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Editorial

Early steps towards gene therapy and drugs for genetic disorders

Till date, more than 1800 gene therapy trials have been completed, are going on or have been approved worldwide. Though thought to be a cure in sight for all genetic disorders more than three decades ago, the dream of gene therapy continues to evade scientists as well as hopeful patients. With the understanding of the molecular genetic basis of many genetic disorders and discovery of techniques to manipulate genes, the era of genetic engineering began. Correction of genetic defects at the level of DNA or replacement of defective genes with the correct copy of the gene appeared an immediate possibility. The first gene therapy was planned for beta thalassemia in 1980. Though the HBB gene is small, appropriate amount of beta globin production is needed to cure beta thalassemia major and it appeared a difficult task. The protocol lacked appropriate ethical review and was considered scientifically premature and was stopped. In 1990, American doctor William Anderson performed one of the first successful gene therapy trials on a 4 year old girl named Ashanti DeSilva with a rare genetic immune system disorder called severe combined immuno-deficiency (SCID) caused by deficiency of adenosine deaminase (ADA). The effect was temporary and the patient continued to receive ADA replacement therapy, raising doubts about the efficacy of gene therapy in her. A few more attempts to treat patients with immunodeficiency disorders with gene therapy were made in the 1990s. Gene therapy received a major setback in 1999 with the death of Jesse Gelsinger who participated in a gene therapy trial for ornithine transcarbamylase deficiency (OTC). He died on the fourth day of gene therapy probably due to an immune reaction to the adenovirus used as a vector to carry the gene. In 2002, a French group reported successful gene therapy for X-linked SCID by inserting retrovirus carrying the normal gene into the affected children's blood stem cells. This clinical trial was questioned when two of them developed a leukemia-like condition. However, long term success for up to 8 years in the subjects in this study was documented. After these adverse effects, strict FDA guidelines and ethical regulations were formulated for gene therapy trials.

The best vector to transfer the gene of interest is currently an important limitation. The best vector should be harmless, should be able to carry a large size gene to the target cells, get incorporated in the nuclear DNA without disturbing any important gene, and should be able to produce the necessary gene product in adequate amounts and over a long period. At present most gene therapy protocols use viral vectors and the possibility that it may become infectious, carcinogenic or cause immune reaction continues to pose a big threat. Recent studies have tried liposomes or gene packed in lipids to avoid the use of viral vectors. However, the search for the ideal vector continues.

Of all gene therapy trials at present, only 10% are being done for single gene disorders. Though a complete cure has not been achieved, clinically significant successes are being reported for some diseases such as Leber congenital amaurosis caused by RP65 gene mutations and hemophilia B. Diseases like hemophilia B, where a small amount of the gene product is sufficient for clinical efficacy, are good candidates for gene therapy. Diseases like thalassemia need a regulated expression of the gene and hence are more challenging. For diseases like Duchenne muscular dystrophy the target tissue is big and gene expression in all muscle cells is necessary to be clinically effective. The other challenge for Duchenne muscular dystrophy is the very large size of the gene; a carrier vector for transporting such a large gene is not available. To overcome this, a minigene construct containing only the very important regions of the dystrophin gene has been tried, with limited success. Another strategy called exon skipping therapy is being tried for Duchenne muscular dystrophy. It involves the

use of small oligonucleotide segments to block the expression of the defective part of the gene and restore the reading frame of the gene sequence, so that the gene product contains normal sequence of amino acids before and after the defect. Exon skipping therapy has shown some benefit in Phase II trials and Phase III trials are underway. Though not completed yet, positive results are being reported for gene therapy trials for eye diseases like retinitis pigmentosa, Stargardt disease, age related macular degeneration and choroideremia. Gene therapy trials are also underway for cystic fibrosis, Niemann Pick disease, X linked adrenoleukodystrophy and hyperlipidemias. The recent reports of success and beginning of trial for beta thalassemia have revived a hope for thalassemia, one of the most common genetic disorders in India.

Though initially thought to be a treatment strategy for monogenic disorders, gene therapy trials are now ongoing for cardiovascular disorders, HIV infection, inflammatory bowel diseases and cancers. Cancer-related trials account for 60% of the total gene therapy trials. The first successful cancer gene therapy was reported by NIH, Bethesda using T cells genetically retargeted to attack the cancer cells in two cases of metastatic melanomas. The strategies used are suicidal genes, immunological attack on cancer cells or use of gene therapy to make the cancer cells susceptible to chemotherapy. In 2003, China became the first country to approve a gene therapy based product for clinical use. Gendicine™, developed by SiBiono Gene Tech Co. is an adenoviral vector, wherein the E1 gene is replaced with a human p53 cDNA. Gendicine™ is a non-replicative virus and received approval for the treatment of head and neck squamous cell carcinoma. The European Union approved the first gene therapy product in 2012. Gene pills for cancers do not appear to be a distant dream anymore and may make surgical treatment obsolete for cancers in the future.

As for any other drug, the route of gene therapy from the laboratory to the clinic is a long and arduous one and involves a lot of research in the basic understanding of molecular pathology, techniques of gene manipulation, and study of safety and effects of DNA manipulation. Cell lines and animal models play a big role in this research. In 2005, scientists were able to correct deafness in a guinea pig model by using an adenovirus vector. The Atoh1 gene (which stimulates growth of hair cells) was delivered to the cochlea resulting in regrowth of hair cells and thereby regaining of 80% of the original hearing threshold. In September 2009, the journal Nature reported that researchers at the University of Washington and University of Florida were able to give trichromatic vision to squirrel monkeys using gene therapy. This could have significance on the future treatment of color blindness in humans.

This long journey reflects the difficulties and challenges in gene therapy. As of today, though success has been limited, one can see light at the end of the tunnel and probably clinical success in gene therapy for cancers, genetic and other disorders may not be too far. Over the last few decades parallel to the research in gene therapy, a lot of research has gone into the identification of genetic defects and molecular pathogenesis of diseases. This has rewarded new drugs and treatment strategies. One of them is Losartan for Marfan syndrome. Losartan works downstream on the TGF beta pathway which gets activated in Marfan syndrome and is the root cause of the cardiac and eye manifestations of the disease. Beautiful pieces of work in animal models have improved the understanding of effects of FBN1 gene mutations on the TGF beta pathway and shown the efficacy of Losartan in completely preventing the cardiac and ophthalmic complications of the disease. This has been achieved in a very short span of time. Losartan being a drug already in use, the duration of research to patient application has been very short. Similar types of pathway based treatments are being tried for a group of disorders known as RASopathies and tuberous sclerosis. This issue highlights such new treatment strategies, new molecules for treatment and the wonderful ongoing research in this direction.

More new treatments based on the understanding of molecular pathogenesis of diseases may come in the near future. With the renewal of interest in thalassemia gene therapy, we hope to see successful gene therapy for thalassemia and other diseases becoming a reality.

Shubha Phadke

1st April, 2014

Fructose 1, 6 bisphosphatase deficiency: A treatable cause of recurrent hypoglycemia

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Fructose 1,6 bisphosphatase deficiency (OMIM 229700) is a rare disorder of gluconeogenesis, causing recurrent hypoglycemia and lactic acidosis in infancy. The disease often goes unnoticed during the immediate post natal period, but can present as recurrent, life threatening hypoglycemic episodes in infancy. The attacks are triggered by prolonged fasting, especially during intercurrent illness. This condition, once identified, can be managed by simple measures which will prevent hypoglycemic episodes. We report a case of fructose 1,6 bisphophatase deficiency in a twenty month old male child.

