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Editorial

ELSI: Increasing complexities for researchers, patients and research volunteers

It is said that the modern advancements in medical science have created many ethical issues which the social scientists need to solve. Ethical, legal and social issues (ELSI) of genetics research and their applications in genetic practice have become a major area of work all over the world. Issues like prenatal diagnosis of disorders of varying severity, uncertainty of outcome in some of the prenatally detected cases, selection of suitable embryos for implantation by preimplantation diagnosis and counseling for pre-symptomatic diagnosis of late onset untreatable disorders like Huntington disease are some of the issues faced by a genetic counselor every day. Recent developments during the last decade like use of microarray, genome sequencing in clinical practice and genome wide association studies for research are the hot topics of ELSI these days. The importance of this can be understood by the load of publications in these areas. This year 'Genomic Medicine' has been publishing articles on the various ELSI related aspects which provide an overview of the subject.

The important problem associated with the new technology in genetic diagnosis is the enormous amount of information obtained and many uncertainties created due to ambiguous results of uncertain significance. This is the major problem related to the use of microarray for chromosomal analysis (CMA). The strength of the technique is its ability to screen the whole genome at a very high resolution. This can lead to identification of causative genomic imbalances in as high as 20% cases of mental retardation and other developmental disabilities. But it also leads to identification of many small and large deletion / duplications of unknown significance. Counseling of families for such results is a challenge and sometimes may do more harm than good. New uncertainties are added to the family's problems and concerns about the etiology of developmental disabilities. The problem is compounded when the identified genomic imbalance is associated with late onset cancer or increased possibility of psychiatric problems. Imagine the situation when such a cytogenetic microarray result is obtained on a prenatal sample. A large amount of data is now available on prenatal cytogenetic microarray indicating a good yield; but at the same time there is one percent possibility of results of unknown significance. One can imagine the complexities of pre and post test counseling for prenatal CMA. As interpretation needs testing of the parents as well, detection of cancer related or psychiatric disease related copy number variations in an asymptomatic parent is a major ethical dilemma.

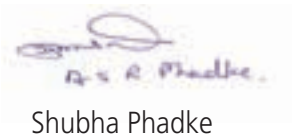
What has been mentioned above for CMA, applies for whole genome sequencing (WGS) or exome sequencing also. These techniques are being used for identification of causative genes in clinical as well as research settings. The huge amount of data generated provides a lot of information which was not asked for. Which of the results should be told to the individual continues to remain a matter of debate. The same issues come up when WGS and genome wide associations are done in volunteers for research. The ELSIs are compounded by the fact that the WGS data is for the lifetime of an individual and the interpretation will keep on changing in the future with the availability of more information. How much information is to be returned to the donor who has donated the sample for research is also being debated a lot.

Whatever may be the techniques or strategies used for research, the most important requisite these days are tissue banking or DNA banking. There are huge repositories of tissue samples, DNA samples and cell lines of patients with common multifactorial diseases, rare monogenic diseases and volunteers. Informed consent of the donor is a must. The question is what and how much information needs to be given and whether it is possible to give

complete information, as the bank itself does not know who will use the sample and for what purposes. As the samples are to be stored for decades, even the researcher may not know what will be the research plans in coming years. So the question has arisen now as to whether 'informed consent' is possible or not. The other issue with such tissue repositories and DNA banks is privacy. The researcher guaranties privacy by way of various mechanisms like coding or completely anonymizing the samples. But in this era of WGS and electronic medical data of whole populations, privacy can never be maintained. With so many complexities, taking consent for a sample or a test in patient care or research settings is extremely difficult. The task of communicating a huge amount of highly complex scientific information and sharing of uncertainties before sampling and after communication of results is extremely difficult. Scientists have been studying ways of providing this information in a digestible form.

Population based screening for at risk alleles, for carrier status for autosomal and X-linked recessive disorders and the rapidly expanding panel of newborn screening are some more challenges of the day. Some of the examples for these are screening for cancer predisposing genes, screening of neonates for untreatable diseases like Fragile X for preventing recurrence in the family or screening of neonates for diseases like Fabry disease or hemochromatosis which have treatments but extremely variable natural course not clear to us today. Though technically everything is possible today a lot of work in the medical aspects including natural courses of the diseases and psychosocial implications is needed before these techniques can be implemented.

In addition to the issues mentioned above new ELSIs visible on the horizon are much more challenging as they deal with the complexities of behavioral sciences. The genetic component in the etiology for behavior is being extensively studied and now genes for some are getting identified. The 'Smart gene' for instance is a gene for memory identified in mouse. Genetics of addiction, homosexuality, criminal behavior, etc are being looked for. Human behavior is a complex, multifactorial and dynamic phenomenon. The identification of contributing genes may or may not find cure for behavioral abnormalities but it is sure to pose many dilemmas for mankind.



Shubha Phadke

1st July, 2012

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Sonographic Diagnosis of Fetal Suprarenal Masses: A Report of Two Cases

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Summary

Prenatal ultrasonography helps in detection of rare fetal lesions like suprarenal masses, with its varied differential diagnoses like neuroblastoma, adrenal hemorrhage, and extralobar pulmonary sequestration. These lesions should be carefully followed during the antenatal period and may require fetal therapy and early neonatal intervention. We present two cases of prenatally detected fetal suprarenal masses; one detected in the third trimester on the right side and the other in the second trimester on the left side. The first baby had neuroblastoma, whereas the second baby was diagnosed to have extralobar pulmonary sequestration with congenital adenomatoid malformation. Both babies got operated postnatally and are doing well.

Case Report

Case 1: A 26-years-old primigravida, married non-consanguineously with no significant family history, was found to have a hypoechoic lesion with hyperechoic areas of 6.3 x 3.9 cm in the region of the fetal right suprarenal gland on a routine ultrasound at 36 weeks gestation. Ultrasonography at 20 weeks gestation was reported to be normal. The lesion was displacing the right kidney inferiorly (Figure 1a). Color doppler study showed blood flow into the lesion. A provisional diagnosis of neuroblastoma was made. Serial ultrasound done weekly, showed slight increase in size (6.7 x 4.7 cm) of the mass, without any changes in the echotexture. There were no lesions in the fetal liver/placenta suggestive of metastasis, no evidence of hydrops fetalis and the amniotic fluid index was normal. The mother did not develop preeclampsia or other symptoms of excess catecholamine secretion. Emergency cesarean section was done in view of non-reassuring fetal heart rate and a live female baby of 2.5 kg was delivered. The baby had to be intubated in view of bradycardia and feeble cry and was on ventilator for 18 hours. The baby had severe pulmonary artery hypertension with tricuspid regurgitation. Ultrasonographic examination on day 2 showed a hypoechoic mass lesion with hyperechoic specks in the region of right suprarenal gland suggestive of neuroblastoma (Figure 1b). Bone marrow aspiration and biopsy were normal and urinary vanillyl mandelic acid (VMA) was not elevated. Laparotomy and right adrenalectomy along with the lesion (measuring 5 x 5 cm) was done on day 8 of life. The mass was well encapsulated, soft, friable and not infiltrating into adjacent structures. Histopathology showed neuroblastoma,

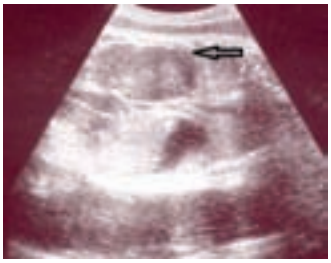

Fig 1a: Antenatal ultrasonographic image showing right sided hypoechoic suprarenal mass with hyperechoic areas

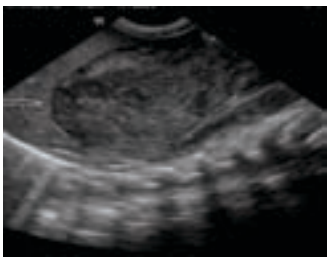

Fig 1b: Ultrasonographic examination of the neonate showing hypoechoic suprarenal mass with hyperechoic specs in the right suprarenal region

undifferentiated stroma, and poor type (Figure 2). No additional treatment was required as tumor could be resected completely and there was no evidence of metastasis. Baby is being followed up with ultrasound abdomen, urinary VMA and bone scan and she is doing well at 4 years of age.

