scientists. IAMG 2023 provided a forum for clinician-scientists interactions which is an important mini-cosmos for the generation and nurture of seedlings of new ideas.

The revolution of next-generation sequencing (NGS)-based diagnostics has metamorphosed the field of genetic diagnostics, and its role is very important whether it is ordered at the first visit or after basic evaluation. The ways to by-pass the limitations of NGS-based diagnostics are discussed in the GenExpress of this issue. Hope we soon have one test for all types of genetic variations, and a big database of disease-causing variations in India. The IndVar database inaugurated at the conference needs to be strengthened. We wish it will be a resource not only for variant interpretation in diagnostics but also a platform to plan and develop collaborations for functional studies amongst Indian medical geneticists.

With improved diagnostics and new therapies and a big hope of therapies for many more diseases, I hope that in the near future, prenatal diagnosis will lead to treatment rather than termination of pregnancy. With the hope that 2024 will usher in many new therapies in the world and in India, I wish you all a very happy new year.

Dr. Shubha Phadke
1st January, 2024

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Clinical Vignette

An Intriguing Case of Neonatal Diabetes Mellitus

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Abstract

Neonatal diabetes mellitus (NDM) is a rare cause of monogenic diabetes diagnosed usually before 6 months of age. We report a case of permanent NDM in a 4-month-old infant girl who presented with diabetic ketoacidosis. She had a past history of refractory epileptic spasms and developmental delay. Genetic analysis showed a heterozygous variant in the *KCNJ11* gene. Around 25% of *KCNJ11* mutations are also associated with neurological features. In this particular child, the clinical features of epileptic spasms, developmental delay and diabetes fit into DEND syndrome which represents one of the most severe forms of permanent NDM.

Keywords: Monogenic diabetes, epilepsy, *KCNJ11*, permanent neonatal diabetes, sulfonylurea

Introduction

Neonatal diabetes mellitus (NDM) presents with hyperglycemia anytime between the neonatal period and infancy, mainly before 6 months of age. It has an incidence of 1 in 90,000 live births with ethnic variability (Iafusco et al., 2012). ATP-sensitive potassium channel mutations (K_{ATP}) constitute the most common cause of permanent neonatal diabetes mellitus (PNDM). K_{ATP} channel is present in the beta cell of pancreas and plays a key role in insulin secretion. This octameric channel is made of two subunits, Kir6.2 and SUR1, coded by the *KCNJ11* and *ABCC8* genes, respectively. Around 25% of *KCNJ11* mutations are associated with neurological features as the K_{ATP} channel is also present in the central nervous system, vascular smooth muscle, and myocardium (Gloyn et al., 2006). We describe a case of NDM with phenotypic features of DEND (Developmental delay, epilepsy, neonatal diabetes) syndrome. It is a rare and severe form of NDM associated with neurodevelopmental delay, motor weakness and epilepsy.

Clinical Report

A 4-month-old female infant, first born to non-consanguineous parents was brought with history of acute onset lethargy and poor feeding. She had a significant perinatal history of being born at term with intrauterine growth retardation (IUGR) by lower segment Caesarean section. Her birth weight was 2.3 kg and she required neonatal intensive care for asymptomatic hypoglycemia and feed intolerance. At 3 months of life, she was diagnosed with epileptic spasms for which she was started on vigabatrin. Magnetic resonance imaging (MRI) of the brain was normal. Electroencephalogram (EEG) showed features of hypsarrhythmia. She did not have social smile and was not recognizing her mother yet. At 4 months of life, in view of poorly controlled spasms, clonazepam and prednisolone were added to the treatment regimen. Within 3 days of starting the new medications the child presented to the emergency room with lethargy and refusal of feeds. There was no family history of neurological disorders or early-onset diabetes mellitus.

On examination, the child was dehydrated, tachycardic and had normal peripheral perfusion. No dysmorphic features were present. Her anthropometric parameters plotted as per the World Health Organization (WHO) growth chart showed weight, length and head circumference at 3rd centile. Systemic examination showed generalized hypotonia. Her capillary blood glucose was 590 mg/dl. Urine ketones were 2+. Venous blood gas showed a pH of 7.12 and bicarbonate of 10.7 mmol/L. This clinical and biochemical picture

was suggestive of moderate diabetic ketoacidosis (DKA). Confirmatory venous random blood glucose was 504 mg/dl and HbA1c was 12.8%. HbA1c, however, cannot be regarded as a reliable indicator of glycemic status below 6 months of age due to the presence of fetal hemoglobin (HbF).

The child was started on intravenous normal saline as per the guidelines of the International Society of Pediatric and Adolescent Diabetes (ISPAD) (Greeley et al., 2022), followed by concurrent insulin infusion at an average rate of 0.04 U/kg/hour. Prednisolone was discontinued. With resolution of DKA, she was started on long-acting insulin glargine, at a dose of 1 unit and pre-prandial rapid acting insulin lispro with 0.5 U adjustment at a dose range of 0.3-0.6 U/kg/day with careful regard to potential hypoglycemia. Pre-feed glucometer blood glucose was checked, and insulin was given for every other feed only if the blood glucose was above 200-250mg/dl in order to prevent hypoglycemia. Anti-epileptic medications were continued as per the pediatric neurologist's advice. However, the child continued to have spasms and on day 4 of hospital stay she was found listless and pale. She required cardiopulmonary resuscitation and while intubating, the findings were suggestive of aspiration. Despite best efforts, the child succumbed and could not be revived.

Genetic testing was performed using a Sanger sequencing-based multigene panel; thirty-six genes associated with monogenic forms of diabetes mellitus were analyzed for pathogenic variations. A novel heterozygous missense variation c.511A>G (p.Thr171Ala) in exon 1 of the *KCNJ11* gene (ENST00000339994) was detected. Segregation analysis showed that both the mother and father of the child did not have this particular variant. This indicated the likely de novo origin of the mutation. The in-silico predictions of the variant are probably damaging by PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/) and damaging by SIFT (https://sift.bii.a-star.edu.sg/) and Mutation-Taster2 (https://www.mutationtaster.org/). Based on the American College of Medical Genetics and Genomics and Association for Medical Pathology (ACMG/AMP) guidelines, this variant was classified as 'likely pathogenic' (PS2 + PM1 + PM2 + PP3) (Richards et al. 2015). Thus, the diagnosis for the child was concluded to be DEND syndrome.

