genetic CLINICS

Newsletter of Genetics Chapter of Indian Academy of Pediatrics

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GeNeDiT

Era of Genetic Medicine

Shubha Phadke

It gives me great pleasure to bring out the first issue of the newsletter of **Genetics Chapter of Indian Academy of Pediatrics** for the medical geneticists and the clinicians interested in genetics. The rapid and exciting advances in the field of research in genetics during last century have found a lot of applications in clinical medicine. The research based specialty of genetics has found its way from laboratory to the clinics. This has led to the development of specialties of medical genetics and clinical genetics. There has been an exponential growth of knowledge of genetics day by day and involves not only classical genetic diseases like Mendelian [monogenic] disorders and chromosomal disorders, but also common multifactorial disorders and pharmacogenetics. Like many others, I have been following the development of medical genetics in India for the last 20 years and contributing to it by way of teaching, training in genetics and establishing and delivering patient care services in the field of genetic disorders. Although Indian doctors have entered relatively late in this field of medical genetics, there appears to be a sudden spurt in the growth of clinical genetic services and research in India over the last 5 years. This made us realize the need to form a platform for interaction of clinical geneticists and clinicians interested in genetics in India. And hence, here is **'Genetic Clinics'**!

Genetics can be seen in two perspectives:- one, as a fundamental science which forms the basis of biology, and secondly, a medical specialty which deals with diagnosis and management of genetic disorders encompassing each and every system of the body. When seen by either of the two perspectives, it is necessary for all medical practitioners to know genetics. Now the knowledge of physiology and pathology has shifted from cellular to molecular level. DNA is the basic molecule of all biological processes and understanding about the structure and function of genes is essential. Like anatomy, physiology and biochemistry, which are taught at the initial part of medical training, equal stress needs to be given on the teaching of basic principles of genetics, gene structure and function in the first M.B.B.S. teaching. The other aspect of genetics is clinical genetics, which includes clinical approach to genetic disorders and clinical presentations suggestive of genetic disorders and the use of DNA based tests and chromosomal analysis. These tests are commonly referred to as genetic tests and are becoming increasingly available in India. Moreover, the samples can be sent anywhere in the world for diagnostic testing. The diagnosis and management of genetic disorders is included under clinical genetics. The management of genetic disorders varies greatly from curative treatment by bone marrow transplantation or surgery to preventive treatment by vitamins, special diets, etc. Many more strategies for successful treatment of genetic disorders are available. But, for many genetic disorders, the treatment is still mainly palliative or supportive and prognosis for survival or quality of life is poor. Due to this, genetic counseling and prenatal diagnosis form the mainstay of management for families at risk of genetic disorders. There is a rapid increase in the diagnostic armamentarium. Newer modalities of therapy like enzyme replacement therapy are found to be successful and many more new approaches like stem cell therapy and antisense therapy are showing promise. With rapidly improving knowledge of molecular bases of genetic disorders, new strategies for treatment are being tried and 'cure' for many so called untreatable disorders is no more a mere distant dream!

At this juncture, all medical fraternity in India need to update themselves with the basic and applied knowledge of genetics, so that the fruits of new developments in genetics reach the Indian patients. The appropriate clinical situations where genetic testing and genetic counseling is required need to be identified by every primary treating physician or a specialist and referred to a clinical genetic centre. As genetic disorders can involve any organ of the body, all the specialists need to be aware of genetic disorders of their specialty. At present, the number of medical geneticists in India is very very small and there is an urgent need of training clinicians in medical genetics. With short term training, interested clinicians can learn the basic principles of genetics and genetic counseling and can take care of common genetic problems.

Realizing the importance of genetics, Medical Council of India has also decided to upgrade the curriculum of genetics in undergraduate and postgraduate medical education. Of course, the implementation of the curriculum involving modern genetics needs training of teachers. Each medical college needs to identify a few teachers and get them trained. These nodal teachers can teach and coordinate courses in clinical and basic genetics at various levels of medical education.

The newsletter **'Genetic Clinics'** plans to function as a forum for teaching and learning of medical genetics for clinicians. The articles will be aimed at presenting approaches to genetic problems and, along with the latest information about the genetic disorders, clinicians can contribute interesting cases with unusual findings, diagnostic dilemmas. We will also try to provide information regarding exciting developments in the field of research in genetics. Hope, the effort succeeds in spreading enthusiasm and awareness about medical genetics in the medical fraternity of India.

