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Editorial

History of Down Syndrome: Journey of Clinical Genetics

Fifty years ago, a French scientist, Lejeune discovered that Down syndrome is caused by an extra copy of the smallest chromosome, i.e. chromosome 21. The phenotypic description of Down syndrome was given by Sir Langdon Down in 1866. But long before that, the characteristic phenotype was identified by Esquire (1838) and Seguin (1846) in groups of 'idiots'. Possibility of the chromosomal origin of Down syndrome was raised by many clinicians and geneticists. But it was only in 1959, that an extra copy of chromosome 21 as the cause of Down syndrome could be demonstrated. This was because of improved techniques in the study of chromosomes, of which the use of phytohemagglutinin to stimulate lymphocytes to multiply and the use of hypotonic solutions to help the spread of chromosomes on the slides need special mention.

The newly developed cytogenetic techniques found their place in evaluation of patients. This was the beginning of clinical genetics. Evaluation of family history was the basis of evaluation of genetic disorders at that time. In the following decades, there was flooding of genetic information about various diseases, due to advances in the field of molecular techniques, which resulted in genetics becoming a mainstream clinical discipline. The entry of genetics into the clinics was basically through three avenues, namely cytogenetics, genetic counseling and prenatal diagnosis. In the last few decades, research in exploration of the genetic basis of common disorders and cancers is bringing genetics to the centre stage of medicine.

The history of developments in medical genetics is reflected in the journey of Down syndrome. Chromosomal analysis for the diagnosis, counseling based on the karyotype, prenatal diagnosis by karyotyping, rapid diagnosis by various molecular cytogenetic techniques and evolution of antenatal screening strategies for prevention of birth of children with Down syndrome are important landmarks in the history of Down syndrome as well as clinical genetics as a medical specialty. In India too, the development of clinical genetics followed the same path. Prenatal diagnosis of Down syndrome by non-invasive methods of analysis of fetal DNA from maternal plasma epitomizes genetic revolution in the practice of medicine. Rapid advancements in the diagnosis and genetic counseling of Down syndrome are being matched by equally significant improvements in rehabilitation facilities for children and adults with Down syndrome and better social acceptance of the problem. The stigma attached to this condition is gradually wearing off and attempts are being made to integrate children with Down syndrome and other causes of mental sub-normality and with special needs, into the mainstream of society. Having said that, it may superficially appear ironic that at the same time attempts are being made to prevent birth of children with Down syndrome by various prenatal screening techniques. The fact remains that a curative treatment for mental handicap associated with Down syndrome is still far from sight and therefore for Down syndrome, as for many other genetic disorders, prevention appears to be a far more feasible and effective option than cure. Various drugs and megavitamin therapies have been tried to improve mental function in Down syndrome without any success. Further understanding of the disease pathogenesis may bring up some new therapeutic strategies.

A sensitivity of up to 96% has been achieved for prenatal screening tests for Down syndrome and going by the present trend, it appears likely that soon, no children with Down syndrome will be born in developed countries.

A lot of studies have been done to understand the pathogenesis of the Down syndrome phenotype. So far, at least 300 genes have been identified to be located on chromosome 21, which is the smallest of all human chromosomes. An extra copy of chromosome 21 means 3 copies of all genes on chromosomes 21 instead of 2 in normal individuals. With use of gene expression arrays of lymphoblastoid cell lines, it has been shown that 22% of genes on chromosome 21 are expressed proportionately (1.5 fold) in Down syndrome as compared to normal. Seven percent of genes are expressed to a greater extent than the expected ratio of 1.5 times of normal, while 71% of expressed sequences are either compensated (56%) or are highly variably expressed (15%) in most individuals. Attempts are being made to identify the contribution of over expressed genes to the phenotype of Down syndrome. The over expression of some of the genes which can be considered harmful include CAF1A, CBS, GARJ (all involved in DNA synthesis and repair); COL6A1 (heart defects), CRYA1 (cataract), DYRK1A (mental retardation), ETS2 (Leukemia and skeletal abnormality, IFNAR (immune function), SOD1 (premature aging) and APP (Alzheimer disease). Similarly, by study of various cases of Down syndrome with partial trisomy of chromosome 21, scientists have tried to identify the critical region for Down syndrome phenotype on chromosome 21. It is

unlikely that a single region on chromosome 21 is the cause of the Down syndrome phenotype. Array comparative genomic hybridization (aCCH) data of individuals with trisomy of a part of chromosome 21 has suggested different susceptibility regions for different phenotypes of Down syndrome. One important way to study a genetic disorder is an animal model. Genes similar (orthologs) to those on human chromosomes 21 are mostly seen on mouse chromosome 16 with the same synteny and orientation, while some are present on chromosome 17 and chromosome 10. Based on this information, mouse models of Down syndrome are available. Experiments in mouse models are likely to provide better understanding of the pathophysiology of Down syndrome and facilitate faster progress towards development of an effective treatment.