Genetic counselling was done for the parents, and they were advised that the risk of recurrence in the next offspring is low though not negligible as germline mosaicism cannot be ruled out.

Discussion

DEND syndrome is a rare, severe form of permanent NDM. The K_{ATP} channel is a key regulator of insulin secretion. Activating mutations in the Kir6.2 subunit cause the K_{ATP} channel to remain open, leading to hyperpolarization of the cell membrane and prevention of Ca2+ influx that is required for exocytosis of insulin into the circulation. In the brain, these channels increase the spontaneous discharge rate of neurons in the ventromedial hypothalamus. IUGR in those affected reflects prenatal insulin deficiency. As described in literature, our case presented after a few months of life with DKA indicating less severe insulin deficiency during the last phase of intrauterine development and at birth. K_{ATP}-NDM is the most common cause of permanent NDM. Ninety per cent of *KCNJ11* mutations cause permanent NDM. The mutation can occur spontaneously (80%) or can be transmitted in an autosomal dominant manner. The mutation identified in our case is a novel de novo variant that has not been reported in literature.

DEND syndrome in India was first reported by Singh et al (2014); the latest follow-up mentioned by them until 2.6 years of age described good glycemic control of diabetes and appreciable improvement in development. Refractory infantile spasms as part of DEND syndrome have been similarly reported by Bahi-Buisson et al. (2007) in a 3-month-old child who also succumbed to aspiration pneumonia at 8 months of life. In a study by Gopi et al. (2021), describing the genotype-phenotype profile of neonatal diabetes mellitus, 20 out of 39 patients had *KCNJ11* mutations, 3 of whom had DEND syndrome – two with the p.Val59Met mutation and one with the p.Val64Met mutation. Severity of developmental delay and epileptic seizures were greater in the patient with p.Val64Met compared to the patients with p.Val59Met; the former also did not respond to sulfonylurea therapy while the latter two patients with p.Val59Met did respond. The two patients with p.Val59Met were also weaned off insulin and continued with sulfonylurea with normal EEG findings off valproic acid. A more severe phenotype is associated with more severe K-ATP dysfunction.

The sulfonylurea class of drugs has been used successfully for treating monogenic NDM affecting the K_{ATP} channel. Often, insulin which is used during initial management after diagnosis of NDM can be completely weaned off in these cases and the child can be transitioned to oral glipalamide. Timely initiation and use of sulfonylurea not only improves glycemic control but also neurodevelopmental outcome. The burden of injections and drug costs resulting from insulin can thus be reduced in cases of NDM that show good response to sulfonylurea.

Conclusion

Permanent NDM caused by *KCNJ11* mutation can rarely present as a severe syndromic form characterized by epilepsy and developmental delay (DEND syndrome) with high risk of early mortality. Neurological features often precede clinical onset of diabetes. Genetic testing forms the most important part of diagnostic evaluation as it helps guide treatment with sulfonylurea drugs.

Acknowledgment: The authors thank the family for their participation in the study.

Conflict of Interests: None

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Clinical Vignette

Unusual Manifestation of a Rare Disorder: Type XIV Osteogenesis Imperfecta Presenting as Fetal Hydrops

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Abstract

Osteogenesis imperfecta (OI) is a group of inherited disorders characterised by decreased bone density and increased susceptibility to fractures. In addition to the classic *COL1A1/ COL1A2*- associated autosomal dominant (AD) OI, close to 20 more types have been identified in recent years. Type XIV OI is a very rare autosomal recessive form of OI caused by biallelic variants in the *TMEM38B* gene. We report here a consanguineous family with recurrent fetal hydrops, where evaluation of the second affected fetus revealed the diagnosis of *TMEM38B* gene-related Type XIV OI.

Keywords: Osteogenesis imperfecta, *TMEM38B* gene, Non-immune fetal hydrops

Introduction

Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous group of disorders of bone mineralization. Based on the clinical manifestations, Sillence et al. (1979) classified OI into four main types namely the classic non-deforming type with blue sclerae (type I OI), the perinatally lethal form (type II OI), the progressively deforming type (type III OI) and the common variable type with normal sclerae (type IV OI). OI is classically associated with heterozygous variants in the *COL1A1* or *COL1A2* genes which code for the α1 and α2 chains of collagen type I respectively. *COL1A1/ COL1A2*- related OI has an autosomal dominant pattern of inheritance. Over the past one to two decades, following the availability of high throughput molecular analysis techniques especially next-generation sequencing, several more types of OIs due to variants in other genes involved in collagen I processing and/ or osteoblast function have been identified. Majority of these have an autosomal recessive (AR) pattern of inheritance. One such AR OI is type XIV OI (OMIM # 615066) which was first described in 2012 (Shaheen et al., 2012). It is caused by biallelic variants in the *TMEM38B* gene (OMIM *611236) which codes for an endoplasmic reticulum membrane channel called the trimeric intracellular cation channel type B (TRIC-B) (Ramzan et al., 2021). It is a rare form of OI with variable degree of severity of fractures and osteopenia. Limited case reports on type XIV are available and presentation with intrauterine hydrops has not been reported previously.

Clinical Report

This 24-year-old second gravida, married consanguineously to her first cousin, presented at 20 weeks gestation with antenatal scan findings of nuchal edema, generalized subcutaneous edema, shortening of all the long bones and bilateral bent femora in the fetus. Her blood group was B positive. The first pregnancy of the couple had been terminated due to similar antenatal scan findings; however, fetal autopsy and/ or genetic evaluation had not been done for the first pregnancy. The couple opted for termination of this second affected pregnancy. Prior to termination, amniocentesis was done, and the sample was sent for karyotyping and DNA extraction and storage. Following termination, the fetus was submitted for autopsy evaluation.