Shubha Phadke
27th July, 2008

Genetic Clinics

Genetic Clinics invites articles related to the field of clinical genetics. Original research articles, approach to common clinical problems, reviews, case reports, letters to the editor, etc are welcome. The articles should be brief and conform to Vancouver style of referencing. We also seek suggestions and constructive criticisms to improve this newsletter. The electronic versions of the articles and correspondences should be mailed to geneticsiap@gmail.com .

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GeNeViSTA

Cytogenetic Testing in Clinical Practice

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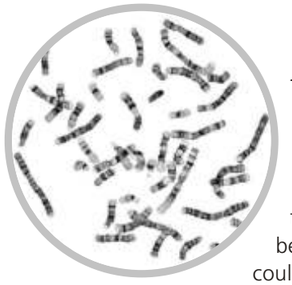


As early as in 1882, Walther Flemming, an Austrian cytologist and professor of Anatomy had published the first illustration of human chromosomes. It then took several decades before Tjio and Levan in 1956 could prove that the total number of chromosomes in a human cell is 46. In 1959, Lejeune studied the chromosomes from patients with Down syndrome and described an extra chromosome in each cell. Since then, several chromosomal abnormalities are well characterized. Here, I discuss briefly on indications for chromosomal analysis.

Structure of a Chromosome

The word 'chromosome' is derived from the Greek words for 'colored body'. Human cells contain 46 chromosomes comprising 22 pairs of autosomes numbered from 1 to 22 and a pair of sex chromosomes (two X chromosomes in females and one X and one Y in males). The numbers are assigned in descending order of length, size and centromere position of each chromosome pair. Each chromosome is made up of a shorter 'p' arm and the longer 'q' arm joined at the centromere. The ends of chromosomes are referred to as telomeres. Metacentric chromosomes have centromere at the middle position of the chromosome. Submetacentric chromosomes have centromere between the middle and the tip and an acrocentric chromosome near the tip. Acrocentric chromosomes may have satellites beyond the centromeres.

Karyotype

Karyotype refers to the ordered display of chromosomes starting from the largest chromosome 1 to chromosome 22 followed by sex chromosomes. A karyotype is prepared either by using computer software or manually arranging the images of chromosomes (cut from a photograph). Chromosomes can be analyzed from any actively dividing cells. Usually, peripheral blood lymphocytes are stimulated to undergo multiplication by phytohemagglutinin in a culture bottle. Other common sources are bone marrow, amniocytes, chorionic villi and skin fibroblasts. The dividing cells are arrested in metaphase by colchicin, a mitotic inhibitor. These cells are then treated with hypotonic solution to destroy the cell membranes and then fixed with fixative made up of methanol and acetic acid. The cell pellet of appropriate quantity is dropped on to glass slides to get 'metaphases' (chromosomes from a single cell are usually found in groups). The chromosomes are then 'banded' using trypsin and stained by Giemsa to give G-bands, with alternate dark and light bands of various sizes along the length of chromosomes. Several other banding techniques are available, but are used in specific indications. Modifications of the technique permit high resolution banding. Metaphases are then seen under a microscope, imaged, individual chromosomes identified based on their size & band pattern & then arranged to get the **'karyotype'** (Fig.1)

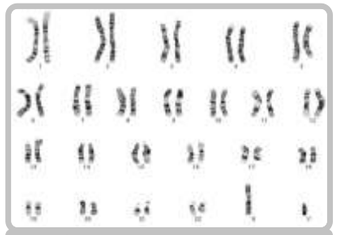
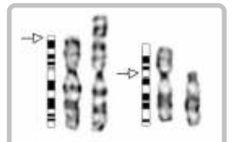


Fig. 1: A normal male karyotype



Partial karyotype showing translocation between chromosomes 7 and 11

Chromosomal Abnormalities

Chromosomal abnormalities are either numerical or structural. Polyploidy refers to the cell that contains a multiple of 23 chromosomes. A triploid cell contains 69 chromosomes and tetraploidy refers to presence of 92 chromosomes. Most commonly seen abnormalities are aneuploidies (not a multiple of 23 chromosomes). These include monosomy (only one copy of a chromosome in otherwise diploid cell) or trisomy (3 copies of a chromosome) and tetrasomy (4 copies of a chromosome). Common examples include trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome), monosomy X (Turner syndrome) and Klinefelter syndrome (47,XXY). A mosaic contains two or more cell lines with different chromosomal constitution.

