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GeneDit

A Million Dollar Question

Editorial

US $ 375,000 per year, US $ 365,000 per year, US $ 200,000 per year- these are costs of medicines per year per patient for some genetic diseases. And these treatments need to be continued lifelong. Many of us cannot even imagine these costs. It is like a mirage - the treatment is available but out of reach of many. Till date most treatments were affordable at least for rich patients, but these newer costly therapies seem to be beyond the reach of rich families as well. These diseases include Gaucher disease for which the deficient enzyme became available for treatment in 1991 as a prescription drug. The successful strategy to target the enzyme to its intracellular location of action was applied to many other lysosomal storage disorders like Hurler disease, Hunter disease, Maroteaux Lamy syndrome, all of which are types of mucopolysaccharidoses and to Pompe disease which is a glycogen storage disease. The results are miraculous. The facial coarsening, skin thickening, joint contractures and organomegaly improve as the intracellular deposited material gets mobilized and broken down. The appearance of these MPS patients, once described as '*Gargoylism*', melts to normal over a period of months to years. Children with Pompe disease, if started on enzyme replacement therapy during the neonatal period, attain normal milestones and do not develop cardiac dysfunction. Of course the treatment needs to be continued lifelong. One more disease which needs mention is Fabry disease, a disease with nonspecific symptoms and a cause of stroke or cardiac dysfunction in young adults. It is also responsible for 1% of cases with chronic renal failure. Due to non specific neuralgic pain without signs and inadequate awareness about the disease, the duration between onset of symptoms and diagnosis, if it happens, is usually more than a decade. Now as the enzyme replacement therapy (ERT) is available, early diagnosis is important. The timely initiation of treatment not only improves the quality of life by reducing pain but also reduces the risk of damage to the heart and kidneys and of stroke.

These enzyme replacement therapies are major milestones in medicine and in the treatment of genetic disorders. The minds where the ideas were generated, beautiful and technologically innovative experiments in laboratories and on animal models and double blind clinical trials confirming the efficacy of the drugs, cost a fortune. No doubt the cost will have to be recovered when the drug is marketed. But the costs are exorbitant as described by treating doctors in the US. Forbes has listed these drugs as one of the ten costliest drugs. Another such drug is Ivacaftor, approved for cystic fibrosis cases with a specific mutation. This drug is one of the fastest drugs to reach the market from its inception. The cost is US $ 311,000 per patient per year. Monoclonal antibody for the treatment of paroxysmal nocturnal hemoglobinuria is costing US $ 409,500 per patient per year. These costs are much more as compared to costly drugs like Zyprexa for schizophrenia (US $ 7,000) and Avastin for cancer (US $ 50,000). Though the cost may be justified as the cost of innovation, who pays for it? Even in developed countries, the rich patients also will not be able to pay from their pockets. It should be remembered that many patient support groups like the Cystic Fibrosis Foundation and the Duchenne Muscular Dystrophy Foundation have been supporting research in the development of therapeutics for these disorders.

The rarity of these disorders contributes to the high costs of these drugs. The limited market for each of these drugs makes them extremely costly. Most of these diseases have a prevalence of 1 per 40,000 or 1 lakh. Cystic fibrosis is relatively common as compared to lysosomal storage disorders. There are about 30,000 people with cystic fibrosis in USA. Out of them only 4-5% have the mutation G551D mutation and only these individuals will be benefited by Ivacaftor. For such rare and neglected diseases, there is a concept of rare or orphan diseases, words which are used interchangeably. There are about 5000 to 7000 rare diseases and 80% of them are genetic. For about 400 of

them the treatment is available. United States has the Rare Diseases Act of 2002 which defines *rare disease* as any disease or condition that affects less than 200,000 people in the United States, i.e. about 1 in 1,500 people. This definition is essentially like that of the Orphan Drug Act of 1983, a federal law that was written to encourage research into rare diseases for possible cures. In Japan, the legal definition of a rare disease is one that affects fewer than 50,000 patients in Japan, or about 1 in 2,500 people. The European Commission on Public Health defines rare diseases as "life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them." They have excluded rare diseases without significant mortality or morbidity. The European Organization for Rare Diseases (EURORDIS), the NIH's Office of Rare Diseases Research (ORDR), the National Organization for Rare Disorders and the Canadian Organization for Rare Disorders (CORD) are organizations working for rare and orphan diseases. India does not have any such separate approach to rare or genetic diseases or public programs for treatment or prevention of them.

Though individually rare, given the large population of India, the absolute numbers of many of these diseases will be quite large. The presence of high degree of consanguinity in some populations makes one feel that the numbers may be higher than expected. As the new treatments are becoming available for rare diseases and the mortality due to infectious and malnutrition-related diseases is decreasing, it is high time that the medical policy makers look at these diseases with priority or at least do not neglect them. The beginning has been made. In many states the government has taken up the responsibility of providing anti-hemophilic factors free of cost to the patients. This is mainly due to the efforts of the long standing and active Hemophilia Federation of India. In some states the decision came through the court of law. Though anti-hemophilic factors for home therapy has not been made available to the patients, serious life-threatening bleeding episodes of many patients are being managed satisfactorily and elective and emergency surgeries are being done, when needed. Some state governments have made iron chelation therapy free for patients with beta thalassemia. All these efforts reflect the initiative taken by active patient support groups.

It is painful for parents and doctors to see a patient suffering or dying of a treatable disorder. This is still a reality in India as government health care is not satisfactory and state-of-the-art treatments though available in India are accessible many a times to only people of high socioeconomic strata. As the country's governance improves and India marches towards the status of a developed country, the optimal health care facilities for common and rare diseases need to be made available for one and all. The main issue of exorbitant prices of these new drugs will continue to prevent access to these newer treatments for Indian patients, rich and poor alike. The drug companies need to think about it. Their golden research needs to reach all patients worldwide. This will not be possible till the prices are reduced drastically. The economics of drug development, profits targeted, etc. are different in this new era of personalized medicine where there is a separate drug for each mutation and there will be new medicine for each cancer genome. These need to be looked at in a global perspective. From our side India needs to look at the issue from multiple perspectives. Encouraging basic research and drug development is a necessity of the present time. Technology and scientists are available in India to tap the research funding. The second is working with drug companies for pricing and also organizing a very good government health care system with a three tier referral system. This will help us to get area-wise data of patients of various disorders needing lifelong treatment. Electronic health records, if implemented for all, will make such data collection easy. The Hemophilia Federation and hemophilia centers, for instance, have data of patients registered with them, though many cases still remain undiagnosed and die undiagnosed in the population. The data and facts about hemophilia patients helped the policy makers in calculating the budget and in effectively planning the hemophilia management program. Collecting data about population based prevalence is difficult or still next to impossible in India. But we doctors, especially geneticists working for these rare disorders, can maintain a registry of these patients, which will go a long way in carrying out research and establishing patient care facilities for these individuals suffering from rare disorders.

The task ahead is difficult but the march towards the goal has already begun!

Dr. Shubha R Phadke
1st July, 2014

Compound heterozygosity for p.F508del mutation and deletion of exons 4-11 in CFTR in an infant with cystic fibrosis- Limitations of ARMS-PCR and Sanger sequencing

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Summary

Cystic fibrosis (CF) is a life threatening genetic condition caused due to mutations in the *CFTR* gene. This is an autosomal recessive condition and usually parents are carriers of a heterozygous mutation in the *CFTR* gene. We describe an infant diagnosed with the severe phenotype of CF and detected to be homozygous for p.F508del by ARMS-PCR. However, parental studies confirmed carrier state in mother but the father showed a wild allele by ARMS-PCR and sequencing. This prompted us to look for uniparental disomy (UPD) and large deletions. UPD was ruled out by studying both intragenic and extragenic markers for chromosome 7. The proband and the father were found to have a large deletion detected by MLPA involving exons 4-11 in the *CFTR* gene which includes the region coding for phenylalanine at position 508. This case highlights the need of caution when interpreting results of molecular genetic testing during genetic counseling. It is the first documented case from India with point mutation and large deletion of the *CFTR* gene giving rise to apparent homozygosity for p.F508del.