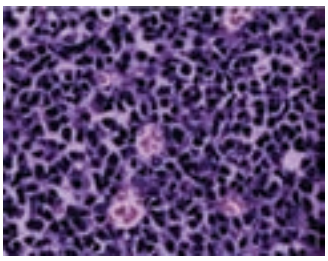

Fig 2: Histopathological section of tumour in case 1. Sheets of small round cells with scanty cytoplasm. Hyperchromatic nucei forming rosettes suggestive of neuroblastoma

Case 2: A 20-year-old primigravida with no significant family history showed an echogenic lesion of 1.9 x 1.7 x 1.6 cm above fetal left kidney with probable diagnosis of suprarenal mass (hemorrhage/ neuroblastoma/ extralobar sequestration of lung) on ultrasound at 20 weeks (Figure 3a). The lesion remained almost of the same size till 37 weeks. There were no features of hydrops fetalis. Mother was asymptomatic. Patient delivered vaginally a live male baby of 2.7 kg with good APGAR score. Ultrasound abdomen on day 2 showed a well-defined hyperechoic mass lesion with a few anechoic areas within, measuring 3.1 x 2 cm in the left suprarenal area. Computed tomography scan (plain and contrast axial) of the abdomen showed a heterogeneously enhancing mass lesion measuring 3.8 x 1.8 cm with few hypodense non-enhancing areas suggestive of necrosis in the left suprarenal region. Superomedially the mass was seen to abut the left crus of the diaphragm and causing mild displacement of aorta to the right side; inferiorly it was seen to extend till the upper pole of the left kidney causing inferior displacement of the kidney.

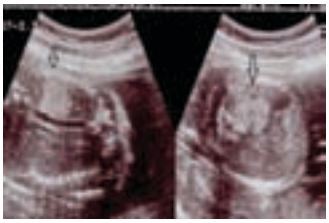

Fig 3a: Antenatal ultrasound image of case 2 showing hyperechogenic lesion in left suprarenal region

The mass was seen to displace the spleen laterally with encasement of the splenic artery. The left suprarenal gland was not seen separately from the mass. There was no evidence of calcification or hemorrhage. Features were suggestive of left suprarenal mass; probably neuroblastoma (Figure 3b). 24 hours urinary VMA (Vanillylmandelic acid) and HVA (Homovanillic acid) levels were normal. Laparotomy was done on day 12 of life and the mass was found in the posterior mediastinum between the crus of diaphragm below and pleura above (outside the pleural investment). Histopathology showed congenital cystic adenomatoid malformation (CCAM) of lung- type 2 (Figure 4). Final diagnosis was extralobar sequestration of lung with CCAM. He is 4 years of age now and is doing well.

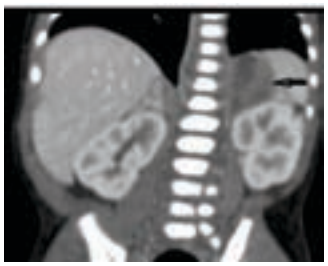

Fig 3b: CT scan of abdomen of the case 2 during neonatal period showing heterogeneously enhancing lesion in the left suprarenal region with few hypodense areas

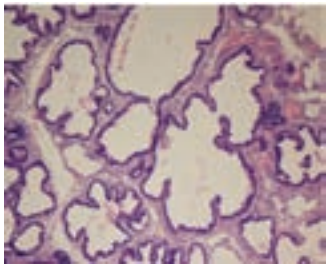

Fig 4: Histopathology of tumor of the case 2 showing cystic spaces and alveoli like structures lined by small cuboidal epithelium

Discussion

Antenatally diagnosed fetal pathology helps in appropriate monitoring of the fetus and reduces perinatal morbidity/mortality by early intervention in the fetus/neonate. Neuroblastoma originates from neural crest cells of the sympathetic nervous system; the incidence being 1 in 7000 births. Both sporadic and familial cases occur. Familial cases represent 20% of cases and show complex genetic

inheritance. The mass usually develops in the third trimester (has been diagnosed as early as 26 weeks) as a retroperitoneal tumor separate from the liver and superior to the kidney. Neuroblastoma can have a solid, purely cystic or complex sonographic appearance.[1] It can metastasize to the liver and placenta.[2] Hydrops fetalis may develop rarely due to catecholamine release and may lead to hypertension and preeclampsia. CT scan/ MRI, bone marrow aspiration, urinary VMA/HMA levels and tumor oncogenes help in diagnosis and staging.[3,4] Amplification of MYCN (N-myc) proto-oncogene has prognostic importance independent of stage and age and is associated with advanced tumor stage and poor outcome. Hyperdiploidy of tumor cell DNA content is associated with better prognosis. Genetic abnormalities including loss of heterozygosity of 1p, 11q, and 14q and gain of 17q, are commonly found in neuroblastoma tumor tissue.[5] Biologic factors that correlate with prognosis include the level of nerve growth factor receptor (Trk-A) expression, multidrug-resistance-associated protein, and telomerase activity. Differential diagnoses include adrenal hemorrhage, extralobar pulmonary sequestration and mesoblastic nephroma. Treatment includes complete resection of the tumor and additional chemo-radiation depending on the stage of the disease. Though in our study the fetus had not developed hydrops, the baby had low APGAR at birth. Echocardiogram showed pulmonary artery hypertension and tricuspid regurgitation. Tumor markers were normal in our baby (they are elevated in 95% of cases). More mature tumor excretes more VMA. Histologically, the lesion in our case was a poorly differentiated neuroblastoma which may explain the normal levels. The baby did not require additional chemo/radiotherapy after complete resection of the mass as the lesion was still confined to the adrenal (stage I) because of early antenatal diagnosis.

Extralobar sequestration (ELS) is a non-functioning lung tissue without connection to the normal tracheo-bronchial tree. It originates from an out-pouching of the foregut, separate from normally developing lung, which loses connection with the foregut, isolating the parenchyma from the tracheo-bronchial tree. In 50% of cases, lesion may be associated with cystic adenomatoid malformation, called hybrid lesions. Based on human and murine investigations, a number of genes have been implicated in lung development and cellular signaling. HOXB5 is important in the patterning of airway branches during mouse lung morphogenesis. FGF7 has been implicated as an important stroma-derived mediator of epithelial cell growth. Over-expression of FGF7 in mice results in lung lesions that resemble congenital pulmonary airway malformations. Platelet-derived growth factor–BB (PDGF-BB) is a mesenchymal growth factor that stimulates lung growth by increasing cell proliferation. Congenital pulmonary airway malformations (CPAM) that grow rapidly and progress to hydrops, requiring in utero resection, have been found to have increased mesenchymal PDGF-B gene expression and PDGF-BB protein production compared with age-matched normal fetal lung. There have been reports of CPAM and bronchopulmonary sequestrations (BPS) occurring in families. Although these molecular genetic pathways have been proposed to be altered in lung lesions, there is currently no clinical genetic testing available in clinical laboratories for patients who have been diagnosed with pulmonary lesions.[6] Ultrasonologically, it is homogenously echodense, usually left sided and detected in the second trimester. ELS is most commonly found in the thorax but rarely it is found in the posterior mediastinum or below the diaphragm (10 to 15%). Color doppler showing blood flow from systemic arteries of aorta to the fetal lung is pathognomonic.[8] Usually, sub-diaphragmatic ELS presents as a lesion in the suprarenal region, but in our study a posterior mediastinal lesion presented as a suprarenal mass. Other associated anomalies include bronchogenic cyst, cardiovascular malformations, bronchopulmonary foregut connection, pectus excavation, and diaphragmatic hernia. Serial

ultrasound every 2 to 4 weeks is done to detect fetal hydrops. If there is development of hydrops before 32 weeks thoracocentesis may be required to salvage the fetus, but if hydrops develops after 32 weeks, steroid administration and delivery should be performed.[9] Resection of all lung masses after birth should be considered even if asymptomatic, as there is high rate of infection, air trapping and malignancy. Bronchopulmonary sequestration is an important differential diagnosis for an echogenic lesion in the left suprarenal region detected in the second trimester.