Structural chromosomal abnormalities are identified by the band pattern. Balanced rearrangements have no loss/gain of chromosome material whereas unbalanced rearrangements have either loss or gain of chromosomal segments. Deletions refer to loss of a part/segment of a chromosome. In duplication, an extra copy of a genomic segment results in a partial trisomy. In inversion, a segment of chromosome is broken at two places and rejoined in the reverse orientation. Inversions may be pericentric when the breaks are on either side of the centromere or paracentric when they are on one side. Translocation involves transfer of a segment of a chromosome to another chromosome. Reciprocal translocations represent one of the most common structural rearrangements in man. It results when two different chromosomes exchange segments. Robertsonian translocations are non-reciprocal and occur when the long arms of any two acrocentric chromosomes join to produce a single metacentric or submetacentric chromosome. Other structural abnormalities are isochromosome (both the arms are similar), ring, dicentric or acentric chromosomes. Microdeletions are small deletions that usually escape detection during routine karyotyping because of the small size of the deletions. A specific test like FISH (Fluorescent in situ hybridization) is necessary to detect these abnormalities.

When to order a Karyotype?

Karyotype is one of the most commonly used 'genetic' tests. By asking for a karyotype, the clinician intends to look for structurally visible chromosomal abnormalities under the microscope. These include numerical and large structural chromosomal abnormalities. Such situations are common in clinical practice.

i) Suspected known Chromosomal Syndromes

Down syndrome is by far the commonest chromosomal abnormality encountered by a pediatrician in the clinics. In most situations, the diagnosis is obvious by clinical examination alone. However, newborn babies may have only few identifiable features at birth posing diagnostic challenge to even an experienced pediatrician. About 4% of cases of Down syndrome result from Robertsonian translocations. In these situations, one of the parents may be a normal carrier of this translocation, which increases the risk of recurrence of Down syndrome to 5-15% (100% if the translocation involves two 21 chromosomes). Here the risk of recurrence thus increases from 1% in the family with Down syndrome due to trisomy 21. To give a definite risk of recurrence, karyotype of affected child is essential in all cases of Down syndrome.

The definitive diagnoses of trisomy 18, trisomy 13, Turner syndrome, Klinefelter syndrome are established by karyotyping.

ii) Special Chromosomal Studies

In some situations, specific studies on chromosomes aid the diagnosis. Fragile X syndrome (fragile site on X chromosome) and chromosomal breakage syndromes like Fanconi anemia, Bloom syndrome, ataxia telangiectasia etc illustrate conditions where modified cytogenetic studies confirm the clinical diagnosis.

iii) Unexplained Mental Retardation

All children with mental retardation need to have a karyotype with good resolution (around 550 bands should be visible on haploid set of chromosomes). The overall yield of karyotype is reported to be in the range of 4-28% (selection criteria varies in different studies, some include Down syndrome). As cognition is likely to be determined by several genes spread throughout the genome, even a small aberration is expected to have significant effect on mental function.

iv) Disorders of Sexual Development

Individuals with ambiguous genitalia, delayed or incomplete pubertal development, oligo / azoospermia, primary amenorrhea need a karyotype. Often Turner syndrome, Klinefelter syndrome are diagnosed in this manner. Many a times they aid further diagnostic evaluation as in a case of ambiguous genitalia.

v) Short stature in a pre-pubertal female

Turner syndrome should be ruled out as short stature can be the only manifestation of this condition in pre-pubertal females.

vi) Pregnancy loss and infertility

Chromosomal structural rearrangements can often lead to recurrent spontaneous abortions and infertility. The chance of karyotypic abnormality is higher (about 5.5%) if the first trimester losses are 3 or more. Some of these families may also have abnormal offspring with malformations and mental retardation due to unbalanced chromosomal abnormalities. Hence, karyotype not only identifies the cause of poor reproductive outcome, but also serves to offer counseling and prenatal testing for future pregnancies.

vii) Parents of a child with structural chromosomal abnormality

Some of the structural chromosomal abnormalities arise from balanced rearrangements in parents who run the risk of future offspring with chromoso-mal abnormalities and birth defects. Parents of a child with translocation Down syndrome need karyotyping.

viii) Malignancies

Some hematological malignancies are known to be associated with chromosomal abnormalities. Chronic myeloid leukemia requires karyotype for diagnosis (to look for Philadelphia chromosome, a balanced translocation involving chromosomes 9 and 22) as well as assessing the response to therapy.

ix) Child with monogenic disorder

Usually children with known monogenic condition do not require karyotyping. It may be considered if the child has additional unexplained mental retardation or if the child has more than two monogenic disorders.

x) Prenatal diagnosis

In pregnancies at risk of a chromosomal abnormality, karyotype may be done from chorionic villi or amniocytes. Commonly, couple with previous child with chromosomal abnormality, advanced maternal age, carriers of balanced chromosomal rearrangements, fetal malformation detected by sonography, positive triple test, fetal markers of aneuploidy are offered prenatal fetal karyotyping.