On autopsy, the fetus was found to have a body weight of 350 g (~70th centile), crown-heel length of 22 cm (8th centile), crown-rump length of 15 cm (7th centile), foot length of 3 cm (2nd centile),

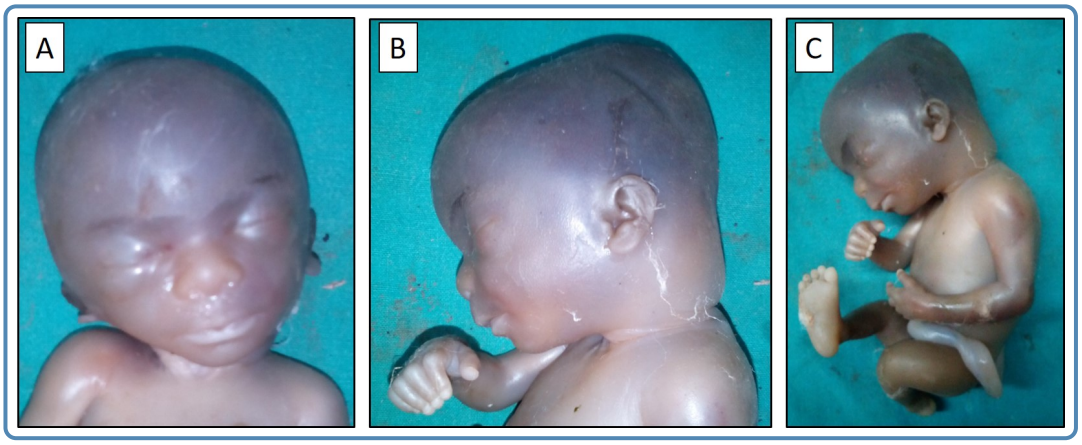

Figure 1 **Figure 1A & 1B.** Frontal and lateral views of the fetal head and face showing the scalp edema, nuchal edema, and craniofacial dysmorphism in the form of a globular head shape, depressed nasal bridge, broad nose, low-set ears and microretrognathia. **1C.** Lateral view of the fetal body showing the generalized subcutaneous edema.

head circumference of 17.5 cm (56th centile) and chest circumference of 14.5 cm (60th centile). Craniofacial dysmorphism was noted in the form of a globular head shape, depressed nasal bridge, broad nose, low-set ears and microretrognathia (**Figure 1A & 1B**). There was scalp edema, nuchal edema, and generalised subcutaneous edema (**Figure 1B & 1C**). On external examination, the chest and back were normal, and the abdomen appeared to be distended. The thighs appeared short and bent. Other limb segments appeared to be proportionate and symmetric. Bilateral upper limb measurements were as follows: proximal segment 4 cm, middle segment 3.5 cm, and distal segment (hand) 2 cm. Bilateral lower limb measurements were as follows: proximal segment 4 cm, middle segment 4 cm, and distal segment (foot) 3 cm. Normal male external genitalia and normal anal opening were noted. Internal dissection revealed bilateral pleural effusion and ascites. The intrathoracic and intraabdominal organs including the heart, lungs, great vessels, stomach, small and large intestines, liver, and spleen appeared to be grossly normal. The kidneys and the urinary tract also appeared to be normal. The placenta was normal, and the cord had three vessels. Fetal skeletal radiographs showed bent and shortened femora with acute angulation in the femoral shaft bilaterally. The ribs appeared to be thin and wavy, and poor mineralization of the long bones and cranium was noted (**Figure 2**). Histopathological evaluation of the placenta and the intrathoracic and intra-abdominal organs did not reveal any significant abnormality. Based on the clinical and radiographic findings, the possibility of a skeletal dysplasia with poor bone mineralization especially osteogenesis imperfecta was considered.

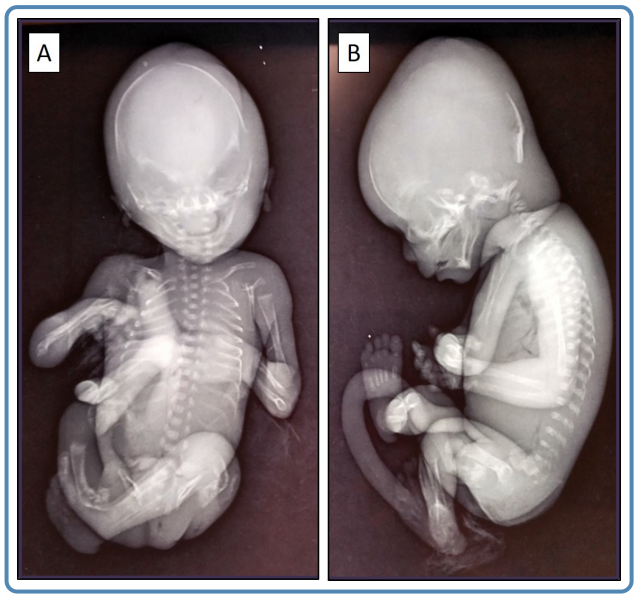

Figure 2 **Figure 2A & 2B.** Fetal skeletal radiographs (anteroposterior and lateral views) showing bent and shortened femora, thin and wavy ribs, and poor mineralization of the long bones and cranium.