Conclusions

Prenatal diagnosis of fetal pathology helps in proper parental counseling, in planning referral, and to decide the time, mode and place of delivery. It reduces perinatal morbidity/mortality by early intervention in the affected fetus/neonate.

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Retinitis Pigmentosa: Light at the end of the tunnel

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Introduction

Retinitis pigmentosa (RP) refers to a heterogeneous group of inherited ocular diseases that result in progressive retinal degeneration affecting 1 in 3,000 to 5,000 people. It is characterized by progressive peripheral vision loss and night vision difficulties. RP is a misnomer, as the word retinitis implies an inflammatory response, which has not been found to be a predominant feature of this condition. Affected individuals first experience defective dark adaptation or "night blindness," followed by constriction of the peripheral visual field (tunnel vision) and, eventually, loss of central vision late in the course of the disease.

Retinitis pigmentosa is most commonly found in isolation, but it can be associated with systemic diseases which demonstrate retinal changes identical to RP. RP is classified as non syndromic or "simple" (not affecting other organs or tissues); syndromic (affecting other systems such as hearing); or systemic (affecting multiple tissues). The most common systemic association is hearing loss seen in up to 30% of patients. Many of these patients are diagnosed as Usher syndrome.

With advances in molecular research, it is now known that RP constitutes many retinal dystrophies and retinal pigment epithelium (RPE) dystrophies caused by molecular defects in more than 40 different genes for isolated RP and more than 50 different genes for syndromic RP. Not only is the disease genetically heterogeneous, it also has significant phenotypic variation. Patients with the same mutation can have different disease manifestations and may have different retinal findings.

Clinical presentation

The classic symptoms of RP include night blindness, the development of tunnel vision, and slowly progressive decreased central vision starting at approximately 20 years of age. [1,2,3]

Nyctalopia: The earliest symptom in RP is most commonly night blindness and is considered a hallmark of the disease. Patients may also report a prolonged period of time needed to adapt from light to dark.

Visual loss: Peripheral vision loss is often asymptomatic, painless and slowly progressive; however, some patients notice this vision loss and report it as tunnel vision.

Photopsia: Many patients with RP report seeing flashes of light (photopsia); in contrast to an ophthalmic migraine, the photopsia may be continuous rather than episodic.

Upon examination, patients have decreased visual acuity, constricted visual fields, dyschromatopsia and the classic fundus appearance with dark pigmentary clumps in the mid-periphery and perivenous areas ('bone spicules'), attenuated retinal vessels, cystoid macular edema, fine pigmented vitreous cells, and waxy optic disc pallor. RP is associated with posterior subcapsular cataracts in 39 to 72% of patients, high myopia, astigmatism, keratoconus, and mild hearing loss in 30% of patients (excluding patients with Usher syndrome).

There are other eye syndromes and conditions that are similar to retinitis pigmentosa, most of which are either confused with RP or are initially misdiagnosed. A physical examination can be helpful to rule out syndromic RP, which are conditions that have pigmentary retinopathy and other system disorders. Diseases such as Usher syndrome, myotonic dystrophy, Laurence-Moon syndrome and Friedreichs ataxia can present with similar symptoms at some stage in their respective diseases. The mucopolysaccharidoses (eg, Hurler syndrome, Scheie syndrome, Sanfilippo syndrome) can manifest with pigmentary retinopathy like RP. Clinical features of a few common syndromes associated with RP are described in Table 1.

Table 1. Clinical features of common and severe types of syndromic Retinitis Pigmentosa

SYNDROME	ASSOCIATED FEATURES	ETIOLOGY & COMMENT
Usher syndrome (Accounts for 10 % of cases of RP)	Deafness	• Hearing loss in this syndrome can be congenital with complete hearing loss or can occur in middle age with less profound changes in hearing. • Most cases are autosomal recessive • Mutations have been found in more than 12 genetic loci and 8 identified genes.
Kearns-Sayre syndrome	External ophthalmoplegia, lid ptosis, heart block, pigmentary retinopathy	• Vision loss tends to occur later in life with moderate visual field loss and night vision difficulties. • The cardiac conduction block can be life-threatening; an electrocardiogram is essential to help rule out this syndrome. • Caused by a mitochondrial genetic defect
Abetalipoproteinemia	Diarrhoea, ataxia, and pigmentary retinal degeneration.	• Caused by the lack of apolipoprotein • Fat malabsorption leads to the deficiency of fat-soluble vitamin. • High-dose therapy with vitamins A and E can prevent or limit the extent of the retinal degeneration.
Alport syndrome	Glomerulonephropathy causing renal failure, progressive deafness and ocular anomalies	• Hereditary disorder of the basement membrane • Approximately 85% of cases are X-linked and about 15% are autosomal recessive; autosomal dominant inheritance is rare. • Caused by mutation in the gene encoding the alpha-5 chain of basement membrane collagen type IV [COLIV]
Refsum Disease	A tetrad of RP, peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid (CSF) without an increase in the number of cells. Other variable features include cardiac dysfunction, nerve deafness, ichthyosis, and multiple epiphyseal dysplasia	• An autosomal recessive inborn error of lipid metabolism • All patients have accumulation of phytanic acid, in blood and tissues • Caused by mutation in the gene encoding phytanoyl-CoA hydroxylase (PHYH, or PAHX); or the gene encoding peroxin-7 (PEX7)
Bardet-Biedl syndrome	Polydactyly, truncal obesity, kidney dysfunction, short stature, and pigmentary retinopathy.	• Known causative genes are about 15 with 3 modifier genes leading to 15 types • Vision loss occurs in the second decade and progresses to severe vision loss by middle age • Renal dysfunction can be severe and life-threatening • Intelligence is usually subnormal • BBS had been originally thought to be a recessive disorder, but clinical manifestation of some forms of BBS requires recessive mutations in 1 of the 6 loci plus an additional mutation in a second locus ('triallelic inheritance),' Burghes et al. suggested the term 'recessive inheritance with a modifier of penetrance.'

An eye examination will often reveal the early sign of RP, as the condition usually begins in childhood and develops over a period of 40 to 50 years. Tests to determine the retina's integrity include refraction tests, visual activity, color defectiveness determination, papillary reflex response, a slit lamp examination, retinal photography, an ultrasound of the eye, intraocular pressure determination, fluorescein angiography, and an electroretinogram (ERG). These tests all help to determine what the eye sees, how well the eye sees it, and the activity which is performed by the eye in order to see.

Genetics of Retinitis Pigmentosa [2,3,4,5]

Gene mapping and gene discovery have revealed that the molecular genetics of RP is unusually complicated. Genes associated with RP encode proteins that are involved in phototransduction (the process by which the energy of a photon of light is converted in the photoreceptor cell outer segment into a neuronal signal), the visual cycle (production and recycling of the chromophore of rhodopsin), photoreceptor structure, and photoreceptor cell transcription factors. However, the function of many genes associated with RP remains unknown.