Case Report

A twenty month old boy, the only child of third degree consanguineous parents, was brought to us for evaluation of recurrent hypoglycemic episodes, preceded by fever, vomiting and loose stools. During each episode, he developed fast breathing and became lethargic and less responsive. He was admitted thrice for the same complaint. During one such episode, he developed generalized tonic clonic seizures and hematemesis. He was apparently normal till 1 year of age, with normal age-appropriate developmental milestones.

In between the episodes of illness, he was well and was growing normally. He did not have any history of neonatal hypoglycemia or jaundice. He did not have any features suggestive of hepatic failure. He was not noticed to have any hyperpigmentation. He never had any specific aversion to a particular food and the illness was never precipitated by any particular food intake. No abdominal distension was noted nor did he have any peculiar body odor.

On examination during acute illness, he was less responsive and had acidotic breathing. He had features suggestive of shock. He did not have any abnormal odor and his liver measured 6 cm below the right costal margin, with a span of 9 cm. His spleen was not palpable. His weight was 9 kg, height 84cm and head circumference 47 cm (all within normal limits). When he was re-examined after the acute illness had settled, his liver measured 4 cm below the right costal margin with a span of 6cm.

His investigations revealed hypoglycemia (random blood sugar 20 mg/dL), positive urinary ketones, severe metabolic acidosis (pH 7.02, bicarbonate 12), elevated lactate (34mg/dL), normal ammonia levels, elevated uric acid level (10mg/dL) and normal liver function tests. During the episode, his blood and urine were collected and tandem mass spectroscopy of blood and gas chromatography of urine were done. Urine GCMS showed grossly elevated levels of lactic acid and ketones and significantly elevated levels of glycerol suggestive of fructose 1,6 bisphosphatase deficiency. Liver biopsy revealed fatty infiltration. Enzyme assay of fructose 1,6 bisphosphatase could not be done. Molecular study revealed a homozygous mutation (p.Gly260Arg) in exon 6 of FBP1 gene, which is a known mutation.

He was managed with intravenous glucose and sodium bicarbonate, which caused immediate reversal of his condition. He was discharged with advice on prevention of hypoglycemic episodes during intercurrent illness.

Discussion

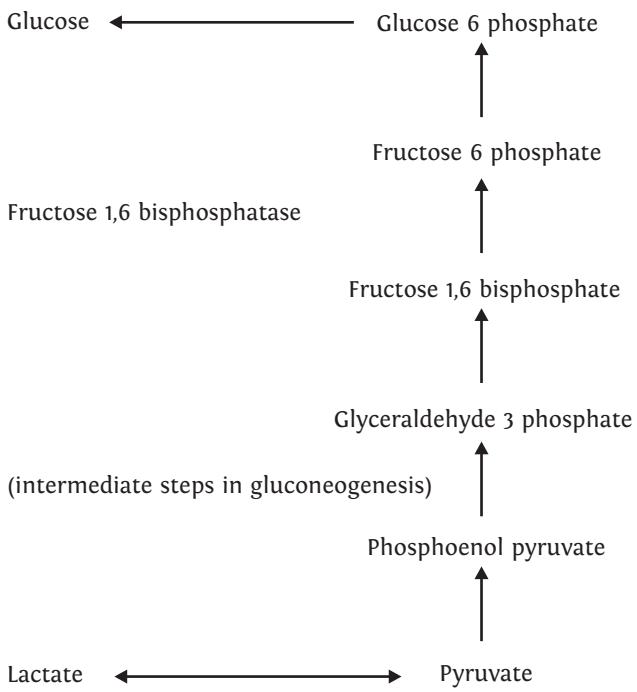
Recurrent hypoglycemia can be a presentation of various genetic and non genetic disorders. Table 1 lists the various causes of recurrent hypoglycemia during infancy. Accurate etiological diagnosis is rewarding as management can markedly improve the outcome.

Table 1: Causes of recurrent hypoglycemia in infants and children

Disorder	Hepatomegaly	Acidosis	Ketones	Lactate	Lipids	Characteristic features	Management
Hyperinsulinemia	No	No	No	Normal	Normal	Macrosomia; increased insulin during hypoglycemia; rapid development of fasting hypoglycemia Most common cause of persistent hypoglycemia in infancy	Medical: Somatostatin, diazoxide Surgical: removal of focal adenomas to subtotal pancreatectomy
Hypopituitarism	No	No	Ketonuria++	Normal	Normal	Short stature after infancy, microphallus, cholestatic jaundice in neonatal period; associated with syndrome of septo optic dysplasia	Growth Hormone replacement
Adrenal insufficiency	No	+	Ketonuria +	Normal	Normal	Hyper pigmentation, salt craving, may have ambiguous genitalia, hyponatremia, hyperkalemia	Corticosteroid replacement
Ketotic hypoglycemia	No	No	+++	Normal	Normal	Severe with fasting, markedly decreased alanine Most common form of childhood hypoglycemia	Dietary: frequent feeding of high carbohydrate, high protein diet, especially during intercurrent illness Remits spontaneously by 8-9 years
Fatty acid oxidation defect	+/- with abnormal LFT	No	Absent	Normal	+++	Severe hypoglycemia with missed meals	Avoidance of fasting Supplementation of carnitine
Galactosemia	+++	No	Ketones +	Normal	Normal	Hypoglycemia after milk/milk products, neonatal jaundice	Elimination of galactose from diet
Glycogen storage disorder (Type I, III, VI)	+++	No	++	Increased	Increased	Growth failure, increased lipids, increased uric acid, 'doll facies' in Type I GSD	Dietary: Frequent feeding Uncooked corn starch Limiting fructose, sucrose, sorbitol and lactose (GSD type I)
Fructose1,6 bisphosphatase deficiency	+++	++	Ketonuria+++	Increased	Increased	Uric acid elevated	Avoiding starvation Frequent feeding , especially during inter current illness
Fructose intolerance	+++	No	+	Normal	Normal	Failure to thrive, hepatic failure, prolonged bleeding time	Complete elimination of sucrose, sorbitol and fructose from diet Good long term prognosis

Fructose 1,6 bisphosphatase deficiency is one of the easily recognizable disorders presenting with hypoglycemia. It is an autosomal recessive disorder which causes impairment in gluconeogenesis and was first described in 1970.[1] Fructose 1,6 bisphosphatase is a key enzyme in gluconeogenesis and is needed for formation of fructose 6 phosphate and inorganic phosphate from fructose 1,6 bisphosphate (Figure 1).[2] This leads to life

Figure1: Gluconeogenesis in brief



threatening hypoglycemia and metabolic acidosis in new born infants and young children.[3] Affected children can also present with hyperventilation attacks, ketosis and apnea. Elevated levels of glycerol in urine is the main abnormality detected in urine organic acid analysis of such patients.[4] Elevated lactate and normal blood ammonia are other biochemical findings. The disorder can be lethal in the new born period if left unidentified, but early diagnosis and proper treatment ensures excellent prognosis. Low levels of hepatic fructose 1,6 bisphosphatase was used initially as a diagnostic method, but now it has been replaced by mutation analysis of FBP1 gene.[5] The most common mutation detected is a 1 bp insertion in the FBP1 gene. If mutation is identified in the proband, DNA based prenatal diagnosis or neonatal diagnosis can be provided as the risk of recurrence in the sib of an affected child is 25%.