Developments in Down syndrome research and clinical approach not only reflect developments in the field of molecular medicine and clinical genetics respectively but are also likely to provide better understanding of the genetics of common disorders. The phenotype of Down syndrome includes congenital malformations like cardiac anomalies, Hirschsprung disease, developmental delay, hypothyroidism, cataract, Alzheimer disease and premature aging. All of these disorders occur independently in normal individuals and are thought to have multifactorial/polygenic origin. Hence, better understanding of the pathogenesis of Down syndrome is likely to provide therapies not only for Down syndrome but also for these common ailments. In the journey of Down syndrome, there have been many other accompanying genetic disorders. Use of DNA based diagnosis; genetic counseling and prenatal diagnosis are important clinical developments of twentieth century for the patients and families with genetic disorders. Identification of causative genes has lead to improved understanding of pathogenetic mechanism and development of new strategies for treatment. The twentieth century gave us a wealth of information about genetic disorders and their preventive aspects; everybody wishes that the twenty first century will find cure for many genetic disorders and Down syndrome. We hope that gene therapy to repair genes and chromosome therapy to silence the extra chromosome become a reality in near future. Till then, obstetricians, pediatricians and geneticists should strive to increase awareness about the primary prevention of this condition and at the same time, work for the betterment of children and adults with Down syndrome and their families.

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1st April, 2010

Raine Syndrome

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Summary

A fetus at 20 weeks of gestation was identified to have proptosis, short broad nose with depressed nasal bridge, carp shaped mouth, micrognathia, narrow thorax and calcification of brain on ultrasound. Autopsy of the fetus confirmed the above findings. In addition, the fetus had generalized osteosclerosis, leading us to the diagnosis of Raine syndrome. Only 13 cases have been reported in the literature so far.

Key words:

Raine syndrome, Osteosclerosis, Cerebral calcification. Prenatal diagnosis

Introduction:

Raine syndrome is a rare, lethal, osteosclerotic dysplasia inherited as an autosomal recessive condition[1]. Infants present with respiratory distress and succumb in the neonatal period. A radiograph of the fetus helps in arriving at the diagnosis.

Case Report:

A twenty-seven year-old lady was referred for a fetal scan. The lady had a third degree consanguineous marriage. Her first pregnancy ended as an early first trimester abortion. The second pregnancy resulted in a male baby born at term. The baby developed respiratory distress and died on the third day. The antenatal scan in her third pregnancy revealed calcification in the fetal brain. Cytomegaloviral infection was suspected and the pregnancy was terminated. No specific tests were performed to identify the etiology. She was referred to us in her fourth pregnancy for an anomaly scan. The scan at 20 weeks revealed calcification of cerebral cortex, a choroid plexus cyst, proptosis, micrognathia, narrow thorax and short femur length (at the 5th centile for gestational age).

Fig 1: The fetus with proptosis, mid facial hypoplasia and abnormal mouth.

The unfavorable prognosis was explained. Fetal blood karyotype was normal. An attempt to store fetal DNA was made. The patient continued the pregnancy. A repeat scan after 2 weeks showed intrauterine fetal demise. Pregnancy was terminated. Autopsy of the fetus confirmed external features noted in the antenatal ultrasound (Fig 1). A cleft in the soft palate was also noted. Histopathologic examination confirmed calcification in cerebral cortex and choroid plexus (Fig 2a). Fetogram confirmed generalized osteosclerosis, narrow thorax and mild platyspondyly (Fig 2b). We diagnosed Raine syndrome. The classic facial features along with generalized osteosclerosis are the hallmarks of this condition.

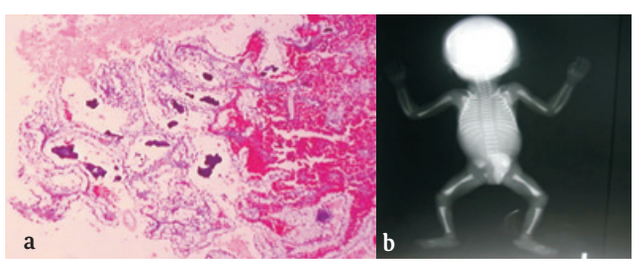

Fig 2: Calcification of brain (a) and generalized osteosclerosis (b)

Discussion:

Also known as Lethal Osteosclerotic Dysplasia, Raine first described this condition in 1989, a unique combination of findings of microcephaly, proptosis, midfacial hypoplasia and osteosclerosis[1]. The presence of intracranial calcifications in this condition was reported in 1996 by Al Mane[2]. Choanal atresia has been reported. Even after treatment, fetuses do not survive because of the hypoplastic lungs. So far only 13 cases of Raine Syndrome have been reported.

Raine syndrome is an autosomal recessive condition with 25% risk of recurrence. Mutations in FAM20C gene on chromosome 7p22 have been associated with Raine Syndrome.[3] Uniparental isodisomy of chromosome 7 and 7p telomeric microdeletion have also been reported in affected subjects. The extent of the deleted region at the 7p telomere has been established by genotyping micro-satellite markers across the telomeric region. This region is delimited by marker D7S2563 and contains 5 transcriptional units. Sequence analysis of FAM20C, located within the deleted region, in six additional affected subjects revealed four homozygous mutations and two compound heterozygotes. FAM20C is a member of the FAM20 family of secreted proteins, and its mouse orthologue (DMP4) has demonstrated calcium-binding properties.