Non syndromic RP can be inherited in an autosomal dominant (ADRP, 15-20%), autosomal recessive (ARRP, 5-20%) or X-linked manner (XLRP, 5-15%). Simplex cases (i.e., a single occurrence in a family) represent 40-50% of all individuals with RP and may result from a de novo mutation or they may be individuals with relatives who are affected (perhaps mildly) but whose disease is not known to the affected individual. X-linked RP can be either recessive, affecting males only or dominant, affecting both males and females with females being mildly affected. Rarer forms like digenic RP occurs in individuals who are heterozygous for both a ROM1 mutation and a RDS mutation. Besides these, some mitochondrial forms have also been described. The genetic heterogeneity makes it a complex disorder. For most RP genes studied to date, many different disease-causing mutations have been identified, although in most cases a few specific mutations are "common" among affected individuals or certain ethnic groups.

Adding to this multiplicity of mutations, different mutations in the same gene may also cause different diseases. For example, different mutations in RHO, the gene encoding rhodopsin, may cause ADRP, AD congenital stationary night blindness (CSNB) or, rarely, ARRP. Mutations in RDS, the gene encoding peripherin, may cause ADRP, AD macular degeneration, or digenic RP. Clinical severity and disease phenotype often differ among individuals with the same mutation; most likely as the result of genetic and/or environmental factors.

These complexities of genetic heterogeneity and phenotypic variability are addressed in Table 2. This table enlists only few of the genes associated with RP and also indicates additional diseases that may be associated with specific genes.

Table 2. Genetic loci more commonly associated with retinitis pigmentosa

Gene	Type of RP	Other associated phenotypes
RHO	25-30% of ADRP ARRP-rare	Dominant CSNB
PRPF31	15-20% of ADRP	-
RDS	5-10% of ADRP	Digenic RP with ROM1; dominant MD; dominant adult vitelliform MD
RP1	5-10% of ADRP	-
IMPDH1	3-5% of ADRP	-

Gene	Type of RP	Other associated phenotypes
ABCA4	~5% of ARRP	Recessive Stargardt disease, and cone-rod dystrophy
USH2A	4-5% of ARRP	Usher syndrome type2
PDE6B	3-4% of ARRP	Dominant CSNB
RPE65	2% of ARRP	LCA (7-16%)
RPGR	70% of XLRP	CSNB; cone dystrophy 1; atrophic MD; RP plus deafness
Rp2	8% of XLRP	Peri papillary and macular atrophy

[ADRP: Autosomal dominant RP; ARRP: Autosomal Recessive RP; XLRP: X-Linked RP, CSNB: congenital stationary night blindness; MD: Macular degeneration; RPE: retinal pigment epithelium; LCA: Leber congenital amaurosis]

DNA testing is available on a clinical basis for RLBP1 (Bothnia type ARRP), RP1 (AD, RP1), RHO (AD, RP4), RDS (AD, RP7), PRPF8 (AD, RP13), PRPF3 (AD, RP18), CRB1 (AR, RP12), ABCA4 (AR, RP19), and RPE65 (AR, RP20) and includes testing for prenatal diagnosis. For all other genes, molecular genetic testing is available on a research basis only. Because of the wide variety of subtypes of RP or related pigmentary retinopathies, the definitive test for diagnosis is identifying the particular genetic defect. Genetic sub-typing will become more useful as therapies begin to target specific genetic subtypes. In addition, identifying the gene may prove helpful in determining the prognosis and in providing genetic counseling.

Treatment [1,3,6]

Retinitis pigmentosa, unfortunately, is not a condition that can be treated at the time of this writing. Ophthalmologists can make recommendations which may be helpful in delaying the disease's progression, but a continual worsening of vision is expected. Some experts recommend the use of sunglasses to help delay in progression. Others claim, with mixed results, that a high intake of Vitamin A palmitate as well as additional antioxidants may help to slow the progression of the disease. Though most patients do not become completely blind, near total blindness is expected by the time a patient reaches between 45 and 65 years of age. In some cases, total blindness does occur. The few treatments that have been tried in various studies are discussed in table 3.

Table 3. Pharmacotherapy tried and recommended in Retinitis pigmentosa.

Vitamin A / beta-carotene : Antioxidants may be useful in treating patients with RP	Beta-carotene in doses of 25,000 IU has been recommended. A recent comprehensive epidemiologic study concluded that very high daily doses of vitamin A palmitate (15,000 U/d) slow the progress of RP by about 2% per year.	The effects are modest; therefore, this treatment must be weighed against the uncertain risk of long-term adverse effects from large chronic doses of vitamin A. No clear prospective evidence in favour of vitamin supplementation yet exists.
Docosahexaenoic acid (DHA) : DHA is an omega-3 polyunsaturated fatty acid and antioxidant.	Studies have shown a correlation of ERG amplitudes with patients' erythrocyte-DHA concentration. Other studies reported trends of less ERG change in patients with higher levels of DHA	A recent study compared DHA plus vitamin A to vitamin A alone in patients with RP over 4 years. In this study, the benefit of DHA was not seen. Further clinical trials may have to be done to determine DHA benefit.
Acetazolamide: Macular edema can reduce vision in the later stages of RP	Oral acetazolamide has shown encouraging results with some improvement in visual function. Studies have demonstrated improvement in Snelling visual acuity for patients who have RP with macular edema.	Adverse effects, including fatigue, renal stones, loss of appetite, hand tingling, anemia, may limit its use. Topical acetazolamide can be effective but has not been found to be as effective as oral therapy
Calcium channel blockers	Diltiazem has shown some benefit in some animal models of RP, but they have been ineffective in other models.	No current recommendations exist regarding the use of calcium channel blockers in patients with RP
Lutein/zeaxanthin: are macular pigments that the body cannot make but instead come from dietary sources.	Lutein is thought to protect the macula from oxidative damage, and oral supplementation has been shown to increase the macular pigment.	A NIH clinical trial, the Age-Related Eye Disease Study II (AREDS II), is beginning to test the effectiveness of lutein and zeaxanthin to slow age-related macular degeneration. Their ability to prevent cone photoreceptor cell death (such as what occurs in RP) has not been shown.
Valproic acid	Oral valproic acid has shown benefit in clinical trials, and larger clinical trials are underway.	-
Vitamin E is probably a medication with potential adverse effect in RP	Doses as high as 800 IU/d have been recommended for patients with RP.	Berson et al, have reported that high doses of vitamin E (400 U/d) may be modestly deleterious in patients with RP

A promising future for treatment of Retinitis Pigmentosa[5,7,8,9,10,11]

There is a large amount of research being performed internationally for future treatment for retinitis pigmentosa. As we acquire more knowledge about influencing gene function, treatment for RP is likely to become available. Promising research involves growth factors such as ciliary neurotrophic factor, synthetic nucleic acid nanoparticles, stem cell therapy and gene therapy with recombinant adeno-associated virus. Scientists and ophthalmologists are also investigating retinal transplants and artificial retinal implants.

Growth factors

Generic gene therapy strategies that aim not to correct the gene defect but to ameliorate its consequences offer the possibility of therapies that are widely applicable across a range of conditions. One potential strategy in these cases is to halt or delay the process of cell death, so that useful visual function can be maintained throughout the lifetime of an affected individual. It has been shown in a variety of experimental models over the last three decades, that neurotrophic factors have the potential to delay neuronal apoptosis. Neurotrophic factors are small proteins which have relatively short half lives and the requirement for repeated administration has limited their clinical application. Since these proteins do not ordinarily cross the blood-brain barrier, previous approaches have relied upon intrathecal infusion pumps or similar complex devices to sustain elevated neurotrophin levels within the central nervous system (CNS). However, sustained delivery through viral vector mediated expression of genes encoding neurotrophic factors may circumvent the potential side effects of repeated administration.

Ciliary neurotrophic factor (CNTF) has been shown to slow retinal degeneration in a number of animal models.[7] Phase II clinical trials are underway using an encapsulated form of RPE cells producing CNTF (Neurotech) for patients with Usher syndrome and RP. These encapsulated cells must be surgically placed into the eye. Phase I clinical trial results have been encouraging.