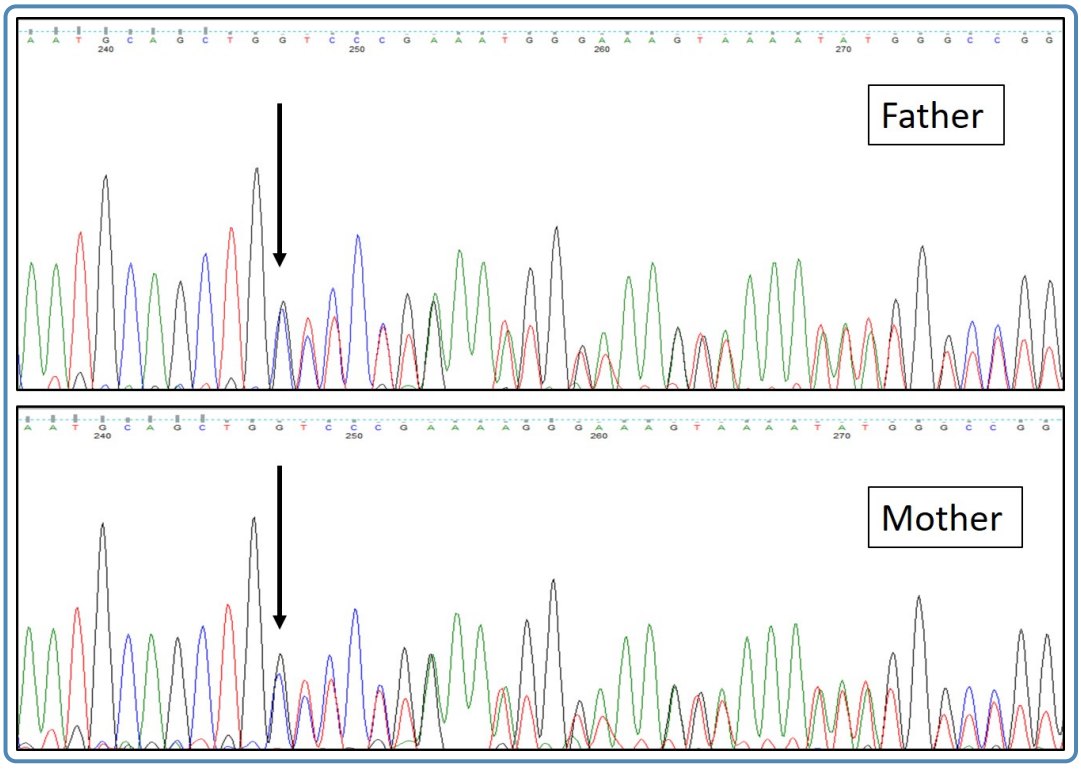

Figure 3 **Figure 3.** Targeted Sanger sequencing of both parents showing heterozygous carrier status for the variant c.115_116insC (p.Ala40SerfsTer43) in the *TMEM38B* gene (ENST00000374692).

Karyotype of the amniotic fluid was reported to be normal. In view of the likely diagnosis of osteogenesis imperfecta based on the fetal autopsy findings, whole-exome sequencing (WES) was done in the stored fetal DNA, which revealed a homozygous novel frameshift variant c.115_116insC (p.Ala40SerfsTer43) in the *TMEM38B* gene (ENST00000374692). The variant is absent in the population databases gnomAD (https://gnomad.broadinstitute.org/) and 1000 Genomes (https://www.internationalgenome.org/1000-genomes-browsers/). It is classified as a 'likely pathogenic' variant (based on the criteria PVS1 + PM2) as per the variant classification guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al., 2015). Through targeted Sanger sequencing, both parents were confirmed to be heterozygous carriers of this variant (**Figure 3**).

Based on the autopsy and molecular genetic findings, the diagnosis for the fetus was concluded to be *TMEM38B* gene-related type XIV osteogenesis imperfecta with non-immune fetal hydrops.

Discussion

Type XIV OI was first described by Shaheen and co-workers in 2012 (Shaheen et al., 2012). They described 12 affected individuals from three families in Saudi Arabia with clinical symptoms of OI. By autozygosity mapping and linkage analysis they found a novel recessive OI locus which mapped to chromosome 9q31.1-31.3. They identified a novel truncating deletion of exon 4 in the *TMEM38B* gene within that locus. The same exonic deletion was reported by Volodarsky and group in affected members of three unrelated Israeli Bedouin consanguineous families (Volodarsky et al., 2013). At present, 17 mutations in the *TMEM38B* gene are listed in the Human Gene Mutation Database (HGMD; https://www.hgmd.cf.ac.uk/).

TMEM38B codes for trimeric intracellular cation channel type B which is present in the endoplasmic reticulum. This cation channel regulates intracellular calcium influx. The role of fine-tuned intracellular calcium levels in the proliferation, differentiation, and cellular function of numerous cell types including osteoblasts has

been clearly established (Berridge et.al, 2000; Zayzafoon, 2006).

The clinical manifestations and molecular basis of type XIV OI were studied in depth by Webb and coworkers (Webb et al., 2017). They studied eight patients with type XIV OI and in addition to the usual manifestations of OI, they described previously unreported features like periosteal cloaking, coxa vara and extra-skeletal manifestations like muscular hypotonia and cardiac abnormalities. They analysed bone biopsy samples of the patients and demonstrated decreased trabecular bone volume as well as reduction of osteoblast and osteoclast numbers with more than 80% reduction in bone resorption. They concluded that in addition to an intrinsic osteoclast defect leading to low bone turnover, there are intracellular calcium flux abnormalities in type XIV OI which possibly cause the muscular and cardiovascular features seen in this condition. Thus, type XIV OI has a distinctive pathogenesis from most other forms of OI which are associated with defects in the formation, folding, or posttranslational modifications of collagen.

Published literature related to type XIV OI is limited and most reported cases have had postnatal onset of manifestations. Recently, Kodama and group published a case report of a newborn with multiple fractures of intrauterine onset caused by a novel splice variant in the *TMEM38B* gene (Kodama et al., 2023). However, presentation of type XIV OI as fetal hydrops has not been previously reported. Though the exact pathogenetic mechanism for the fetal hydrops in our case remains to be established, it is possible that the calcium influx defects resulting from biallelic variants in the *TMEM38B* gene may have led to congestive cardiac failure and third-space fluid accumulation.