Case Report

A 5 month old boy diagnosed with CF was referred to the Clinical Genetics Unit of Christian Medical College, Vellore by the Department of Child Health for molecular confirmation and genetic counselling. He was the first offspring of non-consanguineous parents born through LSCS. He weighed 2.5 kgs at birth and was admitted in the nursery for one week with respiratory distress probably secondary to meconium aspiration and managed conservatively.

Previous history of recurrent hospital admissions for pneumonia, passage of oily loose stools and failure to thrive was obtained from the parents. The current admission was for severe pneumonia leading to unstable vital signs and probable hypoxic seizures requiring ventilation.

He had achieved partial head control and had been immunised till the age of 6 weeks. The family history was unremarkable.

His length at 55cms and weight at 2.5kgs, were <3SDs below the age related mean; the head circumference at 38 cms was normal. There were no dysmorphic features. Chest examination revealed crepitations and conducted sounds with decreased bilateral air entry. The liver was palpable 1 cm below the right costal margin and rest of the physical examination was normal. The child was treated with infusion of antibiotics and antiepileptics. Stool examination showed numerous fat globules. He was started on nasogastric feeds on day 4 of hospitalization. His high grade fever persisted and he deteriorated despite all supportive measures and succumbed to his illness.

Molecular analysis was done for confirmation of diagnosis and genetic counseling. Preliminary genetic counseling was given and parents agreed for carrier testing as they were considering prenatal diagnosis for future pregnancies.

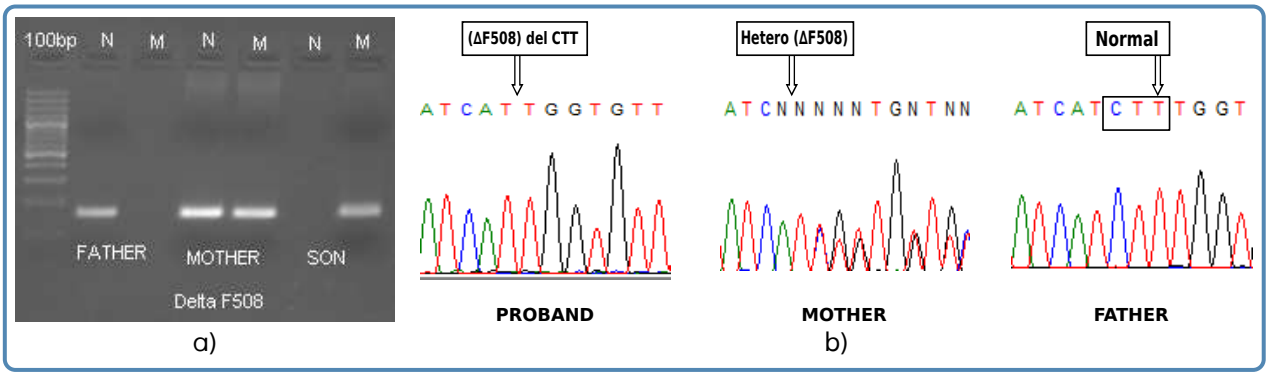

Figure 1 a). Gel picture of ARMS-PCR of proband and parents showing normal father, heterozygosity of del F508 for mother and homozygosity of del F508 for proband. N- normal M- Mutant.
b). Sequencing chromatogram showing homozygosity for p.F508del in proband, heterozygosity in mother but normal result in father.

Material and Methods

Genomic DNA was extracted from leukocytes using QIAGEN Midi Kit. ARMS-PCR was done for the p.F508del mutation.[1] Sequencing was done (Applied Biosystems Genetic Analyzer 3500) to confirm the mutations detected by ARMS-PCR. Further molecular analysis was done using four intragenic (T854T, M470V, TUB9, TUB 20) and two extragenic (XV 2C, KM19) markers for chromosome 7. Specific primers were used according to previously described methods and the amplified products were restriction digested using *TaqI*, *PstI*, *MnlI*, *HphI*, *AvaII*, *PvuII* for XV2C, KM19, TUB9, M470V, T854T and TUB20 respectively.[2] The products of XV2C, KM19, M470V, T854T were separated using 2% agarose gel and TUB 9 and TUB 20 were separated using 8% native polyacrylamide gel electrophoresis (PAGE). Six VNTR markers were studied to rule out false paternity. To identify larger deletions affecting whole exons of the CFTR gene, the sample was sent to the Institute of Human Genetics, University Hospital, Technical University RWTH Aachen, Aachen, Germany where commercially available MLPA (multiplex ligation dependent probe amplification) assay for CF (P091; MRC Holland/Amsterdam/NL) was used according to the manufacturer's instructions.

Results

The mutation analysis for *CFTR* by ARMS-PCR[3] showed a pattern consistent with homozygous mutation for p.F508del. Genetic testing of the parents showed only mother as carrier and father had the wild type allele (Fig 1a). Sequencing results confirmed the pattern seen by ARMS-PCR (Fig 1b). Six VNTR markers confirmed the paternity. Intragenic and extragenic markers for chromosome 7 showed presence of both parental alleles for XV2C, KM19 T854T and TUB20. However the results for markers TUB9 and M470V were not compatible with paternal inheritance as only maternal alleles were detected. (Figure 2a,2b) The interpretation is as follows: the digested product of M470V (g.1540 A>G) using HphI yields one fragments at 492bp for homozygous allele 1, three fragments at 492bp, 301bp and 191bp for heterozygous allele 1 and allele 2, and two fragments at 301bp and 191bp for (homozygous allele 2). The digested product of TUB 9 (g.1525-61 A or G) using MnlI yields four fragments 199bp,147bp, 130bp and 15bp for homozygous allele 1, four fragments at 199bp, 147bp,130bp and 95bp (for heterozygous allele 1 and 2) and five fragments at 147bp,130bp,104bp,95bp and 15bp in the case of homozygous allele 2. Thus UPD was ruled out but deletion/ chromosomal rearrangement was suspected due to presence of only maternal alleles located near exon 10 of *CFTR*. DNA analysis by MLPA at the Institute of Human Genetics in Aachen revealed that the proband carried a large scale heterozygous deletion spanning exons 4-11. The same deletion was detected in the father.