If as few as 5% of cones can be kept alive, a person with RP can continue to function independently. A promising treatment aimed at preserving cones, the retinal cells that provide central and daytime vision, is in a phase I clinical trial. This involves a protein known as rod-derived cone viability factor (RdCVF). It has preserved vision in several preclinical studies.

Stem cell Transplantation

Small patches of retinal or RPE tissue have been transplanted and this technique could be helpful in the following RP forms: RP based on an RPE defect, RP with primary defects in the outer segments, if the disease is due to an overload of the phagocytic activity of the RPE, or if the RPE cannot provide sufficient nutritional support to the outer segments. RPE cell transplants have been placed into the subretinal space to rescue photoreceptors in animal models of RP.

Stem cells are being actively investigated as a potential source to replace damaged RPE or photoreceptor cells. Both adult bone marrow–derived stem cells and embryonic stem cells are being used in animal models with the goal to investigate how to induce appropriate cell integration and differentiation. No current investigational protocols exist in humans for this type of intervention.

Retinal prosthesis (Bionic retina)

A visual prosthesis, often referred to as a bionic eye, is an experimental visual device intended to restore functional vision in those suffering from partial or total blindness. The ability to give sight to a blind person via a bionic eye depends on the circumstances surrounding the loss of sight. For retinal prostheses, which are the most prevalent visual prosthetic under development (due to ease of access to the retina among other considerations), vision loss due to degeneration of photoreceptors

(retinitis pigmentosa, choroideremia, geographic atrophy macular degeneration) is the best candidate for treatment.

A retinal prosthesis or phototransducing chip placed on the retinal surface has been under investigation for several years. The healthy ganglion cell layer of the retina can be stimulated, and implants in animal models have long-term stability. In a study by Humayun et al, this has been shown to be beneficial in human subjects.[9] One patient who had no light perception from RP was able to see and localize a flashlight after the prosthesis. With this prosthesis, an external camera (placed in the patient's eyeglasses) transmits to the retinal prosthesis. Chow et al placed subretinal microphotodiodes (prosthesis) in patients with severe RP. These patients had subjective improvement; however, the improvement was delayed and occurred in retinal areas outside of where the chip was placed. Therefore, the effect was thought to be an indirect benefit to adjacent cells. [10]

An Israeli company is pairing electrodes with living neurons in the eye to create bionic sight for the vision impaired, in a nanotech development that sounds more like science fiction, than real life. Nano Retina's bio-retina is a man-made electronic retina activated by special eyeglasses fitted with a laser energy source. The implantation requires only local anesthesia and a small incision. Vision is restored almost immediately, with a recovery time of one week. Inserted into the retina in a 30-minute procedure, Nano Retina's implant device, about the size of a grain of rice, turns into an artificial retina that melds to the neurons in the eye. It is activated by the wearer using special eyeglasses, transforming natural light into an electrical impulse that stimulates the neurons to send images to the brain.

Argus Retinal Prosthesis

Drs. Mark Humayun and Eugene DeJuan at the Doheny Eye Institute (USC) along with Bio-electronics Engineer Dr Wentai Liu at University of California, Santa Cruz were the original inventors of the active epi-retinal prosthesis and demonstrated proof of principle in acute patient investigations at Johns Hopkins University in the early 1990s along with Dr. Robert Greenberg. Their first generation implant had 16 electrodes and was implanted in 6 subjects between 2002 and 2004. Five of these subjects still use the device. These subjects, who were all completely blind prior to implantation, can now perform a surprising array of tasks using the device. More recently, the company announced that it has received FDA approval to begin a trial of its second generation, 60 electrode implant, in the US. Second generation Argus II trials are currently ongoing in the U.S. and are still waiting on FDA approval for public sale. It was recently approved in Europe; it costs roughly $100,000. The Argus III model is currently in process of improved sight with 240 electrodes. Fig 1 demonstrates the working of a Bionic eye.

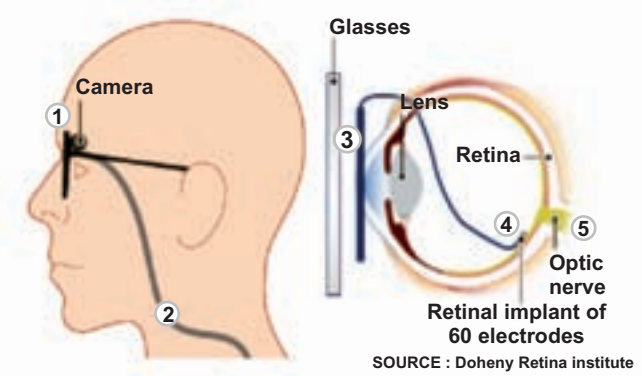

Figure 1. Working of a BIONIC EYE

1. Camera on glasses views image
2. Signals are sent to hand-held device
3. Processed information is sent back to glasses and wirelessly transmitted to receiver under surface of eye
4. Receiver sends information to electrodes in retinal implant
5. Electrodes stimulate retina to send information to brain

Gene therapy [5, 11]

Retinitis pigmentosa is a diverse group of conditions that results from mutations in any one of over 100 different genes. Many of the genes have now been identified and their functions elucidated, providing a major impetus to develop gene-based treatments. Gene therapy is under investigation, with the hope to replace the defective protein by using DNA vector (eg, adenovirus, lentivirus). Advances in molecular genetics have helped identify many of the gene defects responsible, and progress in gene transfer technology has enabled therapeutic strategies to be developed and applied. Gene therapy is now in human clinical trials for Leber's congenital amaurosis, with promising results. In fact, 8 trials referring to gene therapy and RPE65 mutations are open and listed on the clinicaltrials.gov website. The first human clinical trials of gene therapy for RPE65 associated retinal dystrophy have shown promising initial results and have helped prepare the way for further trials of gene therapy for inherited retinal disorders.

Because of the wide heterogeneity of defects in RP, gene therapy must be targeted specifically to each mutation. It is not known which, if any, of the RP forms will show reversibility (even with a nondestructive reinsertion of the appropriate gene in the appropriate locus with appropriate regulation). Whilst gene replacement and gene silencing strategies offer prospects for the treatment of specific inherited retinal disorders, other disorders may be less amenable to these corrective approaches. These conditions include those associated with abnormal retinal development and those in which retinal degeneration is advanced at birth. Furthermore, the development of individualized corrective gene therapy strategies for patients with disorders due to very rare mutations may be unfeasible.

As molecular understanding increases, RP will be further characterized by the specific protein/genetic defect. This characterization will have increasing importance in the determination of a prognosis and will likely allow clinicians to use gene-targeted therapies.

Genetic Counseling [2]

A diagnosis of RP always implies genetic disease. The first step in the management of a patient with RP is to establish the mode of inheritance. Complete detailed pedigree is an essential part of the workup before genetic counseling can begin. The examination of other family members is essential for better appreciation of the range and extent of manifestation shown by other family members and the expected rate of progression. By the age of 30 years more than 90% of patients can be diagnosed with ophthalmoscope, but under age 30 years, ERG testing is indicated if the patient wants to be certain whether any relatives are affected. Two major issues to be addressed are the rate of progression of the disease and the risk to the patient's children. Variable expression and incomplete penetrance particularly in autosomal dominant disease can influence predictions of severity. An affected individual with an autosomal recessive disease has a small risk of having an affected offspring, depending on the frequency of carrier state in population. Inheritance of autosomal recessive traits is also influenced by tradition of consanguinity in the community. Patients with isolated (simplex) RP (i.e. no known affected family members) can be considered to be autosomal recessive, although exceptions exist. All offspring of males or females with autosomal recessive RP are carriers of this condition. Carriers enjoy normal vision but have a small (5%) risk of having affected offspring unless the marriage is consanguineous. If a pedigree with multiple affected members is inconclusive as to whether the disease is transmitted in a recessive or a dominant mode, a digenic mode of inheritance should be considered. In digenic transmission two unrelated mutations (neither of which individually results in RP) cause this disease only in those patients who have both the mutations. Affected individuals can have

asymptomatic parents but 25% chance of having an affected child.