What is the limitation of karyotype as a diagnostic test?

Karyotype detects numerical chromosomal abnormalities and large rearrangements of chromosomes. Small submicroscopic alterations below 4-5Mb size are usually not picked up by routine karyotype. It is important to remember that most Mendelian disorders have mutations involving only one or very few nucleotides, and are not diagnosed by karyotype. It is also worthwhile to note that even though karyotype is of one of the genetic tests with high yield, a karyotype has limited resolution that is reasoned by the large size and complexity of the human genome. Structural abnormalities have provided clues to the location of genes of several single gene disorders like Duchenne muscular dystrophy and contributed immensely to research in identifying disease genes.

GLI3 Gene and Syndromes of Polydactyly

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Abstract:

The similarity between different malformation syndromes has been observed by clinical geneticists since long. With identification of causative genes for many malformation syndromes, the answers for the clinical similarities have been found for some syndromes. Here, we present two cases, one of Greig cephalopolysyndactyly syndrome (GCPS) and the other of Pallister-Hall syndrome (PHS). Both the disorders are caused by mutations in the GLI3 gene. The interesting aspects of genetic etiology are discussed.

Case 1

The first child was a 5 years female. She was born to non-consanguineous parents at term with no antenatal or birth complication. She had a younger sibling who is normal. The parents did not have any anomaly of digits or facial dysmorphism. Their heights were also normal.. There was delayed development and mild dysmorphism noticed since early childhood. On examination, she had a pleasant personality with facial dysmorphism in form of depressed nasal bridge, broad face and forehead, convergent squint and ocular hypertelorism (Fig.1). She had postaxial polydactyly in right hand and brachydactyly in both hands at birth, along with soft tissue syndactyly. Extra postaxial digit on right hand was surgically removed. She was operated for syndactyly as well (Fig.2). Scars following attempt to relieve the syndactyly were seen. Left great toe was broad with preaxial polydactyly (Fig.3). Right great toe and both thumbs were also broad. Mild genu valgum was noted. Her weight was 17 Kg (at 50th centile for age), height was 97 cms (at 3rd centile for age) and head circumference was 49.5 cm (at 50th centile for age and at around 75th centile for her height age). Her DQ was 60% for gross motor, 50% for fine motor and 40% for language and socio-adaptive. Her karyotype at 550 band level was normal. Other investigations showed a normal abdominal ultrasonography and mild ventriculomegaly and prominent cavum septum pellusidum in neuroimaging. Her clinical features were suggestive of Greig cephalopolysyndactyly syndrome (GCPS), though mental retardation and short stature are uncommon in GCPS.

Fig. 1: Depressed nasal bridge, broad face, squint and hypertelorism in GCPS

Fig. 2: Syndactyly and scars following attempt to relieve the syndactyly in GCPS

Fig. 3: Broad great toe with preaxial polydactyly in GCPS

Case 2

The second child was a 3 year old male admitted in the gastro-surgery ward for surgical correction of anorectal malformation. The anesthetists had detected a bifid epiglottis during endo-tracheal intubation. He also had unilateral kidney, undescended testis, oral frenula, mild facial dysmorphism and central (i.e., insertional or mesoaxial) polydactyly in all four limbs (Fig. 4 & 5) characteristic of Pallister-Hall syndrome. His DQ was around 30% in all fields. There was no history of seizure. The family did not opt for further diagnostic work up like neuroimaging.

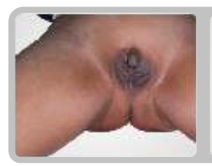

Fig. 4: Anorectal & genital malformation in PHS

Fig. 5: Insertional polydactyly in PHS

Discussion

The first case had features of Greig cephalosyndactyly (GCPS) along with mental retardation and short stature. Cases of GCPS associated with mental retardation and other anomalies are reported usually in association with chromosomal rearrangements or microdeletion[1,2]. Our case did not have structural anomaly involving chromososme 7 where GLI3 is located. Orofaciodigital syndromes are another group of syndromes with similar digital anomalies, midline anomalies and other features. But the present case did not have pseudocleft of the lip and tongue hamartomas typical of orofaciodigital syndromes. Mutation testing in GLI3 gene is necessary for this case as the clinical features are atypical.