The condition should be suspected in any infant who presents with recurrent ketotic hypoglycemia and metabolic acidosis with elevated lactate and normal serum ammonia. Urinary amino acid analysis shows elevated glycerol levels and ketonuria. The treatment is mainly targeted to prevent hypoglycemic episodes during inter-current illness by frequent feeding. In the hospital, intravenous glucose can be administered along with sodium bicarbonate to correct severe metabolic acidosis. The importance of early clinical suspicion and diagnosis cannot be understated in this condition as this remains one among the few inborn errors of metabolism where a specific treatment can be offered.

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Marfan Syndrome: Recent Advances in Diagnosis and Management

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Introduction

Marfan syndrome (OMIM # 154700) is a heritable disorder of fibrous connective tissue, which affects multiple systems and has significant clinical variability. The estimated world-wide prevalence of Marfan syndrome is one in 5,000 to 10,000 individuals.[1] The condition is named after Antoine Marfan, a French paediatrician who first described the typical clinical features in a five year old girl in 1896.[2] It has an autosomal dominant pattern of inheritance and is caused by heterozygous mutation in the gene encoding fibrillin-1 (FBN1).[1]

Clinical Features

Cardinal manifestations of Marfan syndrome involve ocular, skeletal, and cardiovascular systems but other systemic abnormalities such as pulmonary, cutaneous, and neurological abnormalities also occur as a part of the syndrome.[1]

Myopia is the most common ocular feature seen in Marfan syndrome. Ectopia lentis i.e. displacement of the lens from the centre of the pupil, though a hallmark feature of the disease, is seen in only around 60% of affected individuals. Retinal detachment, glaucoma, and early cataract formation are the other eye anomalies associated with this condition.[1]

Skeletal system involvement is characterized by bone overgrowth and joint laxity. Dolichostenomelia (disproportionately long extremities compared to the trunk, manifesting as increased arm span-to-height ratio and decreased upper-to-lower segment ratio), arachnodactyly (thumb sign and wrist sign), overgrowth of the ribs leading to chest deformity (pectus excavatum or carinatum) and vertebral column deformity (scoliosis/ kyphosis/ lordosis) are the common skeletal features of the disorder. Craniofacial features include a long and narrow face, downward slanting palpebral fissures, malar hypoplasia, micro/ retrognathia, high arched palate and crowding of teeth (Figure 1).[1]

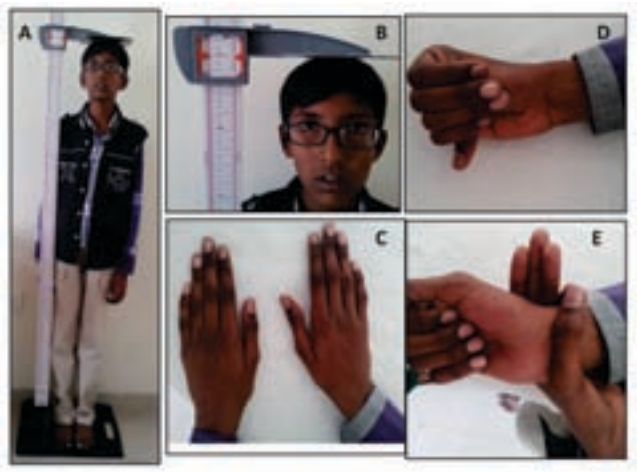

Figure 1: A. 10 year old boy with Marfan syndrome B. Close up of the patient's face C. Arachnodactyly D. Positive thumb sign E. Positive wrist sign

Cardiovascular manifestations are the major cause of serious morbidity and early mortality in Marfan syndrome and include dilatation of the aorta, aortic dissection and rupture, mitral valve prolapse/ regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery.[1]

Other systemic features of the disorder include dural ectasia (stretching of the dural sac in the lumbosacral region), skin striae, hernias, lung bullae and spontaneous pneumothorax.

Genetics of Marfan syndrome

Marfan syndrome is caused by heterozygous mutation in the FBN1`gene (OMIM * 134797) which encodes the fibrillin-1 protein. FBN1 is located on the long arm of chromosome 15 (15q21.1) and is one of the largest genes in the human genome with 65 exons spanning more than 600kb. Fibrillin-1 is a matrix glycoprotein made up of 2,871 amino acids and has five structurally distinct regions; the largest region comprising about 75% of the protein is made up of cysteine-rich EGF (epidermal growth factor)-like repeats and the other 4 regions include a unique amino-terminal stretch of basic residues, an adjacent second cysteine-rich region, a proline-rich domain, and the carboxy terminus. Fibrillin-1 is an important component of microfibrils which are present in elastic and non-elastic tissues and play an important role in the formation and homeostasis of the elastic matrix, in matrix-cell attachments and in the regulation of some growth factors especially TGF-β (transforming growth factor beta). FBN1 gene mutations result in production of abnormal mutant forms of fibrillin 1, disruption of normal microfibrillar assembly and weakening of the connective tissue. Over 1,000 mutations have been reported in the FBN1 gene; these are distributed through out the sequence of the gene and there is no reported ethnic preponderance of any specific mutations. Different types of mutations in the FBN1 gene which result in Marfan syndrome include nonsense mutations, in-frame or out-of-frame deletions/insertions, splice site mutations that alter the splice consensus sequence or alter splicing, missense mutations that create or destroy a cysteine residue and missense mutations that affect conserved residues in the EGF-like domain consensus sequence.[3]

Marfan syndrome is an autosomal dominant disease characterized by high penetrance but marked clinical variability (including intrafamilial variable expressivity). Although there are no definite genotype– phenotype correlations, mutations in the central portion of the gene in exons 24–32 have been reported to be associated with the most severe and rapidly progressive form of Marfan syndrome termed “neonatal Marfan syndrome”. On the whole, mutations causing in-frame loss or gain of central coding sequences through deletions, insertions, or splicing errors are found to be associated with more severe disease and mutations that create a premature termination codon and result in rapid degradation of mutant transcripts are reported to have milder phenotypes, probably because mutant protein forms with a dominant negative effect have more severe consequences on microfibrillar assembly. Mutations affecting C-terminal propeptide processing have been found to be associated with predominant skeletal manifestations.[1]

Other disease phenotypes associated with FBN1 gene mutations are the mitral valve prolapse syndrome, the MASS phenotype (myopia, mitral valve prolapse, aortic enlargement, and nonspecific skin and skeletal features), isolated aortic aneurysm, isolated skeletal features of Marfan syndrome, familial ectopia lentis, Shprintzen-Goldberg syndrome (consisting of skeletal findings of Marfan syndrome with ocular hypertelorism, craniosynostosis, other craniofacial abnormalities and cognitive impairment), autosomal dominant Weill-Marchesani syndrome (characterized by ectopia lentis, microspherophakia, short stature, brachydactyly and the absence of vascular manifestations), stiff skin syndrome (an autosomal dominant form of congenital scleroderma) and two skeletal dysplasias (Geleophysic dysplasia-2 and acromicric dysplasia).[1]