Conclusion

Type XIV OI is a rare autosomal recessive type of osteogenesis imperfecta, which has a molecular mechanism different from that of the conventional collagen-related types of OI. Ours is the first case of type XIV OI to be reported with the phenotype of hydrops fetalis, to the best of our knowledge. Further studies are expected to expand the phenotypic spectrum of this rare form of OI.

Conflict of Interests: None

Acknowledgments: The authors thank the family for their participation in the study. Molecular genetic testing in this study was performed with funding support obtained from the Science and Engineering Research Board (SERB), Department of Science and Technology (DST), Government of India through the project EMR/2016/003887 granted to the PI Dr Prajnya Ranganath.

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Phenotype First or Genotype First: The Conundrum

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Abstract

Evaluation of patients with suspected genetic disorders as well as gene disease research has predominantly relied on studying the signs and symptoms (phenotyping) of patients or research cohort, followed by doing appropriate genetic tests (genotyping) to diagnose the genetic condition or characterize the causative gene. As the costs of gene sequencing are going down, clinicians and researchers are evaluating the diagnostic yield, cost-benefit ratio, advantages and limitations of this approach versus genotyping all individuals without any phenotypic biases and correlating the genetic results with clinical features as a secondary step. In this article we put forward the debate on the traditional, tried and tested 'Phenotype first' approach versus the contrasting new hypothesis of 'Genotype first' approach for patient care and genomic research.

Keywords: Phenotype, genotype, sequencing, genetic disorders, genomic research.

The Phenotype First Approach

"*Genotype without phenotype leads to missense or nonsense*"- Prof David Rimoin.

The **phenotype** (*phainein*: 'to show', and *typos*, meaning 'type') of an organism is the composite of the organism's observable characteristics or traits which would include the physical form and structure, developmental processes, biochemical and physiological properties, and behaviour, including the products of behaviour. Phenotype results from two basic factors: the expression of an organism's genetic code or its genotype, along with the influence of the environment. The **phenome** refers to the set of all phenotypes expressed by the cell, tissue, organism, and species. **Phenomics** is the systematic study of phenotypes.

In simple terms, phenotyping is documentation of all our clinical examination findings and having some differential diagnosis before ordering any genetic test. In fact, the choice of test whether a karyotype or microarray or exome/ genome sequencing or any other molecular test would be guided by the phenotype. For example, if spinal muscular atrophy (SMA) is the clinical suspicion, then multiplex ligation-dependent probe amplification (MLPA) of the *SMN1* gene would be considered first, while if the phenotype is epilepsy, generally exome sequencing would be the first line genetic test.

Phenotyping is done in various ways that include:

- External evaluation by clinical dysmorphology review, fetal autopsy, etc.
- Internal examination including evaluation for organomegaly, cardiac signs, neuromuscular examination, fundus examination, etc.
- Investigation findings such as tissue histopathology, skeletal surveys/ radiographs, magnetic resonance imaging (MRI)/ computed tomography (CT) scans, electromyography/ nerve conduction studies (EMG/NCS), routine and special biochemical investigations, ultrasound findings etc.

All the above would help in reaching a clinical differential diagnosis based on which the laboratory will search for relevant genes of significance. In fact, a professional genetic

laboratory would ask for detailed phenotypic data before initiating a genomic test.

With the advent and rapid progress of next-generation sequencing (NGS) it had been suggested that NGS will decrease the need for phenotyping in general. However, it is now clear that a phenotype-driven approach is necessary to decipher various genotypes. In fact, a gene is listed in the Online Mendelian Inheritance in Man portal (OMIM) as significant only if it has a defined phenotype. It may be remembered that a correct phenotype will more likely provide you with a correct genotype.

The utility of phenotyping is dual in the current NGS era: a pre-NGS differential diagnostic mode (forward phenotyping) and post-NGS diagnostic assessment mode (reverse phenotyping). Both these are very critical for drawing any meaningful conclusions out of the genetic results.

The points in favour of a 'phenotype first' approach are as follows:

- It helps in more accurate search for genes (as relevant to the clinical examination findings) in the primary investigation step. Further data reanalysis can be guided by pointers based on the phenotype evolution as per the age and natural history of the disorder.
- One cannot rely on the laboratories entirely to give a genetic diagnosis. Providing proper phenotype handles would minimize errors from genome analysts or bioinformaticians who are generally non-clinical personnel. In fact, the Human Phenotype Ontology (HPO) has been developed for the reason that computerised NGS analysis should include the accurate phenotype.
- Phenotype blends and causes for variability in presentation and severity (due to reduced penetrance, variable expressivity, environmental or epigenetic interferences) can only be dissected by phenotyping.
- Planning immediate management for inborn errors of metabolism or prognostication regarding the severity of the condition is enabled by various examination and investigation findings and do not always depend on the genotype results.
- Phenotyping enables assigning significance to variants of uncertain significance (VUS) and sometimes downgrading pathogenic variants (deemed pathogenic by only the in-silico predictions tools or as per the available literature from other populations).
- A proper phenotyping based on examination and investigations will help in deciding on specific gene panels which can save costs and time. Some phenotypes may not need costly NGS-based testing and confirmation of diagnosis may be possible by a simple and less costly targeted test.
- A phenotype-driven approach (with pretest and post-test counselling) will help to reduce the psychosocial anxiety associated with the condition for the patient and reduce medicolegal liabilities for the clinician and the laboratory.

As rightly pointed out by Hennekam et al. (2012), "there will be a critical need for phenotyping and clinical analysis and Medical Geneticists are uniquely positioned to address the need".

The Genotype First Approach

Clinicians have learnt and practiced medicine in the order of history, examination, basic investigations, and advanced investigations.

The '**genotype first**' approach is the process in which the patient/ individual undergoes genomic testing/sequencing with subsequent determination of the associated phenotypes of interest. Radical scientists and researchers believe that the 'genotype first' approach has the potential to take genomic medicine beyond ascertainment biases and can truly take medicine and health towards the prevention of all disease (Wilczewski et al., 2023). At present there are no formal recommendations, but we are gradually moving towards this change in clinical, laboratory as well as research settings.