While some individuals debate the morality of prenatal diagnosis, it is often the only way for a family to prevent the high likelihood of passing RP on to future generations. While there are many who disagree with this, there are those who argue that genetic counseling and genetic selection may be able to eliminate this disease within a fifty year time frame. Genetic testing and counseling is becoming increasingly valuable as the understanding of RP increases. Identification of the patient's genotype offers several advantages. First, it confirms the genetic cause of the condition. In addition, it can occasionally help determine prognosis and may likely prove to be important for future therapy choices. Genetic counseling is very helpful to guide patients on the hereditary nature of their disease and the mode of inheritance. Thus, counseling can help the patients with their future plans, such as pregnancy, job choices, and medical treatments. Moreover, psychological counseling should be made available to these patients when appropriate.

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MESSAGES

1) Genetic heterogeneity and phenotypic variability are the hallmarks of the genetics of RP.

2) Genetic counseling is often the only option for every parent who is likely to pass on the disease.

3) The recent advances in genetics and the promising success of gene therapy are lighting a candle in the darkness and we do see a light at the end of the tunnel!

4) Dr Stephen Daiger maintains a superb up-to-date Web site called RetNet that is dedicated to the molecular genetics of inherited retinal diseases. As shown on this web site, over 196 different genes have been found that lead to retinal disease and vision loss. (http://www.sph.uth.tmc.edu/RetNet/).

5) Information regarding visual prosthetic devices available at: http://en.wikipedia.org/wiki/Visual_prosthesis

6) Patient support groups for retinitis pigmentosa: http://retinaindia.org/

Genome Paths: A Way to Personalized and Predictive Medicine

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Introduction

Impressive progress in the field of comparative and functional genomics has taken place in the 21st century, and it has provided new dimensions to personalized and predictive medicine. The basic mandates of predictive medicine are that no two individuals are the same and these differences can be assessed by carrying out genetic profiling using different genetic markers. Whole human genome has been sequenced which has led to the development of convenient methods for the mapping of new genes (the total number of genes in humans is approximately 22,000). Enormous advancements in molecular techniques have been made which help in identifying mutations for monogenic disorders. Genes for most of the monogenic phenotypes will be mapped soon.

Genetics of multi-factorial diseases

The identification of the genes involved in the genesis of multi-factorial diseases, the so-called "predisposition genes," is much more complicated than the monogenic disorders. According to the current definition, "predisposition genes" are mutant genes (alleles) that are compatible with birth and life but, under certain unfavorable conditions, can contribute to the development of multi-factorial diseases. Sometimes monogenic disorders have helped to resolve the mechanisms underlying complicated multi-factorial diseases. The Van der Woude syndrome is characterized by lower lip pits, orofacial clefts, and even occasional hypodontia. This disorder is caused by dominant mutations in the IRF6 (interferon regulatory factor 6) gene.[1] Scientists have proposed that IRF6 variation may also contribute to isolated cleft lip with or without cleft palate, a heterogeneous birth defect suggested to be caused by as many as three to 14 genes.[2,3] Indeed, studies with a large sample data set have shown that IRF6 variation contributes to a significant proportion of isolated cleft lip with or without cleft palate cases.[2] In a related study, researchers showed that IRF6 also contributes to the isolated tooth agenesis, another heterogeneous phenotype commonly found in the general population.[4] Such results are of interest because they indicate that the same gene can cause a monogenic disease as rare as Van der Woude syndrome and also contribute to much more common multifactorial defects, such as isolated cleft lip with or without cleft palate (frequency of 1:700 births) and isolated tooth agenesis (frequency of 1:100 births), which have more complex genetic etiologies.

Common diseases such as type 2 diabetes and coronary heart disease result from a complex interplay of genetic and environmental factors. Recent developments in genomics research have boosted progress in the discovery of susceptibility genes and fueled expectations about opportunities of genetic profiling for personalizing medicine. Personalized medicine requires a test that fairly and accurately predicts disease risk, particularly when interventions are invasive, expensive or have major side effects. Recent studies on the prediction of common diseases based on multiple genetic variants alone or in addition to traditional disease risk factors showed limited predictive value, and all have investigated only a limited number of susceptibility variants. New gene discoveries from genome-wide

association studies will certainly further improve the prediction of common diseases, but the question is whether this improvement is sufficient to enable personalized medicine. The new gene discoveries may not evidently improve the prediction of common diseases to a degree that it will change the management of individuals at increased risk. Substantial improvements may only be expected if we manage to understand the complete mechanisms of common diseases to a similar extent as we understand those in the monogenic disorders. Genomics research will contribute to this understanding, but it is likely that the complexity of complex diseases may ultimately limit the opportunities for accurate prediction of disease in asymptomatic individuals as unraveling their complete complex pathways may be impossible.

More recently qualitative genetic polymorphisms mainly single nucleotide polymorphisms (SNP) have added new dimensions to the study of genetic predisposition. SNPs occur roughly every 300-400 bp. Thus, the total number of SNPs in the full human genome is estimated at about 13-10^6. It is assumed that about half of all SNPs (5 million) are related to the coding (expressed) part of the genome. It is these substitutions that correspond to the allelic variants of genes that cause or are associated with various diseases. They played a key role in the Human Genome Project. Polymorphisms affecting the coding parts of genes often lead to the replacement of amino acids and the appearance of proteins with new functional properties. Replacements or nucleotide repeats in the regulatory (promoter) regions of genes may have a significant impact on gene expression. Inherited gene changes play a crucial role in determining the unique biochemical profile of each individual and his or her hereditary predisposition to various multifactorial diseases (MD).

Functional gene module

According to research in the prevalence of diseases in twin pairs and medical genetics data, only about 1.5% of human diseases are directly linked to mutations. These are the so-called monogenic diseases. Accuracy in the molecular diagnosis of monogenic diseases is very high and approaches 100%. All other diseases, including common ones such as cardiovascular, cancer, mental, and even infectious diseases, are the result of the combined effect of unfavorable environmental factors and individual characteristics of the genome, somehow predisposing a particular person to a disease. Hence, the origin of their name: multifactorial (combined or complex) diseases (MD). Depending on participation in metabolic chains and associations with a MD, susceptibility genes are conditionally divided into several groups among which are the genes of the detoxification system ("external environment"), the genes of metabolic bypass (genes triggers), cell receptor genes, genes of the inflammation and immune system, and genes associated with the specific MD. Unfavorable allelic variants of these genes can cause atherosclerosis, coronary heart disease (CHD), osteoporosis, diabetes, asthma, tumors, etc. The combinations of allelic variants of different genes involved in normal metabolic processes or are involved in the development of a specific multifactorial pathology are called "gene networks.[5] In each of these networks, the main (central) genes and additional (auxiliary) genes (the so-called genes modifiers) are defined. The concept of genetic networks has further evolved to the study of functional genetic modules (FGM). To this end, a series of studies have compared the MDs and the various genes whose products are involved in the etiology and pathogenesis of these diseases.

A large scale study was conducted on 1,264 multifactorial diseases and their associated 1,777 genes.[6] Important inferences drawn from this study were as follows.

I) MD is characterized by its own set of genes or a gene network which the authors named a "functional gene module" (FGM); both central and peripheral genes can be distinguished by this module.

ii) Most MDs are interconnected through many different genes.

iii) It has been reported that 516 MDs show a lot of genetic linkages i.e. they are associated with many genes (deafness - 41 genes, leukemia - 37, colon cancer - 34).

iv) The mutations of different genes can lead to the same MD, and mutations (polymorphisms) of one gene may be associated with different MDs;

v) The mutations of the central (essential) genes of FGM are often associated with tumors and causes early death.

vi) Mutations (polymorphisms) of the peripheral FGM genes play a major role in the phenotypic variability and the development of MDs.

vii) The presence of overlapping FGM of MDs shows the pathogenetic proximity of different MDs and argues in favor of syntropy – a combination of pathogenetically related "family" of MDs.

viii) Genes included in FGM are essentially "syntropy" genes which are functionally similar but not always identical to "predisposition" genes.[7] The coincidence of many MDs in a large number of associated genes was clearly demonstrated when comparing candidate genes associated with various autoimmune diseases.