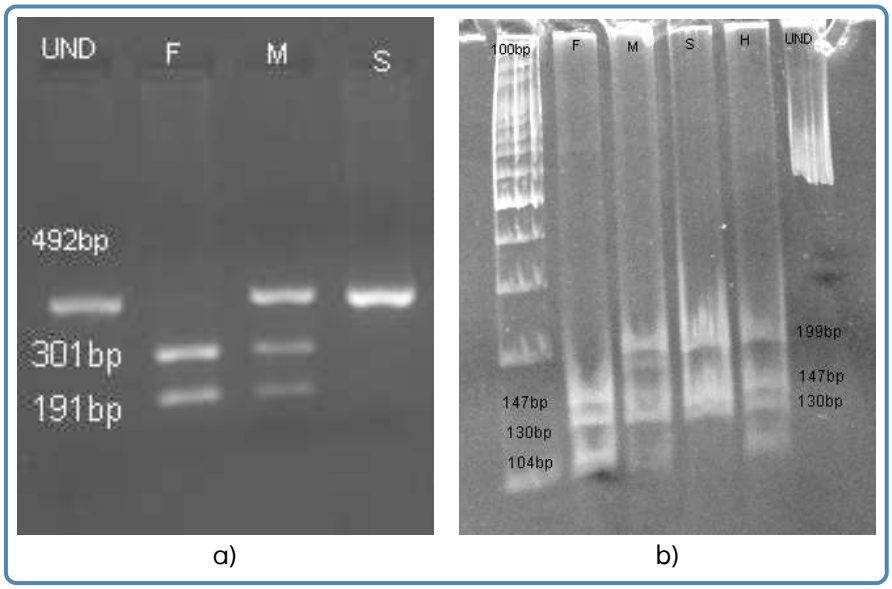

Figure 2 a). Markers status for M470V (HphI digest) F- Father's alleles 2/2 M- Mother's alleles 1/2 S- Son's alleles 1/1 UND– Undigested Product.
b). TUB 9 marker study (MnlI digest) by PAGE Well 1–100bp ladder. The digested product of TUB 9 (g.1525-61 A or G) using MnlI yields four fragments 199bp, 147bp, 130bp and 15bp for allele 1 and five fragments at 147bp, 130bp, 104bp, 95bp and 15bp for allele 2. F- Father has allele 2 which has 5 fragments - 147, 130, 104 bp are seen and the smaller fragments (95 and 15 bp) which are not seen. M- Mother has 1 & 2 alleles (total 6 fragments) -199, 147, 130, 104 bp are seen and the two smaller fragments are not seen. S- Son has allele 1/1 showing 199, 147, 130 bp; the 104 bp is not seen. H- Healthy.

Discussion

Over 1900 different mutations have been identified in the *CFTR* gene (www.genet.sickkids.on.ca/). The most common mutations are c.1521_1523delCTT (p.F508del), c.1652G>A, c.1641G>T and c.489+1G>T.[3] The mutation p.F508del (c.1521_1523delCTT), a deletion of three nucleotides resulting in removal of phenylalanine at position508, is the cause of CF in majority of cases. It has a frequency of 66% in cases of CF worldwide.[4] One study showed that affected individuals of Indian origin have a frequency of p.F508del mutation ranging from 19% to 44%., while another Indian study showed 20 CF cases out of 100 to be homozygous for p.F508del and 13 cases to be heterozygous for this mutation.[5,6] Cases with the p.F508del mutation had a more severe phenotype. Single or multi exonic large deletion may be present in combination with point mutations in *CFTR* on rare occasions.[7] These can account for 1% to 3% of affected individuals.[8] In the present case either maternal UPD or a large gene rearrangement was suspected when routine molecular methods showed apparent homozygosity for p.F508del, which was incompatible with the parental genetic status.

A recent study showed that the frequency of large scale gene deletions differs from population to population. The actual frequency of large scale deletion of the *CFTR* gene is still not clear since routine diagnostic analysis involves detection of point mutations and small indels only and large scale deletions can be missed out. Advanced techniques like MLPA, quantitative PCR and array CGH (comparative genomic hybridization) can be used to rule out the apparent homozygosity of point mutations and indels.[9] Chevalier-Porst et al. reported 24% large deletions in a cohort of 1600 CF alleles tested. This French study reported two patients, a boy diagnosed with classical CF at one year harbouring a deletion of 95.738 kb size which removed the coding sequence from exon 2 to exon 10, and a girl with reported deletion of exon 4–10. Both the cases had the p.F508 mutation in the second allele

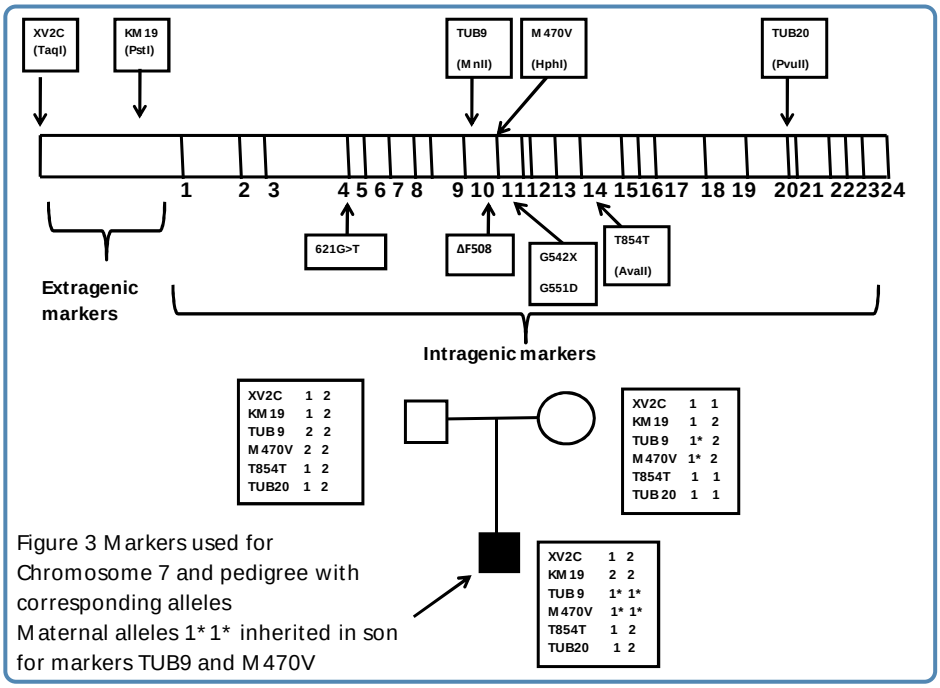

Figure 3 Markers used for Chromosome 7 and pedigree with corresponding alleles. Maternal alleles 1*1* inherited in son for markers TUB9 and M470V.

inherited from the mother while the large deletion was inherited from the father, as in the present case.[10] In this case two extragenic markers and four intragenic markers ruled out UPD. Two intragenic markers near exon 10 showed both alleles to be maternal further increasing the suspicion of deletion. MLPA confirmed a large scale heterozygous deletion involving exons 4–11. This genotype detected was associated with a very severe phenotype in the proband leading to death in infancy. This is the first such case from India described in literature proving the importance of rarer *CFTR* rearrangements which can have implications for genetic counseling and prenatal diagnosis. This also highlights the limitations of ARMS-PCR and Sanger sequencing in detecting large genomic deletions in many single gene disorders. Hence, interpretation of molecular genetic results has to be carried out with caution while counseling a family.

Acknowledgements

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Distal Arthrogryposis

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Introduction

Congenital multiple joint contractures involving two or more body areas are collectively termed as arthrogryposis. Based on the extent of joint involvement (proximal and/or distal joints), neurological involvement, and involvement of other parts of the body/other organs the etiology and prognosis of arthrogryposis differs.[1] Various etiologies of arthrogryposis include single gene mutations, chromosomal anomalies, and intrauterine environmental factors (e.g. fetal crowding, failed termination of pregnancy).[1,2] Distal arthrogryposis (DA) are a subset of arthrogryposis characterized by congenital joint contractures predominantly affecting joints of the hands and feet (distal joints) with or without associated anomalies.[3] Here we discuss DA – its types, clinical presentation, inheritance and genes, prognosis and genetic counseling.

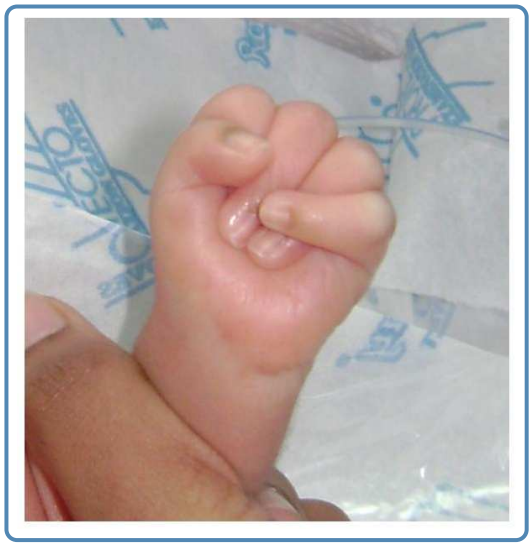

Figure 1 Clenched hand at birth.