Some patients with many but not all clinical features of Marfan syndrome are termed to have Marfan–like syndrome or Marfan syndrome type II. Most of these patients do not have ectopia lentis or prominent dolichostenomelia. Loeys-Dietz syndrome (LDS) is another disorder which shares significant phenotypic overlap with Marfan syndrome; it is an autosomal dominant condition which has the craniofacial features of Marfan syndrome along with pectus deformity, scoliosis, arachnodactyly, joint laxity, dural ectasia, and aortic root aneurysm with dissection, but does not have prominent dolichostenomelia or ectopia lentis. LDS can have additional features such as hypertelorism, broad or bifid uvula, cleft palate, learning disability, Chiari I

malformation, blue sclerae, exotropia, craniosynostosis, cervical spine instability, talipes equino varus, soft and translucent skin, easy bruisability and generalized arterial tortuosity. Both Marfan-like syndrome and LDS are caused by mutations in TGFBR1 or TGFBR2 genes, which encode the type I or type II receptors for transforming growth factor (TGF-β).The type II receptor (TGFBR2) functions as a transmembrane serine/threonine kinase and is required for the anti-proliferative activity of TGF-beta, whereas the type I receptor (TGFBR1) mediates the induction of several genes involved in cell-matrix interactions.[1,4]

Diagnosis

The Ghent criteria which are used for making a definitive diagnosis of Marfan syndrome were originally developed by an international group in 1996 and comprise a set of major and minor manifestations in different body systems. It was perceived that some of the diagnostic criteria in the original Ghent's nosology have not been sufficiently validated, are not applicable in children or necessitate expensive and specialised investigations and also that they do not take into account the variable clinical expression and extended differential diagnosis of Marfan syndrome. A revised Ghent nosology was therefore formulated in 2010, which gives more weight to the cardiovascular manifestations and in which aortic root aneurysm and ectopia lentis are the cardinal clinical features.[5] As per the revised Ghent criteria, diagnosis of Marfan syndrome can be established if[5,6]:

A. In the absence of a family history of Marfan syndrome there is:

- Aortic root enlargement (Z score ≥ 2.0) and one of the following:
  - Ectopia lentis
  - pathogenic FBN1 mutation
  - systemic score ≥ 7
- Ectopia lentis and a FBN1 mutation previously associated with aortic enlargement

B. In the presence of a family history of Marfan syndrome in a first-degree relative there is:

- Ectopia lentis
- Systemic score ≥ 7
- Aortic root enlargement (Z score ≥ 2 in ≥ 20 years or ≥ 3 in ‹20 years)

The systemic score is calculated using Table 1.6

Table 1: Features used for calculation of the systemic score in the revised Ghent nosology[1,5,6]

Feature	Value
Wrist and thumb sign	3
Wrist or thumb sign	1
Pectus carinatum deformity	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabulae	2
Reduced upper segment / lower segment and increased arm span/height ratios	1
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Three of 5 facial features (dolichocephaly, downward slanting palpebral fissures, enophthalmos, retrognathia and malar hypoplasia)	1
Skin striae	1
Myopia	1
Mitral valve prolapse	1

Genetic testing

Genetic testing of Marfan syndrome using conventional Sanger sequencing technique is difficult because of the large size of the gene. The absence of mutational hot-spots in the gene, lack of any ethnic preponderance of mutations and requirement of analysing all 65 exons make genetic diagnosis expensive and time consuming. However, with the advent of new high through put next-generation sequencing strategies it has become feasible to sequence DNA of the whole coding region of the FBN1 gene to detect potentially pathogenic variants. Capture of the complete FBN1 sequence, including the 5′ promoter region, introns and 3′untranslated region followed by high-through put sequencing of the whole of the FBN1 gene has enabled detection of intronic and regulatory region mutations. The development of RNA sequencing could facilitate sequencing of FBN1 transcripts using RNA from appropriate cell types (for example fibroblasts derived from skin biopsy or aortic smooth muscle cells). RNA sequencing would also allow discovery of abnormal transcription start sites, splice variants and miRNA differences that may affect FBN1 mRNA levels or function.

Management and Surveillance

Marfan syndrome requires multidisciplinary management involving a clinical geneticist, cardiologist, cardiothoracic surgeon, orthopaedician and ophthalmologist. Following an initial detailed evaluation by each concerned specialist at the time of diagnosis, subsequent regular surveillance is essential to monitor for the disease-related complications. Yearly echocardiographic examinations are indicated when the aortic dimension is relatively small and the rate of aortic dilation is relatively slow but more frequent examinations are required when the aortic root diameter exceeds 4.5 cms in adults, the rate of aortic dilation exceeds approximately 0.5 cm per year, and significant aortic regurgitation is present. Annual ophthalmologic evaluation is required to monitor for lens dislocation, glaucoma and cataracts.[1]

The treatment is largely symptomatic and no definite curative therapy for the disease is available at present. Monitoring, prevention and treatment of cardiovascular complications form the most important part of management of Marfan syndrome. Beta blocker therapy is initiated at the time of diagnosis to reduce hemodynamic stress on the aortic wall. Surgical repair of the aorta is indicated once aortic diameter approaches 5.0 cm in adults or older children, the rate of increase of the aortic diameter approaches 1.0 cm per year, or there is progressive aortic regurgitation. Composite aortic valve graft or valve-sparing aortic root replacement are required in case of aorta dissection or rupture. After load reducing agents are added for congestive heart failure. Mitral valve repair/ replacement is done for mitral regurgitation. Clinical trials are now being conducted to study the utility of TGF-β antagonists such as Losartan in controlling abnormal aortic root growth in Marfan syndrome patients. Ocular problems can often be controlled with eye glasses alone. Lens dislocation may require laser treatment or surgical replacement. Surgical intervention may be required for severe skeletal anomalies e.g. repair of severe pectus excavatum or vertebral column stabilization for severe kyphoscoliosis.[1,7]

Genetic Counseling

Marfan syndrome has an autosomal dominant pattern of inheritance. In approximately 75% of cases, the condition is inherited from an affected parent and in the remaining around 25% it occurs due to a de novo mutation in the proband.[1] If a parent is affected, the risk of recurrence in each sib of a proband is 50%. If neither parent is clinically affected, the proband usually has a de novo mutation and therefore the recurrence risk in the sibs is not significant; however, in rare cases, due to germline mosaicism in either parents, the recurrence risk in the sibs may be above the general population risk. The children of an individual with Marfan syndrome are at 50% risk of inheriting the mutant allele and the disorder. Prenatal testing for

pregnancies at increased risk is possible if the disease-causing mutation in the family is known.

Newer therapeutic strategies

Studies into the molecular pathogenesis of Marfan syndrome have led to elucidation of the fact that some of the phenotypic manifestations, especially the aortic root dilatation, result from excess activation of TGF-beta, a cytokine involved in cellular proliferation, migration and programmed cell death. Systemic administration of TGF-beta antagonists was found to reduce or prevent many disease manifestations including aortic aneurysm, emphysema and myxomatous valve disease in fibrillin-1 deficient mice. Angiotensin II receptor blockers such as Losartan decrease TGF-beta signalling and therefore their potential therapeutic benefits in Marfan syndrome are now being extensively studied.