Methodology to study genetics of multi –factorial disorders

There are various approaches which can be followed, the most popular of which is the case control study. The method involves several steps: i) selecting the most probable candidate genes on the basis of the particular disease, ii) the selection of functionally important alleles of the corresponding genes, iii) a population analysis of the allele and genotype frequencies of the corresponding genes on the basis of literature data and the internet, and iv) a comparative analysis of allele frequencies and genotypes of these genes in patients with a clinically confirmed diagnosis and in healthy individuals of the same population. These studies are performed on a small sample size because they are laborious and costly; however, when done with a small sample size the study does not guarantee that the identified allelic differences are the main cause in the chain of pathogenetic mechanisms involved in the particular disease. Some important genes and polymorphisms of the same, or another gene network involved in the disease can be missed, and clinically different forms of the disease under study may have different patterns of candidate genes. An alternative strategy of searching for predisposition genes (linkage analysis) is based solely on the positional cloning of the locus and does not require a preliminary hypothesis about the pathophysiology of the disease. Initially, the method of genome-wide linkage study (GWLS) was the one available and widely used. The GWLS method is used in families with several affected siblings or in extended pedigrees. It is aimed at detecting in patients, blocks of molecular markers that are passed from parents to sick descendants but not to healthy ones. The method allows localizing the gene to within an area of 1-10Mb. These extensive areas on the chromosomes usually include hundreds of genes; thus, the search for the causative gene within a linked locus is a difficult and often impossible task.

More recently genome wide association studies have been performed. This was possible because of the Hap-Map project which has shown that thousands of single nucleotides (SNPs) are distributed throughout the human genome. Further, with new breakthroughs in the technology, now different companies have developed chips on which probes for these SNPs are attached, which can be detected with the help of hybridization techniques.

For example, the widely used chip developed by Illumina (www.illumina.com) comprising 310,000 tag SNPs (Illumina Hap310K) enables estimation of 81% of frequent polymorphisms in the European population. The next development by the same company comprises 550,000 SNP (Illumina Hap550K) and covers more than 90% of the frequent polymorphisms.[8] Genome-wide association screening is conducted on a large number of patients and controls (more than 1,500 – 2,000 people), which ensures highly reliable ($p < 0.000005$) results and includes several stages. At first, hundreds of associations are identified, most of which appear to be false-positive after hundreds of thousands of independent tests. In the next step, associations in independent cohorts of patients and controls are analyzed by the same method. Only the results confirmed in a replication cohort are considered to be reliably positive. At present, the scanning of about 300 different associations of MDs has been carried out by using GWAS. The results of these studies are summarized on the website of the National Institute of Health (USA). The data include the results of GWAS obtained with a reliability of $p < 10^{-5}$ and containing not less than 100,000 SNPs. The website is regularly updated following each publication of new data.[9]

Use of genetic tests in clinical practice

The next step is use of molecular diagnosis for various genetic diseases. Diagnosis of genetic diseases includes the study of somatic rearrangements in cancers, of genetic risk factors (e.g. Factor V, Factor II, and MTHFR gene polymorphisms in deep vein thrombosis), pharmacogenetic studies to look for drug specificity, efficacy and toxicity, and study of mutations in monogenic diseases. There are approximately 4000 known monogenic diseases and 2000 disease causing genes have been isolated. However, in most of the countries gene testing is limited (testing for < 50 genes); in a few countries tests for 300-500 genes are available but nowhere testing for the complete set of genes is existing.

The reason for this limitation is that when the causative mutation is single or only few; it is easier to establish the test but when private mutations are involved the test becomes difficult and less cost effective. Hundreds of mutations are described for many monogenic disorders and for some phenotypes like retinitis pigmentosa and spinocerebellar ataxia, the number of causative genes is more than twenty.

Based on WHO recommendations, genetic testing should be carried out with the voluntary, informed consent of the patient i.e., after he or she reaches adulthood. Formally, this means that important genetic information could become available relatively late, when its benefits to the subject and his close relatives have largely been lost. However, taking into account the importance of these data for children's health, the harmonious development of their personality, rational nutrition, effective education, athletic training, optimal professional guidance, and the opportunity to prevent the development of several diseases with a late manifestation, introducing genetic passports at an early age would seem to make sense today.

Introduction of the technology of genome-wide screening for the identification of candidate genes of MDs, comparison of the individual profiles of the allelic variants of candidate genes of patients affected with a particular multifactorial disease and of obviously healthy people, supported by the outcomes of prospective genetic testing will open a wide avenue to a new and promising era of predictive medicine for humanity. The main task of modern genomics is to evaluate the significance of the results of genetic testing to determine the conditions of their implementation in medical practice. Possible solutions to this problem in India include the following:

Biology-driven approach: Candidate gene tests

It is clear from the above discussion that through association studies, both genome wide associations and case-control studies, it is quite difficult to

pinpoint that a particular set of genes is responsible for the causation of disease. Over and above that, there are modifier genes which may add up to more complexities. The search for modifier genes is difficult but worth pursuing – not only for the direct applications in diagnostics but it might open up new treatment strategies and drugs. Although interest has shifted gradually from monogenic to more common multifactorial diseases, it is important to keep in mind that monogenic diseases represent a simpler model of diseases that teach us many things about the genetic basis of more complex diseases The study of Mendelian disorders may also lead to the discovery of novel drug targets. Hence, to conclude, it would be wiser to focus on a more limited number of carefully chosen genes, the so-called candidate genes. The difficulty here is choosing these candidates with significant effect on the disease phenotype. Different approaches can be used to select them. One might look first at the genes involved in the same pathway as the primary mutation in the disease. For example, for familial hypercholesterolemia due to a mutation in the LDL receptor gene, genes of the lipoprotein pathway are good candidates. Alternatively, one might decide to focus on genes located in another pathway and involved in a somewhat more indirect way in the disease consequences. In CF, for example, candidate gene studies have considered genes involved in the inflammatory process. In hereditary hemochromatosis, a recent study showed that genes in the BMP pathway and involved in the expression of hepcidin, a peptide hormone produced by the liver that controls plasma iron concentration, might be promising candidates to explain the penetrance variability of the HFE p.C282Y mutation in homozygote carriers.[10] Interestingly, the authors focused on an indirect measure of disease penetrance, the serum ferritin levels of C281Y homozygotes. This is the first association detected between common variants in genes of the BMP pathway and iron burden. Further studies will need to determine if this is specific to p.C282Y carriers, by testing for the effect of these variants on serum ferritin levels in the general population. Another example involves dilated cardiomyopathy, where candidate genes in different pathways are being studied, in particular the beta-adrenergic pathway and the renin-angiotensin-aldosterone system. New approaches have also been used based on animal models, which allow a better control of the environment[11]

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Remembering Rimoin

On May 28, 2012 the medical genetics community woke up to the shocking news of Dr David L Rimoin succumbing to pancreatic cancer that was detected only a few days ago. A towering figure in the field of Medical Genetics, Dr Rimoin founded the American College of Medical Genetics and the American Board of Medical Genetics. An inspired student of Dr Victor McKusick, Dr Rimoin went on to establish the clinical specialty of Medical Genetics, the way we practice now and will for decades to come. He was a true team leader, nurturing many pioneers in clinical skills as well as research. He was loved by his colleagues as a friend and guide. He enjoyed training young scientists in skeletal dysplasia, who are now spread across the globe.