Definition and Diagnostic criteria

According to Bamshad et al., DA are defined as disorders predominantly affecting the limbs in the form of congenital joint contractures in two or more body areas without any underlying neurologic and/or muscle pathology.[3]

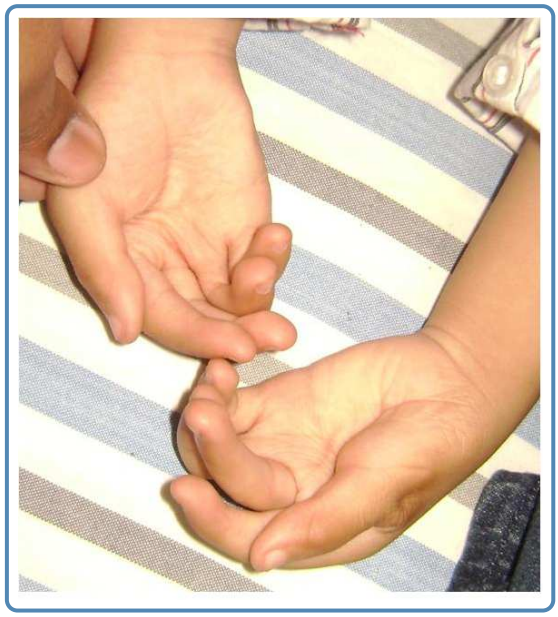

Figure 2 Ulnar deviation of fingers with contractures, faint flexion creases and adducted thumb.

A diagnosis of DA should be considered in any child with predominant involvement of joints of the hands and feet, presenting with upper extremity features of clenched fingers at birth (Fig 1), ulnar deviation of fingers, flexion contractures of fingers (Fig 2), and hypoplastic and/or absent flexion creases, and lower extremity features of clubfoot, calcaneovalgus deformities, metatarsus

varus and/or vertical talus (prominent heels or rocker bottom feet)(Fig 3). There might be variable involvement of proximal joints of both the upper limb and lower limb. Based on the associated anomalies in systems other than skeletal system (face, eye, spine and other organ systems), DAs are further classified into subtypes.[3]

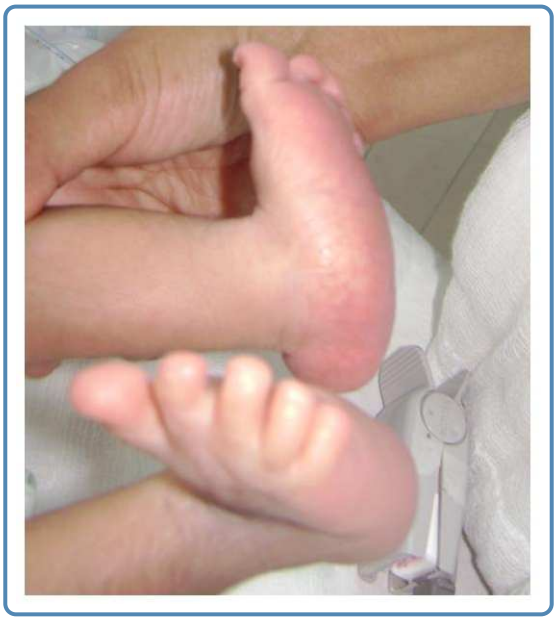

Figure 3 Rocker bottom feet.

The clinical features of DAs show marked interfamilial and intrafamilial variability. In some families a carrier might be completely unaffected or might have mild clinical manifestations like absent palmar flexion creases, toe contractures, mild flexion contractures of fingers noticed at birth etc. As suggested by Bamshad et al. the above mentioned definition/diagnostic criteria (two major diagnostic criteria involving the upper limb and lower limb) of DA should hold true for at least one member of the affected family and for other family members mild clinical features can be considered for the diagnosis. Further, molecular genetic testing might help to confirm the diagnosis in mildly affected individuals and obligate carriers.[3]

Incidence

Incidence of arthrogryposis is around 1 in 3000 births.[1]

Inheritance and Genes

Most of the DAs are inherited as autosomal dominant disorders with both interfamilial and intrafamilial variability.[1,3] Some of the DAs are also inherited as autosomal recessive disorders.[3,4] Most genes causing DA are the ones that code for contractile proteins of fast-twitch muscle fibers.[3]

Classification

Based on the above definition and diagnostic criteria, 10 types of DA have been identified. Table 1 summarizes the clinical features and genetics of different types of DA.

Clinical features

Majority of DAs are inherited as autosomal dominant disorders with variable clinical features.[1,3] DA type 1 is classified into type 1A and 1B based on the chromosomal locus, otherwise clinically they are indistinguishable. In DA type 1, around 98% of the cases have typical manifestations of the hand and 88% have typical manifestations of the feet. The face is normal and there are no associated anomalies.[9] DA type 2 is classified into 2A and 2B, which are differentiated by the facial features. Facial features of DA2A include deep-set downslanting eyes, hypertelorism, small mouth, puckered lips, H-shaped chin dimple, small nose, long philtrum, and mild micrognathia.[10] Some of the other features in DA2A include scoliosis, hip dislocation, strabismus and cryptorchidism. Facial features in DA2B include triangular face, downslanting eyes, prominent nasolabial folds, small mouth and pointed chin. Variable clinical features include proximal joint involvement, short stature and short webbed neck.[9,10] In a recent article by Beck AE et al. mutations in four genes (*TNNI2*, *TPM2*, *TNNT3* and *MYH3*) have been found to cause both DA1 and DA2B; therefore, authors suggest that DA1 and DA2B should be considered as a single disorder representing a spectrum of manifestations. On sequencing of these four genes, mutations were found in 29% of DA1 cases and 40% of DA2B cases.[5]

DA type 3 is characterized by finger contractures and cleft palate. Variable features include hip dislocation, patellar dislocation, talipes equinovarus, hearing impairment, scoliosis and limitation in elbow joint movements.[3,5]

Type of DA	Clinical features	Intelligence	Synonyms	Inheritance	Genes
DA type 1 (1A & 1B)	Typical involvement of hands and feet	Normal	–	AD[#]	*TNNI2*, *TMP2*, *TNNT3*, *MYH3*, *MYBPC1*[5,6]
DA type 2A	Typical involvement of hands and feet, typical facies[*]	Normal	Freeman-Sheldon syndrome	AD	*MYH3*[7]
DA type 2B	Typical involvement of hands and feet, typical facies[*]	Normal	Sheldon-Hall syndrome	AD	*TNNI2*, *TMP2*, *TNNT3*, *MYH3*[5,6]
DA type 3	Finger contractures, cleft palate, talipoequinovarus	May have intellectual disability	Gordon syndrome	AD	–
DA type 4	Finger contractures, scoliosis	May have intellectual disability	–	AD	–
DA type 5	Finger contractures, ophthalmoplegia, ptosis	Normal	–	AD, AR[θ]	*ECEL1* (AR)[4]
DA type 6	Finger contractures, sensorineural hearing loss	Normal	–	AD	–
DA type 7	Trismus, camptodactyly on dorsiflexion of wrist	Normal	Trismus-pseudo-camptodactyly syndrome	AD	*MYH8*[8]
DA type 8	Typical involvement of hands and feet, multiple pterygia, typical facies[*]	Normal	–	AD	–
DA type 9	Finger contractures, arachnodactyly, external ear deformity	Normal	Congenital contractural arachnodactyly (Beals syndrome)	AD	*FBN2*

[*] For facial description see text.
[#] AD – Autosomal dominant.
[θ] Autosomal recessive.
TNNI2 – Troponin I; TMP2 - Tropomyosin 2; TNNT3 – Troponin T3; MYH3 – Myosin heavy chain 3; MYBPC1 – Myosin-binding heavy protein C; MYH8 - Myosin heavy chain 8; FBN2 – Fibrillin 2.