Losartan was demonstrated to halt abnormal aortic root growth and prevent aortic aneurysm in a mouse model with a fibrillin-1 mutation by Dietz and colleagues in 2006.[8] This was found to be the result of both a reduction in hemodynamic stress and antagonism of TGF-β signalling in the vessel wall. Subsequently, a small cohort study of losartan in 18 pediatric patients with Marfan syndrome showed a significant reduction in the rate of aortic root enlargement.[9] Thereafter,more studies have been conducted in small cohorts of patients either comparing the efficacy of losartan versus beta blocker therapy (BBT) or studying the combined effect of losartan and BBT on the cardiovascular complications of Marfan syndrome and most of them have found that losartan provides more effective protection to slow the progression of aortic root dilation.[10,11] Groenink and colleagues have recently reported the results of a large, randomised, controlled multicentre clinical trial, wherein a total of 233 operated and un-operated adults with Marfan syndrome underwent randomization to either losartan (n = 116) or no additional treatment (n = 117) and the primary endpoint considered was aortic dilatation rate as determined by magnetic resonance imaging. Losartan treatment was found to reduce the dilatation rate of the aortic root and in patients who had already undergone aortic root replacement it was seen to reduce the dilatation rate of the aortic arch.[12]

With more and more studies showing promising results, TGF-beta antagonists such as losartan are likely to soon become the mainstay of treatment for the life-threatening cardiovascular complications of Marfan syndrome.

Key Messages

- Marfan syndrome is a hereditary connective tissue disorder affecting multiple body systems.
- Establishment of a definitive diagnosis of Marfan syndrome is based on the revised Ghent nosology.
- Pathogenesis of Marfan syndrome has not been fully elucidated but fibrillin-1 gene mutations are believed to exert a dominant negative effect and lead to excessive TGF-β signaling.
- High throughput molecular techniques such as whole genome, transcriptome as well as exome sequencing and gene expression studies using microarrays are being explored to understand the molecular mechanisms behind the high level of phenotypic variability in Marfan syndrome.
- Newer therapeutic strategies especially those targeting the TGF-β signalling pathways are being developed for management of the life-threatening cardiovascular complications of the disease.

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GeNeMail

Dear Dr Shubha and Dr Ashwin,

Season's Greetings! Thanks for sending me the latest issue of the Genetics Clinic Jan-Mar 2014. I am happy to see that with each issue the quality and content of the newsletter are getting better. I hope soon the newsletter is replaced by an excellent academic journal. Thanks for the touching obituary of Professor S S Agarwal. Please pass on my condolences to the bereaving family.

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Treatment Strategies for Triplet Repeat Disorders

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Triplet repeat disorders or trinucleotide expansion disorders (TRDs) are a class of genetic disorders caused by tandem expansion of a set of triple nucleotides beyond a certain limit in some specific genes. The first TRD was identified in 1991 and till now more than 20 disorders are known (Shown in Table 1). The characteristic features of TRDs are somatic and germline instability with a tendency to expand/contract during cell division.[1] Even after two decades of discovery and understanding of pathogenesis of these conditions, no definite curative treatment has been developed for any of these conditions. Because of similarity in molecular defect and pathophysiology it is hypothesized that common treatment approaches can be effective in many of these disorders. This article focuses on various therapeutic approaches which are being currently explored to treat this group of disorders.

Table 1, Characteristics of a few Triple Repeat Disorders, pathophysiologic mechanisms and their therapeutic strategies.

Name of triple repeat disorder and Type of triple repeats	Number of normal repeats	Repeats in disease condition	Gene	Pathogenetic mechanisms of the disease	Therapeutic Approaches
Huntigton disease CAG	6-29	38-180	HTT (exon 1)	Polyglutamine expansion	Mainly symptomatic, [Tetrabenazine is FDA approved], Antisense oligonucleotides, Antioxidants, modulators of neurotransmitters, Caspase inhibitors and Stem cell transplantation.
Spinocerebellar ataxias CAG	‹35	41-83	Coding part of the gene	Polyglutamine expansion	Antisense oligonucleotides, Exon skipping, Histone deacetlyase inhibitors
Myotonic dystrophy type I	5-37	›50	DMPK (3' UTR)	RNA toxicity disorder	Antisense oligonucleotides, ribozymes
Fragile X syndrome CGG	6-53	›230	FMR1 (5' UTR)	Loss of function	Histone deacetylase inhibitors, modulation of neurotransmitters
Friedreich ataxia GAA	5-30	70-1000	FXN (intron 1)	Loss of function	Antioxidants, Coenzyme Q^{10}, Iron chelators, Histone deacetylase inhibitors

Classification of Triplet repeat disorders

TRDs may be classified on the basis of type of sequence of triple nucleotides (CAG ,CTG, CGG, GAA, GCC), location of expanded repeats (noncoding / coding part of the gene), mode of inheritance (dominant/ recessive), pathogenesis (RNA toxicity, toxic polypeptides having expanded tracts of polyalanine or polyglutamine) or functional effects on gene (loss of function/toxic gain of function). For describing therapeutic approaches it would be easy to classify these disorders on basis of functional consequences.

Pathogenesis of TRDs

The hallmarks of each of TRDs are progressive nature and selective loss of certain group of cells. The pathogenic mechanisms in each of these TRDs usually are multiple ranging from epigenetic modification (methylation and/or histone deacetylation) and gene silencing (Fragile X syndrome, Friedreich ataxia), RNA mediated toxicity (Mytonic dystrophy I and II, spinocerebellar ataxia 8 and Fragile X tremor ataxia syndrome), interference with transcriptional regulation, binding with transcriptional factors (Myotonic dystrophy), abnormal accumulation of toxic protein aggregates (polyglutamine expansion disorders like Huntington chorea and Spinocerebellar ataxias) and oxidative damage to the cells (Friedrich ataxia, polyglutamine disorders).[1-4] Involvement of synaptic plasticity, metabolism of neurotransmitters and excitotoxicity have also been implicated important factors in pathogenesis.

Treatment strategies:

1) Symptomatic treatment

Currently, symptomatic treatment is being offered as the mainstay for TRDs. These include physiotherapy, orthopaedic aids, behavioural modification, counseling regarding occupation and reproductive issues and pharmacotherapy for symptoms like abnormal movements, muscle spasm and systemic manifestations like diabetes mellitus, cardiac problems and infertility in certain disorders. These modalities do not address primary pathology and do not have any effect on disease progression. Among these only Tetrabenazine is the approved by the US Food and Drug administration for treatment of Huntington disease (HD).[5] Few other drugs are in different phases of clinical trial including Mexiletine, Methylphenidate, (phase II/III trials in Myotonic dystrophy type I), idebenone and acyl L carnitine(open label) in Friedreich ataxia (FA), riluzole, various neuroleptics (phase III) in Huntington disease (HD), arbaclofen (phase III) in Fragile X syndrome (FRAXA) and lithium carbonate (phase III) in spinocerebellar ataxias [clinicaltrials.gov].

2) Gene replacement or gene augmentation therapy

This attractive approach is mainly for TRDs with loss of function of the gene. The two TRDs which have loss of function of the gene include FA and FRAXA. There have been a few studies published on potential gene therapy in FA fibroblasts and mouse models. Lim et al have demonstrated the functional validation of frataxin gene transfer via HSV1 viral vectors in mouse models after selective knock out of this gene in mouse brain.[6] Transfer of gene by systemic approach, crossing of blood brain barrier, regulation of expression and safety of these viral vectors are significant problems which need to be answered in future trials. Another approach for augmentation of gene function can be induction of gene expression by various techniques. Pharmacological treatments which have been tried include cisplatin, hemin and sodium butyrate. Various demethylating agents and histone deacetylator inhibitors (HDAC) are also in trials which decrease methylation and increase acetylation of histones respectively thus modifying the epigenetic changes.[7,8] In vitro use of 5-azadeoxycytidine and L-carnitine have been shown to decrease DNA methylation of gene promoter site of FMR1 gene. Another recent approach which is being explored as treatment option for FA is use of TALE proteins.[9] These proteins fuse with transcription activation domain of a gene and

increase the expression of gene located nearby. Among HDACs, benzamide derivatives have shown short term upregulation of frataxin protein in FA lymblastoid cell lines and modest improvement is sense of direction, locomotion and motor coordination in mouse models.[7] However their use in human beings is limited by presumed high chances of toxicity.