The other case had features typical of Pallister-Hall syndrome. Both the syndromes are inherited in autosomal dominant fashion and there is no significantly increased risk in the sporadic cases with normal parents. Study of mutations will help in confirming the clinical diagnosis and also can help to provide definitive prenatal diagnosis to allay the anxiety of the family. Ultrasonographic examination can also look for digital anomalies.

Both the above disorders, GCPS and PHS are genetically related (allelic) autosomal dominant disorders due to mutations in GLI3 gene (chromosomal locus 7p13[3]). They however have different phenotypic manifestations. The features of the syndromes with similar features of midline anomalies associated with polydactyly are compared in table1.

GCPS is characterized by pre-axial polydactyly or mixed pre-and postaxial polydactyly, syndactyly, ocular hypertelorism, and macrocephaly (found in around 52% patients). Some individuals with GCPS can have a high, prominent, or bossed forehead. Intelligence and height is usually normal or near normal in most cases.

Features of Pallister-Hall syndrome comprise of central (or postaxial) polydactyly, hypothalamic hamartoma, bifid epiglottis, imperforate anus or anal stenosis, and other anomalies[3]. PHS displays a wide range of severity. It is often assumed that PHS is severe and Greig cephalopolysyndactyly syndrome is mild. Some individuals with PHS show multiple severe anomalies such as pituitary dysplasia with panhypopituitarism and laryngeal clefts or other airway anomalies, which may be life threatening in the neonatal period. However, many individuals with PHS are mildly affected with polydactyly, asymptomatic bifid epiglottis and hypothalamic hamartomas.

Other syndromes with midline anomalies and polydactyly are 'acrocallosal syndrome' (ACLS) and subtypes of oral-facial-digital syndrome. Acrocallosal syndrome (ACLS) includes pre-or postaxial polydactyly, syndactyly, agenesis corpus callosum (rare in GCPS), ocular hypertelorism, macrocephaly, moderate to severe mental retardation, intracerebral cysts, seizures, and umbilical and inguinal hernias. The disorder appears to be inherited in an autosomal recessive manner[4,5]. GLI3 mutations have been also described in a few individuals with acrocallosal syndrome. Some forms of pre and post-axial polydactyly are also caused by GLI3 mutations[6]. However, polydactyly, by itself has been shown to have genetically heterogeneous; thus involving different genes.

Genotype-phenotype correlation of GLI3 mutations

Some genotype-phenotype correlation has been demonstrated as per the class of mutations and their locations. Mutations of all types can cause GCPS whereas the mutations that cause PHS are frameshift mutations. Haploinsufficiency, actual or functional, for GL13 causes GCPS[7], whereas truncation mutations generally cause PHS[8]. Among all frameshift mutations in GLI3, mutations in the first third of the gene are only known to cause GCPS. Frameshift mutations in the middle third of the gene cause PHS, and rarely GCPS. Frameshift mutations in the last part of the gene cause GCPS. However, there is no apparent correlation of the mutation position within each of the three regions and the severity of the respective phenotypes.

Table 1: Comparison of features of syndromes with midline anomalies and polydactyly

FEATURES	Greig Syndrome	Pallister Hall Syndrome	Oro-Facio-Digital Syndrome Type I	Acrocallosal Syndrome
Hypertelorism	+ +	+	+	+
Macrocephaly	+	-	-	+
High forehead	+	-	-	+
Frontal bossing	+	-	-	-
Broad nasal root	+	+	+/-	+/-
Flat midface	-	+	-	-
Midline hemangioma	-	+	-	-
Ear anomalies	-	+	+	+
Tongue & mouth anomalies	-	Frenula in mouth	++	-
Hyploplastic alae nasi	-	-	+	-
Midline cleft/ pseudocleft	-	-	+	-
Hypothalamic hamartomas	-	+	-	-
Panhypopitutarism	-	++	-	-
Hypoplastic corpus callosum	+	-	+	+
Cerebelar hypolplasia	-	-	+	+
Seizure	-	Gelastic seizure/easy to control	Myoclonic	Difficult to control
Mental retardation	+	+	+	++
Insertional polydactyly	-	Y shaped metacarpal/metatarsal	-	
Post axial polydactyly	+	+	+	+
Preaxial polydactyly	At least 1 limb / broad thumb / toe	+/-	+	+
Cutaneous syndactyly	+	Variable	+	+
Clinodactyly 5th	-	-	+	-
Bifid epiglottis	-	+ (characteristic)	-	-
Tracheal / Lung	-	+	-	-
Anal anomaly	-	Imperforate anus	-	-
Renal	-	+	+	-
Inguinal hernias	-	-	-	+
GLI3 mutation position	all	Central	-	5' end
GLI3 mutation type	all	Frameshift	-	point mutation
Inheritance	AD	AD	AR/XL	AR
Prevalence	Rare	Very rare	-	-
Outcome – Variable	-	Neonatal Death (hypoadrenalism)	-	-