Table 1 Clinical characteristics, inheritance and the known causative genes of different types of DA

DA type 4 manifests with finger contractures and scoliosis. Variable features include intellectual disability and limitation of elbow joint movements.[3,5]

DA type 5 is inherited as both an autosomal dominant and autosomal recessive disorder. Along with finger contractures and feet involvement, eye findings are peculiar to patients with DA5. Variable eye features include ophthalmoplegia, strabismus, ptosis, pigmentary maculopathy, keratoconus and an abnormal electroretinogram. Some cases are known to have pulmonary hypertension secondary to restrictive lung disease.[3,5] Based on the eye and other findings, DA5 has been classified into four subtypes (DA5A-D).[4] DA5D is inherited as an autosomal recessive disorder.

DA type 6 is characterized by distal limb contractures and sensorineural hearing loss.[3,5]

DA type 7 is characterized by inability to open the mouth and flexion of fingers on dorsiflexion of the wrist. Variable clinical features include talipes equinovarus, hip involvement, short leg muscles and short stature.[3,5]

In DA type 8, along with typical manifestations in the hands and feet, patients present with multiple pterygia, scoliosis with vertebral segmentation defects, facial features, short neck and short stature. Facial features include ptosis, downslanting eyes, low set ears, and high arched palate. It is an autosomal dominant disorder, with most cases occurring sporadically due to de novo mutations. The other conditions which present with similar clinical features include autosomal recessive multiple pterygium syndrome (Escobar syndrome), X-linked multiple pterygium syndrome and a lethal form.[3,5]

DA type 9 is characterized by finger contractures and crumpled ears. Variable clinical features include scoliosis, limitation of elbow and hip joint movements, valvular heart disease and talipes equinovarus.[3,5] DA9 is caused by *FBN2* (fibrillin 2) gene mutations, with most of the mutations occuring in exon 23 to exon 34. Some patients with the severe form of DA9 can simulate neonatal Marfan syndrome.[11] Crumpled ear is used as a hallmark to identify patients with DA9.

Management and Genetic counseling

Management of patients with DA should involve various specialties (clinical genetics, orthopedics, neurology, pediatrics and physiotherapy). Joint contractures and skeletal complications (scoliosis) are managed by physical therapy and/or surgery. Patients requiring surgery might face difficult intubation and are at risk of malignant hyperthermia (documented in some of the subtypes). Inheritance is autosomal dominant in most of the cases. Mutations can occur de novo (sporadic), in which case the risk of recurrence in siblings is negligible. If the mutation is inherited from one of the parents, the risk of recurrence is 50% for the siblings. Molecular genetic testing and identification of the causative gene mutation help in providing an accurate risk of recurrence and appropriate genetic counseling. In cases with autosomal recessive inheritance, the risk of recurrence in siblings of an affected individual is 25%.

Prenatal diagnosis can be achieved by ultrasound (less accurate) and molecular genetic testing, if the underlying gene mutation is known (more accurate).

Author suggests readers the recent article on *Arthrogryposis: Diagnostic approach to etiology, classification, genetics and general principles* by Dr Judith G Hall published in *E J Med Genet* (2014) for updated clinical approach and list of genes.

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GeNeViSTA

Approach to a Child with Dysmorphism/ Congenital Malformation

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Definition

Dysmorphology is a discipline of clinical genetics which deals with the study of abnormal patterns of human growth and with the recognition and study of congenital human structural anomalies and patterns of birth defects.

Congenital malformations/ birth defects can be sub-classified as major or minor anomalies.

- Major anomalies are those that interfere with the normal functioning of an individual and pose a significant health problem or risk to life. E.g. congenital heart defects, neural tube defects, omphalocele, cleft palate etc.
- Minor anomalies do not interfere with the normal functioning of an individual and usually are only of cosmetic significance. E.g. simian crease, accessory nipple, clinodactyly, pre-auricular skin tag etc.

Major anomalies are present in 2-3% and minor anomalies are present in around 15% of live births. Minor anomalies are usually associated with an increased risk of associated major anomalies and therefore presence of minor anomalies should prompt a thorough search for associated major anomalies.

Classification of congenital anomalies

Congenital anomalies are classified, on the basis of the developmental stage in which the insult occurred, the process that caused the change and the end result, into:

- Malformation: Primary intrinsic developmental defect usually caused by genetic/ environmental/ multi-factorial causes (recurrence risk varies accordingly) which occur during the period of organogenesis which is up to 8 weeks post fertilization for most organs. E.g. neural tube defect, ventricular septal defect, polydactyly etc.
- Deformation: Distortion of a normally developed structure caused by mechanical forces usually in the latter half of gestation and most often involving musculo-skeletal tissues. E.g. club foot, torticollis, plagiocephaly etc.
- Disruption: Breakdown of an intrinsically normally developing/ developed tissue due to some disruptive event such as a mechanical, vascular or infectious insult. E.g. amniotic band sequence.
- Dysplasia: Abnormal cellular organization within a tissue, almost always of genetic cause. E.g. skeletal dysplasias.

A syndrome is a recognized composite pattern of 2 or more anomalies with a common specific aetiology. E.g. Turner syndrome, fetal phenytoin syndrome etc.

An association is a non-random occurrence of 2 or more anomalies that occur together more frequently than expected by chance alone, but without a known specific aetiology. E.g. VACTERL (vertebral defects, anal atresia or stenosis, cardiac defects, tracheo-esophageal fistula, radial defects and renal anomalies, limb defects) association.

A sequence is a pattern of anomalies resulting from a single primary anomaly or factor E.g. Potter sequence (Primary anomaly - bilateral renal aplasia/ dysplasia → decreased fetal urine production → severe oligohydramnios → compressive effects → flattened facies with flattened nose, deformed ears, pulmonary hypoplasia & positional limb defects).

Approach to a case with dysmorphism

The following step-wise clinical approach should be followed in the assessment and management of an individual with dysmorphism or congenital malformation(s):

1. Suspicion of a genetic etiology
2. Clinical evaluation
   - history
   - physical examination
3. Investigations
4. Analysis and diagnosis
5. Confirmation
6. Intervention:
   - treatment
   - counseling
   - prenatal diagnosis
7. Surveillance & follow up

Suspicion of a genetic etiology

A genetic aetiology should be suspected in any individual with the following:

- Congenital anomalies: at least 1 major/ > 2 minor anomalies.
- Growth deficit (short stature/ failure to thrive)
- Developmental delay, intellectual disability or developmental regression
- Failure to develop secondary sexual characteristics
- Abnormal genitalia
- Appears 'different'/ 'unusual'

History

A detailed history covering the following aspects should be obtained:

- Prenatal history:
  - Teratogenic exposures especially in the first trimester of pregnancy: infections/ medications/ drugs of abuse/ maternal illness/ radiation exposure
  - Prenatal complications and antenatal ultrasonographic findings
- Perinatal history:
  - Presentation/ mode/ complications of delivery
  - Gestational age and condition (Apgar score) at birth
  - Birth weight, birth length and head circumference; body proportions
- Neonatal course:
  - Feeding and activity
  - Any adverse events/ complications
- Post neonatal:
  - Physical growth
  - Developmental milestones
  - Neurological symptoms especially seizures / visual or hearing deficits/ behavioural phenotype
  - Other systemic symptoms
- Family history:
  - At least three generation family history / pedigree
  - History of recurrent pregnancy losses/ infertility
  - Specific information/ medical records of other affected family members
  - Consanguinity in parents
  - Ethnic background

Physical examination

A thorough clinical examination must be done taking the following aspects into consideration:

- General principles:
  - Thorough head to toe examination to be done.
  - Measurements to be taken and compared with standard tables/ graphs of age and gender norms.
  - Both parents and other available family members to be examined for similar or related features.