3) Treatment modality based on pathogenetic mechanisms

Type I metabotropic glutamate receptor (mGluR) signalling pathway is thought to play an important role in pathophysiology of FRAXA. Agents with antagonistic effect on mGluR have been shown to improve neuroanatomical and behavioural phenotype of FRAXA in Drosophila model. Arbaclofen, a drug which belongs to group of GABA-B agonist, is another agent which has been shown to improve social behaviour in mouse models and has completed a randomised double blind placebo controlled phase III trial in FRAXA patients. Minocycline, a drug which has been studied in double blind placebo controlled cross over trial in children with FRAXA and has showed improvement in behavioural abnormalities. Minocycline is thought to act through decreasing the increased metalloproteinase-9 levels in brains of knock out mouse model for FRAXA.[10] Same way, in case of FA, dysfunction of mitochondrial protein containing iron-sulfur complex have been implicated as important factor in pathophysiology and disease progression. Various iron chelators have been considered as a treatment option with minimal success. Recently mitochondrial specific iron chelator Pyridoxalisonicotinoyl Hydrazine has shown promising results.[1,4]

4) Treatment approaches in RNA toxicity TRDs

RNA mediated toxicity is implicated in Myotonic dystrophy type I (DMI) and type II (DMII), Fragile X tremor ataxia syndrome (FRTAS) and spinocerebellar ataxia type 8 (SCA8). RNAs with expanded CUG repeats acquire toxic gain of function and these abnormal transcripts accumulate in the nucleus in the form of intranuclear inclusions. These RNA aggregations sequester various RNA binding proteins (muscle blind and CUG binding protein1) and other proteins which regulate transcription and splicing and RNA processing. Ribozymes and Antisense oligonucleotides (AON) mediated silencing/suppression of these expanded RNA repeats and prevention of protein binding are two main therapeutic approaches which are being explored as promising therapeutic approaches in in vitro studies and mouse models. To be safe in vivo, these ribozymes/AON should target only expanded RNA repeats and not the wild transcript or any other RNA containing long CUG repeats. Barriga et al have studied multiple AON and have found that that length of AON and chemical properties are important determinants of their activity.[11] It is also hypothesized that abnormal RNA transcripts acquire small hair pin like conformation and can be selectively targeted by small interfering RNA (SiRNA) complementary to long repeated tracts.

5) Polyglutamine disorders

The examples of this group of disorders are Huntington disease, Dentatorubral-pallidoluysian atrophy (DRPLA) and number of Spinocerebellar ataxias (SCA). The common factor is expanded CAG repeats in coding part of a gene, which translates to long repeats of polyglutamine in polypeptides. The expanded polyglutamine form abnormal aggregates and affect the function of normal protein too (toxic gain of function). These protein aggregates are cleaved by cellular ubiquitin proteasomal system leading to release of toxic polypeptide fragments. The aggregation and cleavage of toxic protein is postulated to cause selective neuronal dysfunction and their death. These disorders are relentlessly progressive in nature and ultimately lead to significant morbidity. Various mechanisms which have been hypothesized to cause neurotoxic effects of these protein aggregations are interference in transcription regulation, neurotransmitter regulation, excitotoxicity and oxidative stress.

Various therapeutic agents are being tried to modulate each of these mechanisms. At gene level,

AON which block the function of abnormal expanded alleles have shown promising results in in vitro studies and animal models. However these AON will bind to normal alleles as well. Difference of single nucleotide polymorphism between normal and mutate allele can be a basis for preferential selection of mutation alleles by these AON. Also the safety of viral vectors and involvement of widespread but specific group of neurons pose important considerations. Evers et al have performed a study on use of AON as exon skipping agent and removing CAG repeats from ataxin3 gene responsible for SCA3.[12] Compounds like Benzothiazole, Congo red, Trehalose and chaperone based therapy have been shown to reduce protein aggregation and ameliorating some behavioural phenotypes in HD mouse model. Caspase inhibitors (minocycline) which inhibit proteolytic cleavage have been shown to increase life span in HD mouse models.[13] A randomised multicenter double blind pilot study (DOMINO, phase III trial) on use of minocycline in HD patients is recently completed and results have not been found to be promising.[14] Agents decreasing protein-protein interaction like Cysteamine and antibodies to polyproline region of mutant huntingtin protein have also been studied with limited success. For the modulation of various neurotransmitters, several studies have explored the effects of glutamate and N-methyl-D-aspartate receptors inhibitors (riluzole, amantidine, ketamine and baclofen). Antioxidants including ascorbate, Vitamin E, Idebenone (derivative of coenzyme Q10) creatine have shown limited success in ameliorating some features in animal models. Out of these, creatine and Idebenone have reached phase III clinical trials.

6) Protein or cell replacement

Various neurotrophic factors including brain derived neuronal factors, glial derived neurortrophic factors have been infused to stimulate growth of neurons in HD mouse models with varying degree of success. Furthermore, research in area of stem cell transplantation in neurodegenerative condition has a lot of potential to be developed as novel therapeutic approach and warrant further studies[15]. Stem cells provide a presumed source to replace lost neurons. Neuronal, mesenchymal and genetically modified stem cells when transplanted in HD animal models have provided positive response. The availability, type of stem cells, administration and safety of stem cell bases therapy are the questions which will be answered by future studies.

The limited success in dozens of therapeutic approaches in TRDs points towards the underlying complex and partially understood genetic mechanisms. In vitro studies and animal models have been important pillars for these trials. With advancement of knowledge of pathogenetic mechanisms we hope to see a better future for the families suffering from these conditions.

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Genzyme -SIAMG Fellowship - an unforgettable experience

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I came to know about the SIAMG – Genzyme clinical genetics fellowship when I had been to the IEMCON conference in New Delhi in April 2013. There was a strong desire to improve my knowledge of genetics which would add to my fetal medicine career. However, I had second thoughts about joining the fellowship program in the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), because of my lack of knowledge of Hindi and because I would have to leave my practice in Chennai for 3 months. As the fellowship came with a monthly stipend, my financial assistance was taken care of and I decided to join the program.

When I reached SGPGIMS, I got accommodated very soon in contrast to what I had expected and everybody was very helpful right from the Head of the Department to the other faculty members, residents and technicians. Soon I almost became like a newly joined resident.

The genetic feast would start every day by 8.30 AM with seminars or case presentations followed by OPD at 10 AM. In the afternoon I used to attend to antenatal USGs which would sometimes extend up to 7PM.

I had an opportunity to be a part of the ICMR course on basic genetics and genetic counseling for 15 days, where I was taught about the basics of genetics, laboratory techniques like karyotyping and molecular diagnosis. I also learnt how and when to use these techniques in patients. The technique of using databases like OMIM for literature search was also taught to me. All these made me become so much interested in Genetics that at the end of the course I was able to get the answer to the photoquiz in Genetic Clinics (which was Yunis Varon Syndrome – a condition I had never seen before).