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Contributed by:
Dr Parag Tamhankar & Dr Prajnya Ranganath

The Perfect Mis~Match[1]

The archetype gene fusion BCR-ABL1 gives a great insight into tumour biology, and aids diagnosis and therapy of chronic myeloid leukemia. In a recent article in Nature Reviews Cancer (July 2008 issue), Chandan Kumar Sinha et al from Comprehensive Cancer Center, University of Michigan Medical School provide a brief look into the complexities of gene fusions. Gene fusions have been described in papillary thyroid cancers (RET-NTRK1), follicular thyroid carcinoma (PAX8-PPARG), mucoepidermid carcinoma (MECT1-MAML2), renal carcinoma (TFE3-TFEB) and in midline carcinomas (BRD4-NUT). Steps included in detecting gene fusions are COPA (Cancer outlier profile analysis) in which 'outlier' genes emerge from the microarray data analysis. These outlier genes form the candidate genes for further cytogenetic and molecular analysis.

The next step- Exon walk PCR involves a quantitative real time PCR specific to exons of all part of the gene. Any sharp divergent expression pattern from different parts of the gene indicate that the gene may be split or rearranged. Further step RACE (rapid amplification of cDNA ends) is used to identify the 5' and 3' ends of the cDNA transcript to identify the fusion product. This is finally confirmed by FISH (fluorescent in-situ hybridization techniques). These steps have helped identify TMPRSS2-ERG fusion as the incriminating one in prostate cancer. This gene fusion has been associated with androgen treatment resistance, higher risk of metastasis and death from prostate cancer. Identification of these gene fusions may open up new therapeutic options for prostate cancer.

Sequencing all Exons of Genome, all in a Days' Work??[2]

The entire human genome map has been sequenced after a decade of painstaking research. However replicating this feat on a daily basis was a dream until some time back. Routine sequencing is usually performed on amplified PCR (polymerase chain reaction) products which are usually small parts (exon) of a gene. Therefore sequencing multiple genes at a go was definitely not a single day's job. This has been changed with the introduction of 'genome-wide exon in-situ recapture' by Hodges et al. This involves a microchip-based process in which genomic material is broken into pieces by sonication. The resultant pieces are captured on to a chip which has various sequences corresponding to all variations of protein forming genes. Then after a thorough wash the rest of the non-protein encoding DNA is washed away. The captured DNA fragments are then eluted by heating and their ends are bound with a common linker. Then using primers for this common linkers all the DNA fragments are amplified using PCR. Rapid high throughput sequencing is then used to identify the relevant sequences.

Looking Up Down Syndrome.[3]

Maternal screening for Down syndrome has until today looked at indirect serum markers. Amniocentesis though an accurate diagnostic method is fraught with a small but significant risk to both mother and fetus. With recent advances in proteomics we are now looking at presence of fetal proteins in maternal circulation for a rapid, non-invasive and accurate diagnosis and not just a screening test. Kolialexi et al from Athens University School of Medicine, Greece compared levels of nine serum proteins in mothers with Down syndrome fetuses with that of gestational age-matched mothers with normal fetuses. They found that serum levels of ceruloplasmin precursor, apolipoprotein E precursor, alpha -1- antitrypsin precursor, serum amyloid P component precursor, alpha-1-microglobulin precursor, transthyretin precursor, histidine rich glycoprotein precursor, alpha albumin precursor, were increased in mothers with Down syndrome fetuses, while serum level of clusterin precursor was decreased in them. These nine proteins measured in the second trimester of pregnancy are related to fetal growth and development. They conclude that long term cohort studies are necessary to validate their preliminary findings.

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One year old girl, presented with growth, retardation, developmental delay, microcephaly, camptodactyly. Note the eye changes and characteristic skin lesions.

GIVE THE DIAGNOSIS

The answers should be sent to geneticsiap@gmail.com

The names of responders with the correct diagnosis will be published in the next issue.

Training in Medical Genetics

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Department of Medical Genetics offers the following courses/training programs:

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