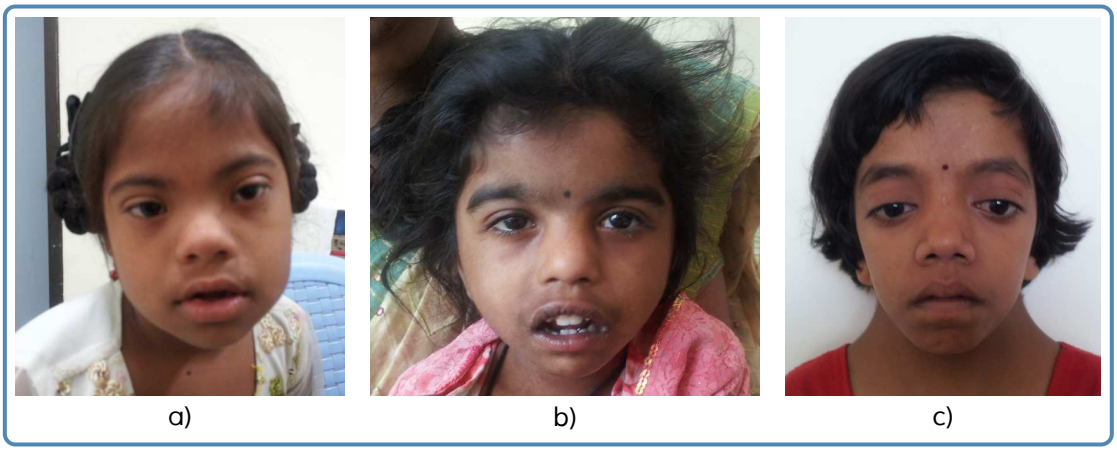

Figure 1 Typical gestalt of some syndromes. a). Down syndrome; b). Cornelia de Lange syndrome; c). Noonan syndrome.

- Clinical photographs to be taken with informed consent of individual/ parent/ guardian: for records, syndrome search, referral and study of evolution of the phenotype.

- Anthropometric measurements:
  - Height/ length, weight, head circumference
- Assessment of proportionality & symmetry:
  - Upper segment/ lower segment ratio
  - Arm span
  - Individual limb segment measurements (in specific cases)
- Head to toe assessment: (for exact description of each feature refer to Am J Med Genet A 2009 Jan; 149A (1) & Aase JM Diagnostic Dysmorphology textbook).
  - Each body part to be examined carefully from head to feet to look for anomalies
  - Cranium – size; fontanelles; sutures; shape and symmetry
  - Scalp hair - colour and texture; distribution; hair whorl patterns; position of anterior and posterior hairline
  - Face
    * overall impression of facial appearance: *gestalt* e.g. Down syndrome facies, coarse facies, myopathic facies. See figure 1.
    * overall shape, symmetry and size of face: triangular/ broad/ round
    * face to be divided into sections: forehead, midface and oral region
    * face to be viewed from front and from side
    * lateral profile better for: depth or height of structures such as nasal bridge, position of mandible relative to maxilla and midface development
  - Facial measurements:
    * Interpupillary distance, inner canthal distance, outer canthal distance, interalar distance, philtral length, upper lip thickness, lower lip thickness, intercommisural distance
    * Measurements to be compared to age and sex norms ($<$ or $>$ 2SD $\Rightarrow$ abnormal)
  - Forehead - Size: small/ broad/ tall; Shape: sloping/ frontal bossing/ bitemporal narrowing/ metopic prominence; Supraorbital ridges: prominent/ underdeveloped
  - Maxilla/ midface –
    * Cheek bone: prominent/ underdeveloped/ fullness
    * Malar region: prominence/ flattening
    * Midface: prominence/ retrusion
    * Nasolabial folds: prominent/ underdeveloped

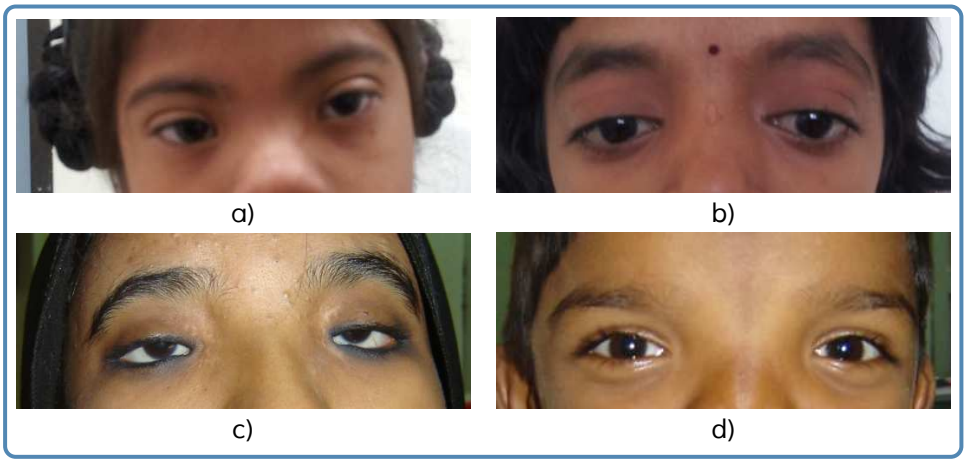

Figure 2 Dysmorphic findings in the eyes. a). Upslanting palpebral fissures and epicanthal folds; b). Downslanting palpebral fissures; c). Blepharophimosis and epicanthus inversus; d). Telecanthus.

- Mandible - size & shape: micrognathia/ retrognathia/ prominence
- Eyes- eyebrows; palpebral fissure length (short/long); palpebral fissure slant (up/down); epicanthic folds; eye spacing (use a rough guide of 1:1:1 for ratio of left palpebral fissure length: inner canthal distance: right palpebral fissure length); palpebral fissure shape; iris colour; pupil shape; cornea/ sclera/ lens; globe position (assessed from lateral view: protuberant vs deep set globes). See figure 2.
- Nose – nasal root; nasal bridge : depressed/prominent/broad; nasal tip: broad/ flattened; columella (the vertical ridge separating the nostrils): wide/ overhanging; nostrils : patency and position (anteverted); alae nasi. See figure 3.
- Mouth and perioral region - mouth size and shape; upper and lower lip shape and thickness; gum thickness; philtrum definition and length; jaw position (prognathia/micrognathia); palate shape
- Oral cavity - teeth/ frenulum/ tongue size and morphology
- Ears
  - * Ear position
  - * Ear rotation (normally 15 degrees posterior to the vertical plane of the head): anteriorly/ posteriorly rotated

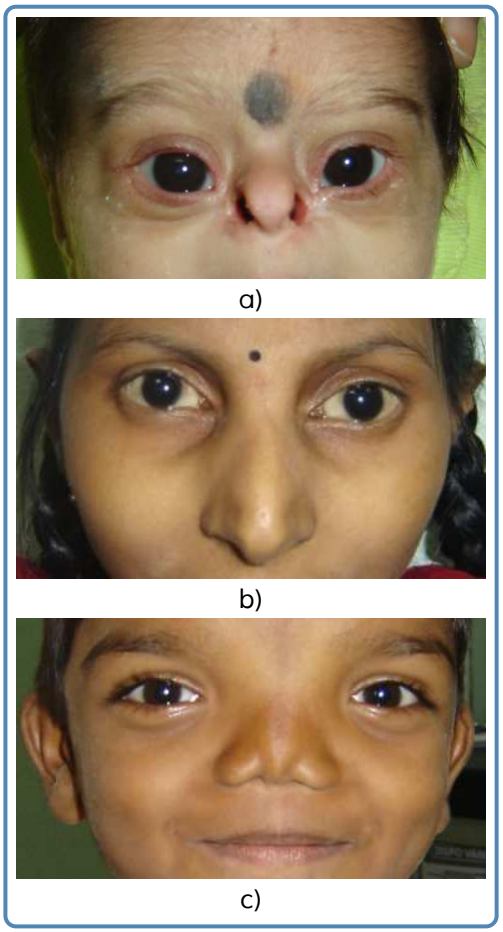

Figure 3 Dysmorphic findings in the nose. a). Hypoplastic alae nasi; b). Beaked nose; c). Broad bifid tip of nose.