Dysmorphology is an art which cannot be taught but can be acquired by observing the masters in the field. So I would never miss the chance to be with Dr Shubha Phadke in OPD, where I slowly started learning the art like Jackie Chan learning Kung Fu in Movies. I was able to diagnose a case of Emmanuel Syndrome and could also solve the next photoquiz in Genetic Clinics (Cutis laxa), which I consider a great achievement.

By seeing patients in the OPD, I was able to understand when to suspect chromosomal abnormality, single gene disorders and metabolic disorders. During my training in Fetal Medicine, I hardly had the opportunity to attend to the autopsy of a fetus completely. But during the fellowship program, I attended around 17 fetal autopsies.

Interpretation of a karyotype report had been difficult for me before joining the program. Now I have learnt the nomenclature used in a karyotype report. In the Cytogenetics Lab, I observed the technique of culturing, harvesting, and slide preparation, I examined slides and I learnt how to report a karyotype. I observed other techniques like DNA extraction, PCR, MLPA and Microarray and also learnt how the results are interpreted and applied clinically.

I was in the USG room daily in the afternoons and came across various fetal anomalies and learnt about counseling for them and also various invasive procedures. I was permitted to do some amniocentesis procedures. Although I cannot explain in words, I can now feel how knowing dysmorphology and genetics can change your approach to Fetal Medicine. One of the most interesting antenatal cases I saw was a case of fetal atelencephaly with 13q microdeletion.

It didn't stop with this. The opportunity to write a paper about Williams Syndrome with Dr. Shubha Phadke was the best one. By this I learnt a lot about the art of writing a paper. I was also impressed by her commitment to work and teaching.

In 3 months, I became a part of the department and it was so difficult for me to come out of it. I enjoyed the parties we had in between. I never felt homesick and never went home for 3 months. The friendly and

positive atmosphere gave me a lot of self confidence.

When I was about to leave, everyone including the residents and the faculty, made me realize how they valued my presence. I was really moved and understood how important it is to value human relationships! Where else will I learn this better? It was reinforced to me that "Hardwork and Sincerity never fails". I have learnt Hindi too!

Now I'm back in Chennai. It is only the beginning but now I know the path to move forward and I have so many hands to hold on to during my journey in Genetics. I want to thank God. SIAMG and Genzyme, for without them I would have missed such a place and people in my life.

GeNeXprESS

Newer therapies on the horizon: A ray of hope, for those who have none.

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Designer Aminoglycoside NB84 in Mucopolysaccharidosis type 1- Hurler [1,2]

Nonsense suppression therapy is a therapeutic approach aimed at treating genetic diseases caused by in-frame premature termination codons (PTCs; also commonly known as nonsense mutations). This approach utilizes compounds that suppress translation termination at PTCs, which allows translation to continue and partial levels of deficient protein function to be restored. Keeling and colleagues have reported two studies wherein they have tested the hypothesis that nonsense suppression therapy can attenuate the phenotype of the lysosomal storage disease mucopolysaccharidosis type I-Hurler (MPS I-H), the severe form of -l-iduronidase (IUDA) deficiency. -l-iduronidase enzyme participates in glycosaminoglycan (GAG) catabolism and its insufficiency causes progressive GAG accumulation and onset of the MPS I-H phenotype, which consists of multiple somatic and neurological defects. Sixty to eighty percent of MPS I-H patients carry a nonsense mutation in the IDUA gene. The first study by Wang et al. showed that 2-week treatment with the designer aminoglycoside NB84 restored enough -l-iduronidase function via PTC suppression to reduce tissue GAG accumulation in the Iduatm1Kmke MPS I-H mouse model, which carries a PTC homologous to the human IDUA-W402X nonsense mutation. The second study by the same group (Gunn G et al.) then reported that long-term NB84 administration maintains -l-iduronidase activity and GAG reduction in Iduatm1Kmke mice throughout a 28-week treatment period along with moderation of the disease in multiple tissues, including the brain, heart and bone. These studies represent the first demonstration that long-term nonsense suppression therapy can moderate progression of a genetic disease.

Activating paternal copy of UBE3A – ATS in Angelman syndrome [3]

A single stranded RNA that is complementary to messenger RNA (mRNA) is referred to as Antisense RNA. The antisense RNA hybridizes with its respective mRNA forming ds-RNA molecule which is rapidly degraded by ribonucleases blocking the expression of the gene. Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by maternal deficiency of the gene UBE3A which participates in many important neuronal functions such as synaptic development and signal transduction. In all cases of the disorder, at least one copy of paternal UBE3A is intact but is silenced by imprinting, by its antisense RNA, UBE3A-ATS, also transcribed from the paternal chromosome. It was speculated that by correcting the expression level of UBE3A via activating the silenced paternal allele, the disease might be treated. Linyan et al. have evaluated the phenotypic effect of activating the paternal allele of the UBE3A gene by depleting its

antisense RNA Ube3a-ATS in mice. This was done by premature termination of Ube3a-ATS by poly(A) cassette insertion. It was observed that this depletion of Ube3a-ATS activates expression of Ube3a from the paternal chromosome, and ameliorates many disease-related symptoms in the AS mouse model, including motor coordination defects, cognitive deficit and impaired long-term potentiation. These studies demonstrate the feasibility and utility of unsilencing the paternal copy of Ube3a via targeting Ube3a-ATS, as a treatment for Angelman syndrome.

Ivacaftor in Cystic fibrosis[4]

Cystic fibrosis (CF) is the most common autosomal recessive disorder in Caucasians. It is a multisystem disease affecting primarily the lungs, pancreas, hepatobiliary system, reproductive tract, gastrointestinal tract, and bones and is due to mutation in the gene that encodes the CF transmembrane conductance regulator (CFTR) protein. Until now, all treatments have targeted the downstream consequences of CFTR dysfunction rather than addressing the underlying CFTR defect. Three new agents, ie, Ivacaftor (orally bioavailable CFTR potentiator that is designed to increase the time that activated CFTR channels at the cell surface remain open), VX-809 (CFTR correctors which facilitate the trafficking of more CFTR molecules to the airway epithelial surface) and Ataluren (CFTR suppressors of premature termination codons), target the basic defects in production of CFTR. O'Reilly et al. have given a comprehensive review of in vitro experiments and clinical trials with these drugs. At present, Ivacaftor has shown the greatest therapeutic promise and trials have shown beneficial effects on lung function, number of respi ratory exacerbations, surrogate markers of CFTR function, nutrition and quality of life. It has been licensed in 2012 and is the first available treatment which addresses the underlying defect. However, it does have significant limitations in terms of cost and the current licensing agreement is only for those patients with a Gly551Asp muta tion, which represents only around 5% of the CF population. Despite these limitations, ivacaftor is an exciting development which may pave the way for other CFTR-modulating treat ments which may benefit more patients of cystic fibrosis.