In the clinical setting

A 'genotype first' approach for patients with suspicion of a genetic disorder, will optimize the health care system capacity. This is particularly true in our part of the world, where there is insufficient medical genetics expertise and no well-defined referral system. Majority of genetic tests are ordered by non-specialist physicians with information about only the basic clinical symptoms of the patient. As the cost of genotyping is going down, this practice will further increase.

It is only when the patient reaches the specialist/ geneticist with the genetic report, that reverse deep phenotyping, segregation studies and reanalysis of the genotyping data are done. Inadvertently, the 'genotype first' approach is already being followed for clinical diagnosis. Also, in our setting, 'genotype first' is more relevant as it reduces the time to diagnosis and is cost effective. In-depth phenotyping like cerebrospinal fluid (CSF) studies, magnetic resonance spectroscopy (MRS), repeated MRIs to look for myelination abnormalities, biopsy and special staining, etc. are cost-prohibitive. If we add up the cost of patient visits back and forth for clinical assessment, then for the reports, and then for advanced tests vs patient getting the genotyping in the first visit, the latter approach has a more favourable cost-benefit ratio.

Even if we leave costly investigations out of the equation, phenotyping by only clinical examination has inherent flaws. First, it is subjective and dynamic**.** The presence or absence of neurologic signs, dysmorphic features, skin findings etc. could be subjective and transient which may bias the analysis of genotyping based on the phenotype. With expanding genetic knowledge, we know that classic phenotypes of genetic syndromes can be seen only in a subset of patients. There is random combination of symptoms, subtle symptoms, and new symptoms being described for genetic syndromes. Genetic analysis based on the clinical differentials will be inaccurate in all patients who do not present with classic phenotypes. This is especially true in the fetal / prenatal setting where clinical details gathered from fetal ultrasound are operator-driven or may be easily missed due to their transient nature.

In the laboratory setting

In the 'genotype first' approach, genes are fully sequenced, and all of the thousands of variants are carefully evaluated for properties that make them more likely to be disease-causing. The variants are not filtered out of the analysis at the first step based on the patient's phenotype. During reporting, variants are compared to the patient's phenotype to see if they explain all, or part, of the phenotype. This allows for identification of variants in patients with atypical or rarely reported presentations and has the potential to diagnose more than one condition. It also allows for the identification of suspicious variants in genes where a disease association is not yet established or only newly described.

In the approach where variants are annotated, classified, and reported only on the basis of symptoms, it is difficult to uncouple the variant classification and reporting in spite of them having evidence of being disease-causing. This will indeed lead to more variants of uncertain significance.

In the research setting

Genotyping of a cohort of individuals followed by reverse phenotyping can help in identification of new causative genotypes. Much of research in autism and neurodevelopmental delay has taken this approach with a good yield. Also, public datasets of NGS have been analyzed for different phenotypes including actionable germline cancer variants, and cardiovascular phenotypes like connective tissue disorders and RASopathies.

Advantages of the 'genotype first' approach in research settings are new gene discovery, new gene-phenotype correlation, better genotype -phenotype correlation, and characterization of background modifiers causing variable expression and penetrance. A novel genotype disease association can never be established by phenotype ascertainment bias.

Genotype-phenotype associations are limited in known genes when researchers select participants strictly based on the phenotype. For example, severe metabolic derangements like insulin resistance, severe diabetes, end organ complications due to *LMNA* gene mutation without the typical signs and symptoms like lipoatrophy could be established only by the 'genotype first' approach (Decaudain et al., 2007).

In population research

The 'genotype first' approach has the potential to shift from reactive medicine to preventive medicine. Multiple studies have demonstrated that population genotyping can identify pathogenic/ likely pathogenic variants in genes related to adult-onset conditions particularly unmasking the risk of malignancies like *BRCA* genes, *NF1*, etc. (Safonov et al., 2023).

Conclusion

The 'genotype first' approach is gaining momentum due to several factors like wider and more accessible NGS, evolving artificial intelligence (AI) tools, public genomic databases, and availability of electronic medical records (EMRs). With technological evolution 'genotype first' is a rapidly advancing approach for genomic research avoiding the phenotypic ascertainments

(Wenger et al., 2021). However, in clinical settings, it comes with various challenges like absence of a single genomic test for detection of all type of genetic variations and all genetic disorders, along with management and counselling of patients with genetic findings and no phenotypic expression of these findings. Overall if we move towards a time where universal genome sequencing is offered as part of routine health care, we should be well versed with the complexities of interpretation of genotyping and of genotypic expression (phenotype) (Bodian et al., 2016).

The debate will continue but genotyping and phenotyping are like two legs taking an individual forward; sometimes one puts the right foot first and sometimes left! Judicious use of the right diagnostic technique and at the right time requires wisdom. Astute clinicians will understand the power of both and are more likely to make the correct diagnosis in less time and at a lower cost. In addition to phenotyping skills and the knowledge of genetic disorders, clinicians of the genomic era need to be empowered with the skill to negotiate the maze of databases to solve the diagnostic conundrum.