    * Ear shape and structure
    * Accessory structures: pits/ skin tags
  - Skeleton-
    * Neck: length/ shape (webbed)
    * Shape of thoracic cage
    * Sternum: length & shape (pectus carinatum/excavatum)
    * Spine: length/ straight/curved
    * Limbs: length/shape/ symmetry
  - Joints – contractures; range of joint movement: laxity/ restriction; soft tissue webbing across joints (pterygium)
  - Skin –
    * Texture: smooth/ coarse/ dry/ ichthyotic
    * Pigmentation: hypo/ hyperpigmentation; patchy / generalized
    * Naevi/ lentigines
    * Redundancy/ laxity
    * Patchy pigmentation may indicate mosaicism
  - Hands and Feet
    * Overall shape and size of hand and foot
    * Digit number
    * Digit shape (e.g. clinodactyly) and length
    * Webbing between digits
    * Palmar, plantar and digit creases
    * Nail morphology
  - Genitalia and Anus
    * Phallus size and morphology
    * Development, rugosity & pigmentation of scrotum
    * Size and position of testes
    * Development of labia
    * Position of anus relative to genitalia and patency of anus

- Systemic Examination: cardiovascular/ per abdomen/ neurological/ respiratory
- Physical features not found as normal or familial traits and which are present in only a few conditions or are pathognomonic of specific disorders are of more diagnostic help. These are said to be 'good handles' for diagnosis e.g. white forelock of hair which is a good diagnostic clue for Waardenburg syndrome.

Radiographs

The following radiographic assessment helps in the diagnostic evaluation:

- X ray wrist + hand (anteroposterior (AP) view) in cases with short stature: for bone age assessment
- Genetic skeletal survey for suspected skeletal dysplasias/ disproportionate short stature:
  - AP & lateral views of skull
  - AP & lateral views of spine (cervical to sacrum)
  - AP view of pelvis with bilateral hip joints
  - AP view of one hand and one foot
  - AP view of one upper limb (shoulder to elbow; elbow to wrist)
  - AP view of one leg (knee to ankle)

Imaging studies

The following imaging modalities may be used in the evaluation:

- Neuroimaging:
  - MRI brain: in presence of neurological deficits/ seizures/ microcephaly or macrocephaly
  - CT Scan brain: for suspected TORCH infections/ cranial contour abnormalities/ craniosynostosis (3D CT)
- USG abdomen/ 2D Echo: to look for visceral malformations

Analysis

- All clinical and laboratory findings must be analysed together in order to get a diagnosis; all features must fit into the diagnosis as far as possible
- If the condition cannot be diagnosed based on previous experience or existing knowledge, one should take the help of resources such as dysmorphology databases (e.g. LDDB - London Dysmorphology DataBase and POSSUM – Pictures of Standard Syndromes and Undiagnosed Malformations), online resources (OMIM – Online Mendelian

Inheritance in Man) and dysmorphology textbooks.

Genetic Testing

The following genetic tests can help in confirming the aetiology in affected cases:

- Karyotyping: to be done in cases with:
  - congenital malformations
  - prenatal onset growth retardation
  - disorder of sexual development
  - developmental delay
  - history of multiple miscarriages in the family
- Fluorescence in situ hybridization (FISH)/ Multiplex ligation - dependent probe amplification (MLPA): when the phenotype is suggestive of a specific microdeletion syndrome e.g. Di George syndrome (22q microdeletion)/ Angelman syndrome (15q microdeletion)/ Williams syndrome (7q microdeletion)
- Metabolic testing: Relevant biochemical investigations should be done if a metabolic etiology is suspected. Metabolic disorders with dysmorphism include:
  - Mucopolysaccharidoses, oligosaccharidoses, mucolipidosis, GM1 gangliosidosis
  - Peroxisomal disorders
  - Disorders of cholesterol metabolism (e.g. Smith Lemli Opitz syndrome)
- Single gene mutation analysis: DNA-based molecular genetic tests to be done when a specific monogenic disorder is suspected.
- Cytogenetic microarray (CMA) study:
  - Can be done in any case with multiple malformations with or without associated intellectual disability and without any other identified genetic/ non-genetic cause
  - CMA scans the entire genome for copy number variations (microdeletions/ microduplications)

Intervention

- Appropriate medical/ surgical management wherever feasible: eg. surgical correction of cardiac defect, correction of hearing deficit etc.
- Genetic counseling
- Prenatal diagnosis wherever feasible

Genetic Counseling

- Deformations/ disruptions have low risk of recurrence (but can recur if the causative intrauterine environmental factor persists or recurs in the next pregnancy).
- Denovo chromosomal abnormalities and microdeletions have a risk of recurrence of $< 1\%$
- In single gene disorders, risk of recurrence will vary according to the mode of inheritance: autosomal dominant (50% in sibs and offspring if inherited and nil in sibs if de novo)/ autosomal recessive (25% in sibs)/ X-linked (50% in male sibs)

Prenatal Diagnosis

- Targeted mutation analysis/ chromosomal analysis/ metabolic testing in fetal tissue depending upon diagnosis of proband: Chorionic villus sample/ amniotic fluid/ preimplantation genetic diagnosis
- Fetal anomaly scan to look for the same/ associated malformations
- 3D/ 4D USG for better visualisation of the facial profile/ external dysmorphisms
- Fetal echocardiogram for detecting fetal cardiac anomalies
- Limitations of scan based prenatal diagnosis:
  - may not be able to detect certain malformations especially gut anomalies such as malrotation and lower GI obstruction
  - cannot determine intellectual status
  - cannot pick up some features e.g. microcephaly/ lissencephaly until late gestation

Follow up

- To assess growth & development
- To study course of the disease
- To monitor for known/ anticipated associated complications
- To offer newly available diagnostic tests
- To offer newly available therapeutic options
- Sometimes phenotype evolves with age and reassessment at a later age in an undiagnosed case might make diagnosis clear
- To discuss reproductive risks.

Resources for reference

- Books:
  - Aase JM. Diagnostic dysmorphology. 1990. Springer.
  - Hennekam R, Allanson J, and Krantz I. Gorlin's Syndromes of the Head and Neck. Fifth edition; 2010. Oxford University Press.
  - Hall JG, Allanson JE, Gripp KW, Slavotinek AM. Handbook of Normal Physical Measurements. Second edition; 2007. Oxford University Press.
  - Jones KL. Smith's Recognizable Patterns of Human Malformation. Sixth edition; 2005. Elsevier.
  - Langman's Medical Embryology. Sadler TW. Twelfth edition; 2012. Lippincott Williams & Wilkins.
  - Stevenson RE, Hall JG. Human Malformations and Related Anomalies. Second edition; 2006. Oxford University Press.
- Databases:
  - OMIM (Online Mendelian Inheritance in Man) (`http://www.ncbi.nlm.nih.gov/omim`)
  - POSSUM (Pictures of Standard Syndromes and Undiagnosed Malformations)
  - Winter RM, Baraitser M. London Dysmorphology Database

Non-invasive prenatal testing for low risk women and more . . .