Meclozine in Achondroplasia and other FGFR3 related skeletal dysplasias[5]

The drug repositioning strategy, in which a drug currently used for patients with a specific disease is applied to another disease, has the advantage that the identified drug can be readily applied to clinical practice, because the optimal doses and adverse effects are already established. Achondroplasia (ACH) is one of the most common skeletal dysplasias with short stature caused by gain-of-function mutations in FGFR3 encoding the fibroblast growth factor receptor 3. Masaki et al. screened 1,186 FDA-approved compounds to identify meclozine, an anti-histamine drug that has long been used for motion sickness that suppresses abnormally activated FGFR3 signaling in ACH. FGFR3 signal transduction leads to MAPK (mitogen-activated protein kinase) signaling which further causes sequential stimulation of a cascade involving RAS, RAF, MEK, and ERK. The authors have identified that meclozine suppresses fibroblast growth factor (FGF2) mediated phosphorylation of ERK. They have demonstrated that meclozine facilitates chondrocyte proliferation and mitigates loss of extracellular matrix in FGF2-treated rat chondrosarcoma (RCS) cells. The drug has been also shown to ameliorate abnormally suppressed proliferation of human chondrosarcoma (HCS-2/8) cells that were infected with lentivirus expressing constitutively active mutants of FGFR3-K650E causing thanatophoric dysplasia, FGFR3-K650M causing SADDAN (severe achondroplasia with developmental delay and acanthosis nigricans), and FGFR3-G380R causing ACH. It has also been confirmed that meclozine alleviates FGF2-mediated longitudinal growth inhibition of embryonic tibia in bone explant culture. It can be safely concluded that meclozine is a potential therapeutic agent for treating ACH and other FGFR3-related skeletal dysplasias.

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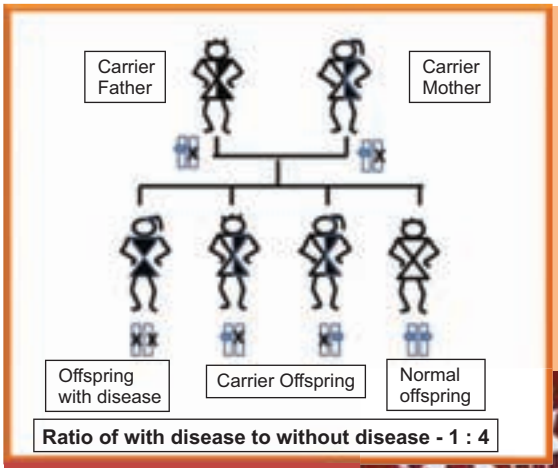
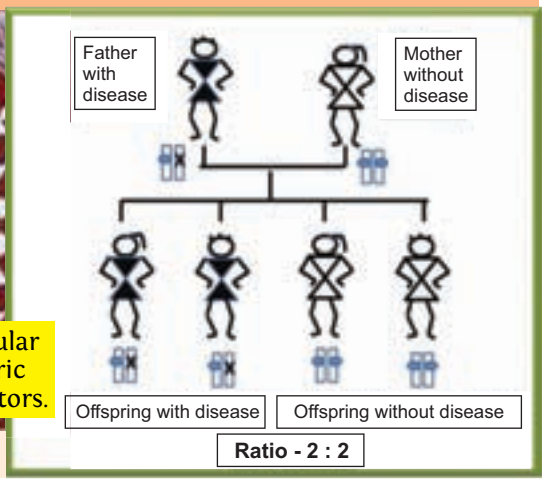
Pedigrees: Warli Style



Warli is a tribe located in the costal regions of Maharashtra – Gujarat border of India. They have a more than 2000 years old tradition of painting. They decorate the walls of huts and houses with paintings depicting people, animals and surrounding nature. The pictures are drawn using simple motifs of triangle and circle.

Warli motifs are popular amongst modern fabric designers and decorators.



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Announcement

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Award Support:
The fellow will be paid stipend for the duration of fellowship as per CDFD rules. No accommodation will be provided.

Schedule:
Next batch starts from July, 2014.
Last date for application: 1st May, 2014

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Announcement

SIAMG Fellowship in Clinical Molecular Genetics

Duration and scope:
Eighteen months training at Centre for DNA Fingerprinting and Diagnostics, Hyderabad

Eligibility:
A post-graduate degree (MD/ DNB) in Pathology/ Microbiology/ Biochemistry/Anatomy/Physiology.

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Schedule:
Next batch starts from July, 2014.
Last date for application: 1st May, 2014

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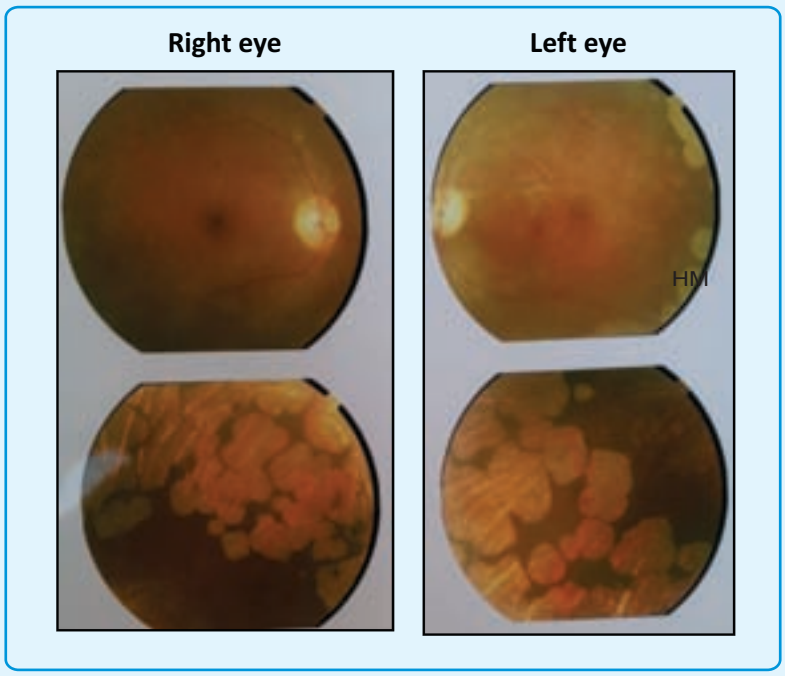
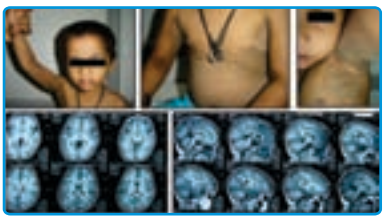
These are the fundus images of a 17 year old girl who presented with night blindness since 10 years of age followed by progressive bilateral diminution of vision. Identify the condition.



Please send your answers by email to editor@iamg.in

Answer to PhotoQuiz 23 of the previous issue

Sjogren-Larsson syndrome (OMIM # 270200)



Sjogren-Larsson syndrome (SLS) is an autosomal recessive disorder characterized by intellectual disability, spasticity of the limbs and ichthyosis. In addition to ichthyosis, hyperkeratosis is another important cutaneous feature and occurs in the palms, soles, neck, flexural areas and around the umbilicus. MRI brain findings include evidence of delayed and incomplete myelination and increased signal intensity in the periventricular white matter in T2-weighted images. Glistening yellow-white retinal dots are another characteristic feature of this condition, but may not be present in all cases. SLS is caused by homozygous or compound heterozygous mutations in the ALDH3A2 gene. This gene on chromosome 17p11 encodes fatty aldehyde dehydrogenase. There have been some reports of clinical improvement in SLS with fat restriction and supplementation with medium chain triglycerides.

Correct responses were given by:
Beena Sivan, Chennai

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