Conflict of interests: None

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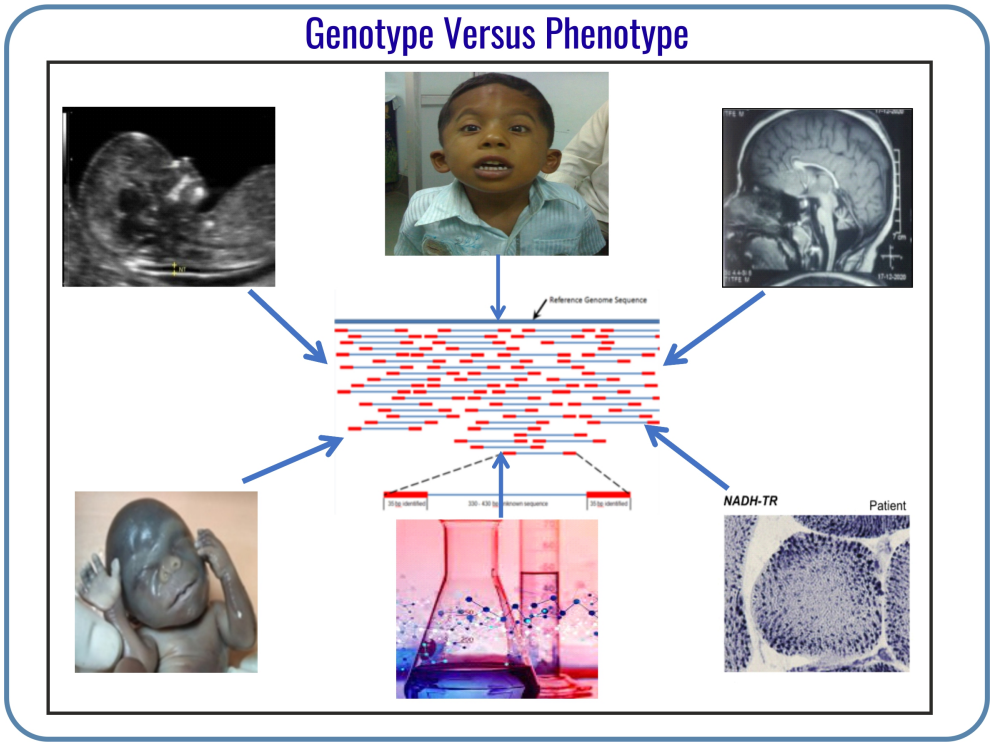

GeNeXpreSS

What Diagnoses Are Missed in Next-Generation Sequencing?

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Exome sequencing is quite popular among the clinicians for diagnosis of rare Mendelian disorders but is often non-diagnostic even when we have a strong clinical suspicion of a monogenic disorder. A proportion of them are solved by whole genome sequencing. Some families still remain undiagnosed with detection of only one of the two variants necessary to confirm the diagnosis of an autosomal recessive disorder. Let us look into some of the recent publications that have solved this problem in some families by identifying the variants that usually escape detection in next-generation sequencing (NGS).

Cryptic second variants in autosomal recessive diseases with one mutation (Moore et al., 2023)

Moore and colleagues investigated definitive autosomal recessive diseases with one hit (only one mutation identified) for the second hit by whole genome sequencing. They studied 31 patients from the 100,000 Genomes Project who had only one mutation despite having a strong clinical suspicion of an autosomal recessive disease. Whole genome sequencing (short read) revealed a diagnosis in eight additional patients by finding the second mutation. These include a patient with cystic fibrosis harboring a novel exonic LINE1 insertion in *CFTR* and a patient with generalized arterial calcification of infancy with complex interlinked duplications involving exons 2–6 of *ENPP1*. They had to undertake optical genome mapping and RNA analysis for the *ENPP1* variant.

Retroelements are missed by exome sequencing and can be the second (missing) mutation in ataxia–telangiectasia (Zhao et al., 2023)

Retroelements (retrotransposons) are stretches of DNA that copy and paste themselves into different genomic locations (transposons). They do this by converting RNA back into DNA through the reverse transcription process. Examples include Long Interspersed Nuclear Elements-1 (LINE-1 or L1), SINE-VNTR-Alus (SVA) and pseudogene insertions. Retroelement insertions are already known to cause Mendelian disorders and might be amenable to antisense oligonucleotide therapy. Zhao and colleagues studied 237 patients with ataxia-telangiectasia who had whole genome sequencing data and checked for retroelement insertions. They observed 15 individuals harboring one of the five retroelements. While one was in the coding (exonic) region, the rest were integrated in the non-coding regions. RNA sequencing, RT-PCR, and/or minigene splicing assays were used to study the functional consequences of these insertions. Twelve out of 14 intronic insertions led to or contributed to loss of ATM function by exon skipping or activating cryptic splice sites. Interestingly, these were second (missing) variants in some and third variant in others! They estimate the contribution of retroelements to the genetic architecture of recessive Mendelian disorders as ~2.1%–5.5%.

Deletions and a complex insertion in hereditary hemorrhagic telangiectasia (Xiao et al., 2023)

Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome is caused by loss-of-function (LoF) heterozygous variants (and a

second hit at in the affected tissues) in *SMAD4*. Xiao and colleagues developed GROFFFY to prioritize variants in non-coding regions rich in transcribed and critical regulatory sequences. This is an analytic tool that integrates coordinates for regions with experimental evidence of functionality. They applied GROFFFY to the whole genome sequence data from solved and unsolved hereditary hemorrhagic telangiectasia recruits to the 100,000 Genomes Project. They detected three ultra-rare deletions within the 3' untranslated region (UTR) of the tumor suppressor gene *SMAD4* which disrupted the sequence context of the final cleavage and polyadenylation site necessary for protein production. In another individual, a complex insertion was identified. Four undiagnosed cases were thus solved.

DNA methylation signature for unsolved cases of Fanconi anemia (Pagliara et al., 2023)

Fanconi anemia results from inactivating biallelic (predominantly) mutations in one of about 20 genes in the DNA repair pathway. The wide spectrum of mutations and structural rearrangements make molecular diagnosis of Fanconi anemia challenging. Assessment of chromosomal fragility is often required to confirm the pathogenicity of the variants and to firmly establish the diagnosis. Pagliara and colleagues studied the peripheral blood genome-wide DNA methylation profiles in 25 subjects with molecularly confirmed Fanconi anemia and observed 82 differentially methylated CpG sites that allow distinguishing subjects with Fanconi anemia from healthy individuals and patients with other diseases. The episignature was validated using a second cohort of subjects with Fanconi anemia involving different complementation groups and documented its sensitivity and specificity. The episignature properly classified DNA samples obtained from bone marrow aspirates, demonstrating robustness. They also trained a machine learning tool for identifying DNA methylation signature for this condition.