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Non-invasive prenatal testing for low risk women[1]

Though non-invasive prenatal testing using massively parallel sequencing of cell free fetal DNA has been in use in clinical practice since 2011, most of the study cohort and the subsequent data relates to high risk pregnancies. The high accuracy of these techniques for aneuploidy detection has been already proved in these cases. A study by Bianchi et al in a large cohort of women with uncomplicated singleton pregnancies has finally proved this can be a useful technique in the general low risk obstetric population as well. The negative predictive value of this screening has been estimated to be nearly 100% with a tenfold higher positive predictive value for trisomy 21. This would bring down substantially the number of procedures due to false positive results. Hence, it is likely to become the test of choice for antenatal screening as soon as the cost of the next generation sequencing technique comes down.

The other side of the coin[2]

In absolute numbers, female feticide especially in countries like India translates into elimination of up to half a million per year. Madan et al have reviewed the impact of prenatal testing on sex ratio in India providing insights into the alarming rate at which the sex ratio is falling every decade in India. Among children between 0 and 6 years, the sex ratio has fallen to 914, which is the lowest since records for this age group have been kept. In some states, it is even below 900. With the availability of home kits using pin prick blood samples, these easy to use tests may thus become a highly misused tool in India and China where female feticide and infanticides are rampant.

The perfect collaboration![3]

Clinicians and scientists in Canada came together as they felt the necessity to provide molecular diagnosis to children with rare diseases for their clinical management as well as offer prenatal testing to families with these disorders. It was named as the FORGE (Finding of Rare Disease Genes) Canada Consortium and included their various genetic, science and innovation centres. Over a period of two years, they screened 264 disorders. Sixty seven genes not previously associated with human diseases (41 of which have been genetically or functionally validated, and 26 are being currently studied) were identified for 146 disorders. They have beautifully discussed the stepwise approach they have used for new gene discovery and its impact on patients and families with rare diseases. The most successful strategies for new gene discovery were: multiple unrelated individuals or families affected by the same recognizable condition and disorders in consanguineous families. The researchers have used two interesting resource tools. PhenoTips was used for phenotyping with standard terminology in very less time and the data was linked with genomic data in PhenomeCentral, an integrated portal developed to facilitate collaboration and gene discovery. The way to go for other countries and continents!

Guidelines for causality of sequence variants[4]

Even the laboratories with the most experienced personnel, most sophisticated bioinformatics tools and other techniques, are often unable to differentiate the actual disease causing variants from the normal human variations. Few recent studies have concluded that as many as 27% of sequence

variants can be assigned as pathogenic when they were either polymorphisms or carried insufficient evidence of the pathogenicity. MacArthur et al. have come up with guidelines for the interpretation of pathogenicity of sequence variations. Determining the pathogenicity not only is important for diagnostic purposes but is equally important for the research as well. The guidelines are evidence based and are devised by a group of experts in the field of genomic research, clinical diagnostics and analysis under the US National Human Genome Research Institute. The implementation of these guidelines would in future require the need to establish updated public databases as well as population specific allele frequencies and large scale genotype data from these populations for well characterized diseases.

References

1. Bianchi DW, et al. *N Engl J Med* 2014; 370: 799-808.
2. Madan K, et al. *Genet Med* 2014; 16: 425-32.
3. Beaulieu CL, et al. *Am J Hum Genet* 2014; 94: 809-17.
4. MacArthur DG, et al. *Nature* 2014; 508: 469-76.

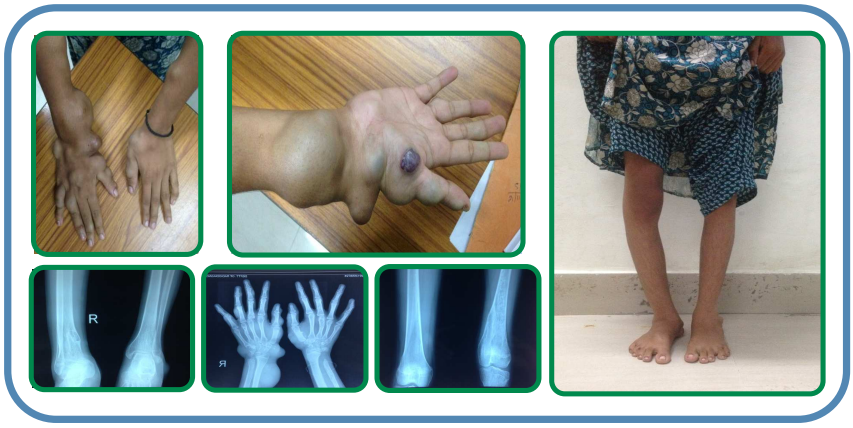
PhotoQuiz - 25

Contributed by: Dr. Meenal Agarwal

Email: meenal91@gmail.com

This 13 years old girl was referred for evaluation of multiple skin hemangioma, bluish swellings over the hands and wrist and leg deformity. Radiographs showed cystic lesions in the bones with subcutaneous calcification.

Please send your responses to editor@iamg.in



Answer to PhotoQuiz 24

Gyrate Atrophy of Choroid and Retina (OMIM # 258870)

Gyrate atrophy of the choroid and retina is an autosomal recessive disorder that results from the deficiency of ornithine ketoacid aminotransferase (OAT), an enzyme that catalyzes the transamination of ornithine to glutamate semialdehyde. The condition is characterized by hyperornithinemia. Night blindness starts in late childhood with gradual bilateral loss of vision progressing to total blindness by 40 to 60 years of age. There are sharply demarcated circular yellowish patches of atrophy in the periphery of the fundus at the onset and the areas of atrophy subsequently enlarge. Gyrate atrophy is caused by homozygous or compound heterozygous mutations in the *OAT* gene on chromosome 10q26. Restriction of arginine in the diet helps to control progression of the disease.

Correct responses were given by:
1. Himanshu Goel, Australia
2. Aruna G, Bengaluru
3. Beena S, Chennai

Announcement

Thirteenth ICMR Course on Medical Genetics and Genetic Counseling

28th July 2014 to 9th August 2014

This course provides an introduction to genetics and aims at training pediatricians, obstetricians and other clinicians in basic & applied aspects of clinical genetics.

Organized by: Dr Shubha Phadke
Department of Medical Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences
Raebareli Road, Lucknow 226 014

For details: http://www.sgpgi.ac.in/conf.html
Contact: shubharaophadke@gmail.com

Announcement

SIAMG Fellowship in Clinical Genetics

Duration and scope:
Three months training in a Medical Genetics centre with clinical and laboratory genetics facilities

Eligibility:
A post-graduate degree (MD/ MS) in Pediatrics, Obstetrics and Gynecology, or General Medicine. Candidates with super-specialization are also encouraged to apply.

Award Support:
Consolidated emolument of Rs. 50,000/- per candidate per month, for three months

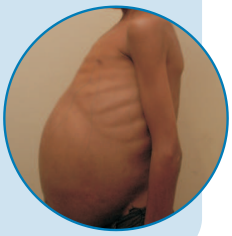
Schedule:
Next batch starts from October 1st, 2014.

For details, please visit: http://www.iamg.in or write to info@iamg.in

Are you aware of anyone with these Signs or Symptoms?

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



POMPE DISEASE

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

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

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

COMPLIMENTARY DBS SERVICE FROM GENZYME FOR DIAGNOSIS OF "TREATABLE LYSOSOMAL STORAGE DISORDERS"

Genzyme is offering complimentary Dried Blood Spot (DBS) testing service for diagnosis of four Lysosomal Storage Disorders: Gaucher disease, Pompe disease, Fabry disease, and MPS I disease.

Each DBS kit contains: Filter Paper, Alcohol Swab, Lancet, Gloves, Zip Lock Pouch with Desiccant, Sampling Instructions, Clinical History Form and Self-Addressed Envelope. To place a request for your complimentary kit, you can sms LSD to 9225592255, or email us at: lsdinfoindia@genzyme.com. You can also contact the Genzyme India office at 09560552265.

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