Clinical geneticists in India had an opportunity to meet and interact with Dr Rimoin and his team of International Skeletal Dysplasia Registry at Lucknow in February 2011 during the first Indo-US symposium on skeletal dysplasia organized by Dr Shubha Phadke. Along with Dr John Graham, he was instrumental in organizing this event with us. The conference was a great success. We could see Dr Rimoin loved Indian food often commenting that he will have to compensate for his overindulgence back home on his return.

I had an opportunity to meet him at the Cedars Sinai Medical Center. It was a really magnificent research atmosphere at the Medical Genetics Institute which he headed and at the Steven Spielberg center, both of which were established by the visionary. Despite his huge commitments, he would be there for all clinics and academic meetings. On my return we had taken several steps to initiate a formal collaboration.

He was the recipient of numerous awards and honors including the American College of Medical Genetics and Genomics Foundation Lifetime Achievement Award conferred at the 2010 Annual Meeting. Known the world over for his book 'Emery and Rimoin's Principles and Practice of Medical Genetics', the entire medical genetics community will deeply miss him. He will be remembered by all those who met him and read his book and research publications specifically on short stature, connective tissue disorders and skeletal dysplasia. We cherish meeting him and still find it difficult to accept his loss.

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The Moments We Treasure!

Too much of next generation sequencing...!

Contributed by Parag M Tamhankar, paragtmd@gmail.com

Learning Tips to Make a Long Story Short[1,2,3]

As geneticists are learning newer ways to read in between the lines of the genetic code, patients and their families are finding it further more difficult to understand what is being said about them. A recent issue of Genetics in Medicine recounts experiences from the pilot eMERGE1 and ClinSeq2 projects. Most research participants were curious to know "all" the results but typically reached saturation after 20-40 minutes of counseling. Even amongst the clinicians there was a divided opinion whether to divulge only those results that had high penetrance or also to include low penetrance alleles. The psychological impact of too much information can be devastating and these new "first families" may often feel isolated and confused. Clearly, an urgent need is felt to have guidelines for transcribing mountains of jargon into molehills of sensible information.

Featuring The Genome in 3-D[4]

If Exome Sequencing is seeing the genome in Hi-Definition, then Hi-C is seeing it in 3-D. Hi-C was developed by Erez Lieberman-Aiden at Harvard for comprehensive mapping of long range interactions of the genome. This technology has recently been used to understand role of spatial organization in producing recurrent chromosomal translocations in mice. Double strand breaks (DSBs) are major drivers of translocation and are normally introduced into both immunoglobulin loci (Ig) and T cell receptor loci during V(D)J recombination. This explains why these loci take part in recurrent translocations in human cancers. However, physical proximity of distant loci having DSBs could influence recurrent translocations. Zhang et al provide evidence for the same by generating a high resolution Hi-C map of the G1-arrested mouse pro-B cell genome and use high-throughput genome-wide translocation sequencing to map translocations from target DNA DSBs within it. This elaborate technique is sure to provide many more such blockbusters in 3-D.

Next Generation Sequencing and the Era of Deep Phenotyping[5]

Deep Phenotyping refers to precise and comprehensive analysis of phenotypic abnormalities in which the individual components of the phenotype are observed and described. A special Issue of Human Mutation (May 2012, freely available online) beckons a new Era of Genetics. Peter Robinson in his editorial article, comments that timeliness and accuracy are often a casualty in genetic medicine. However, deep phenotyping coupled with the next generation technologies could offer a solution. Thakuria et al present their exciting data on metabolomic phenotyping for their first 200 participants –all of whom are scheduled to have their complete genome sequenced at 40X coverage- aimed at revealing the link between carrier statuses of pathogenic mutations and present or future metabolic disease. Schofield and Hancock lament that data on human phenotypic variation is scattered across the globe and there is an urgent need for financially and scientifically sustainable transnational infrastructure of databases. The journal also emphasizes the utility of several computational tools such as ApiAnatomy, PhenX, MouseFinder, Observ-OM and Obser-TAB in deep phenotyping. Hammond and Suttie review the progress in 3D digital imaging and morphometric analysis of the face. Schofield et al explore the possibilities of using the data obtained from International Mouse Phenotyping Consortium and International Knockout Mouse Consortium to improve understanding of human genetics.

References

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4. Zhang Yu et al. Cell 2012; 148: 908-21.
5. Human Mutation, May 2012 Special Issue: Deep Phenotyping for Precision Medicine.

genetic CLINICS

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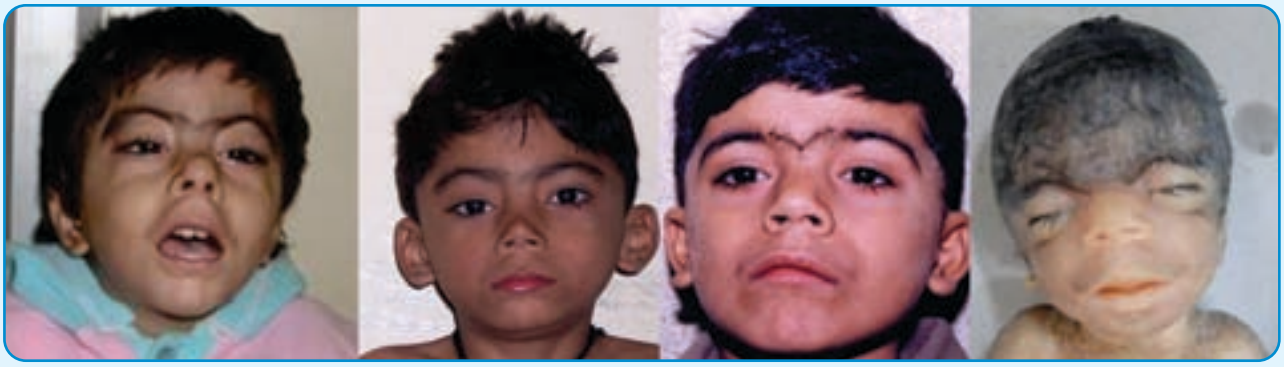
Contributed by: Shubha R Phadke, Email: shubharaophadke@gmail.com

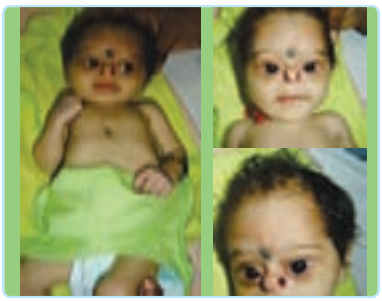
Identify this syndrome of primordial short stature by gestalt. Please send your answers to geneticsiap@gmail.com



Answer to PhotoQuiz 16 of the previous issue

Johanson – Blizzard syndrome (OMIM # 243800)

Johanson-Blizzard syndrome is a rare autosomal recessive disorder characterized by craniofacial dysmorphism, failure to thrive, developmental delay, mental retardation and exocrine pancreatic insufficiency. The craniofacial dysmorphism typically includes hypoplasia or aplasia of the nasal alae, frontal upsweep of hair and cutis aplasia on the scalp. Associated features include hypothyroidism, congenital sensorineural hearing loss, dental anomalies, cardiac defects and genitourinary anomalies. The disorder is caused by homozygous or compound heterozygous mutations in the UBR1 gene on chromosome 15q15.2.



Correct response to PhotoQuiz No. 16 was given by

1. Prashant Kumar Verma, Lucknow
2. Krati Shah, Vellore
3. Patil SJ, Bangalore
4. Himanshu Goel, New South Wales, Australia
5. Sarju Mehta, UK
6. Ranjith Kumar, New Delhi
7. Sreelata Nair, Pathanamthitta, Kerala
8. Radhakrishna Kandula, Visakhapatnam
9. Ravi Goyal, Kota
10. Mohandas Nair, Calicut
11. Saminathan D, Trichy

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