To summarize, we need to look for complex rearrangements, retroelements, and alterations in regulatory regions whenever we do not have a diagnosis for a monogenic disease. Specific DNA methylation signatures might also be a tool for diagnosis of genetically heterogenous conditions like Fanconi anemia.

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Eighth Annual Conference of the Society for Indian Academy of Medical Genetics (IAMG 2023)

The 8th Annual Conference of the Society for Indian Academy of Medical Genetics (IAMG 2023) was organized by Sir Ganga Ram Hospital, New Delhi, and held at the Leela Ambience Hotel, Gurgaon from November 30th to December 2nd, 2023. Centred on the theme ***'Translating OMICS into Clinical Care'***, the conference was aimed to address the nuances of "BIG DATA" for patient diagnosis, novel gene discovery, cutting edge 'omic' technologies and functional assays to provide answers for patients and families with rare, undiagnosed disorders.

The two specialized pre-conference workshops on autism spectrum disorder and 'Hands-on Genomic Sequencing' set the stage, providing deep insights into these critical areas of genetic research. The latter entailed a dedicated interaction with the registered participants with preworkshop tutorials and hands-on genomic data visualization and interpretation. The feedback response to the workshops was very appreciative of the content and conduct of the session towards the aim to hands-on knowledge and ability enhancement.

Day 1 of the conference was replete with expert-led sessions focusing on advanced topics such as gene therapies, the use of animal models in medical research, and the intricate genetics of inflammatory bowel disease. The President's plenary session set the theme of the conference with information of the extensive ongoing genomic research in the country, thinking out of the box in this innovative landscape, especially addressed to the young geneticists, gene-disease correlation, and translation to the clinic. The Dr SS Agarwal Oration was awarded to Dr David Adams, National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH), USA. His oration was exemplary for the work performed with “patients without a diagnosis” despite a multitude of tests and evaluations. The day was further marked by the significant release of Carrier Screening Recommendations by SIAMG, alongside the Society of Fetal Medicine (SFM) and the Federation of Obstetric and Gynaecological Societies of India (FOGSI), followed by a series of intellectually stimulating debates

Day 2 commenced with engaging platform presentations, leading into insightful talks on dysmorphology, multi-omics, and the broad spectrum of applications of genetics in healthcare. A highlight was the presentation of the Dr IC Verma Outstanding Researcher Award to Dr Ashutosh Halder from the All India Institute of Medical Sciences (AIIMS), New Delhi, marking his contribution to the field of medical genetics in the country. An informative panel discussion on providing equitable access to genetic diagnosis and treatment provided many valuable insights. A session titled 'The Firing Brigade' offered young geneticists an exciting opportunity to present and discuss their innovative work in their early career path.

The final day continued the momentum with the presentation of the Dr SS Agarwal Young Scientist Award to Dr Neelam Saini from the Nizam's Institute of Medical Sciences (NIMS), Hyderabad, for her publication in the journal 'Prenatal Diagnosis'. The day was further enriched with discussions on various therapeutic approaches and cancer genomics, culminating in an informative quiz for residents and the valedictory session. This session not only wrapped up the event but also set the tone for future exploration and research in the field of OMICS.

The 182 selected abstracts from attending delegates were selected for poster or platform presentations and were judged by experienced geneticists for their scientific content, innovation, and presentation. Novel two-minute rapid-fire oral presentations were awarded to share the immense work happening in India.

In essence, IAMG 2023 served as a confluence of knowledge, innovation, and inspiration, fostering a spirit of learning and discovery. It was a platform to meet old friends, make new, and foster collaborations to work towards the SIAMG principles of “Test, Treat and Teach” to leave no patient behind.

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Awardees

Dr Shyam S Agarwal Oration for the Year 2023

Recipient - Dr David Adams

Dr David Adams, MD, PhD, Deputy Director of Clinical Genomics at the National Human Genome Research Institute, National Institutes of Health (NIH), Bethesda and Co-Director of the NIH Undiagnosed Diseases Program, is a world-renowned expert in the field of medical genetics. His clinical and research contributions, particularly in the area of undiagnosed rare disorders, have been immense. His current research focuses on the development of informatics tools for Undiagnosed Diseases and bioinformatics approaches for reanalysis of negative or inconclusive clinical genomics studies, and creation of data sharing strategies for undiagnosed disease cases. His other research interests include the molecular biology of oculocutaneous albinism and the mucosal biology of celiac disease. During his distinguished medical career spanning around three decades, Dr Adams has published more than 100 peer-reviewed papers. He has been conferred several awards and distinctions for his outstanding academic and research work including the NIH Director's Award for his work on the NIH Common Fund Undiagnosed Diseases Network Working Group.

Dr I C Verma Outstanding Researcher Award for the Year 2023

Recipient – Dr Ashutosh Halder

Dr Ashutosh Halder, Professor and Head of the Department of Reproductive Biology at the All India Institute of Medical Sciences (AIIMS), New Delhi, is a well-known and respected figure in the field of medical genetics in India. His research primarily focuses on reproductive biology and prenatal genetics, including the genetic basis of recurrent pregnancy losses, premature ovarian failure, preimplantation biology, and fetal malformations. He has published over 100 research papers, edited four books, and authored many book chapters. He is a fellow/ member of several prestigious academic bodies including the National Academy of Medical Sciences and the Indian Academy of Biomedical Sciences. He has led several institutional and extramural research projects as principal investigator. He has mentored around 15 PhD scholars. He is recognized as one of the leading experts in India in the area of molecular cytogenetics and has been instrumental in establishing a state-of-the-art Molecular Cytogenetics laboratory in AIIMS, New Delhi. He is on the editorial board of many journals and is peer reviewer for numerous national and international journals. He is a Core Accreditation Committee member of NABL for Genetics, a Task Force Member and Assessor for Medical Genetics of the National Medical Commission of India, and an expert member of several other national committees.

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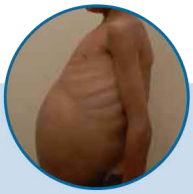

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