Identification of the molecular defect would help the family in prenatal diagnosis in their subsequent pregnancies. Antenatal scan is useful in picking up intracranial calcifications. However, increased bone density cannot be picked up reliably on ultrasonographic examination.

The need for autopsy for unexplained fetal/neonatal deaths is important. If parents are not willing for autopsy, at least a photograph and a radiograph would help in reaching the etiological diagnosis and providing accurate counseling to the family.

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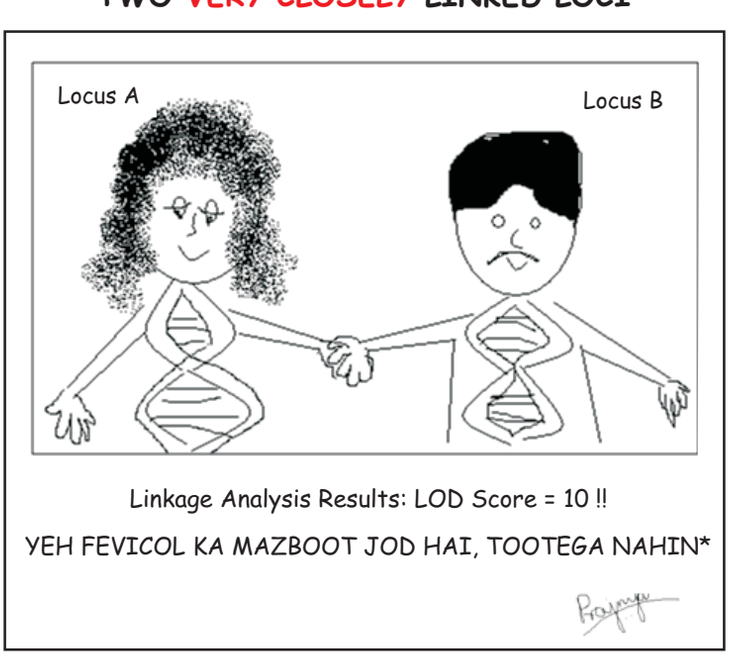

(* Linked together by the everlasting, unbreakable bonds of Fevicol)

Genetics of Diabetes Mellitus

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Background

There is a continuous spectrum of diseases from the disorders that are strictly genetic and caused by fully penetrant mutations with minimal contribution from the environment to those caused predominantly by environment factors (like teratogens) with minimal contribution from genetic factors. Between these two extremes lie the incompletely penetrant disorders, oligogenic disorders and the polygenic disorders, creating a smooth continuum from strictly genetic to multifactorial diseases. Some of the isolated developmental abnormalities such as cleft lip/palate, congenital heart defects, congenital dislocation of hip and neural tube defects do not generally follow Mendelian patterns of inheritance. The same is true for common diseases like bronchial asthma, diabetes, epilepsy, coronary artery disease, hypertension, manic depressive psychosis and schizophrenia. In these conditions, there is a tendency towards clustering in the family, more than would be expected by chance. These conditions are probably the results of combined actions of major and minor genetic factors together with the environmental factors, each of which makes only a varying degree of contribution to the final phenotype. This type of inheritance is termed as multifactorial inheritance. Diseases inherited in this manner are known as *complex diseases*. Multifactorial inheritance may involve small number of loci (oligogenic) or many loci (polygenic). The monogenic disorders account for a small part of mortality and morbidity in the general population, which is mainly contributed by complex disorders. Complex diseases have a low heritability (tendency to be inherited) as compared to single gene disorders. For example, only 2-5 per cent of the close relatives of individuals with diabetes also suffer from diabetes, much lower than would be the case for a single gene disorder like cystic fibrosis. This indicates that no single genetic factor is responsible for the disease.

Genetics of Diabetes Mellitus

Diabetes mellitus is a common and rapidly growing medical problem arising from a combination of environmental and genetic factors. It is heterogeneous in etiology. Clinically it is divided into two types-

Type 1 diabetes (Insulin dependent diabetes mellitus)

Type 2 diabetes (Non Insulin dependent diabetes mellitus)

Other rare forms of diabetes that are inherited in monogenic fashion are maturity onset diabetes in the young (MODY), and diabetes due to mutations in mitochondrial DNA.

All forms of diabetes have very serious effects on health. In addition to the consequences of abnormal metabolism of glucose (e.g., hyperlipidemia, glycosylation of proteins, etc.), the associated long-term complications like cardiovascular, peripheral vascular, ocular, neurologic and renal abnormalities are responsible for morbidity, disability and premature death in young adults. Furthermore, the disease is associated with reproductive complications causing problems for both; the affected mothers and their children. Although improved glycemic control may decrease the risk of developing these complications, diabetes remains a very significant cause of social, psychological and financial burden in populations worldwide.

Type 1 diabetes (T1D)

T1D becomes clinically apparent after a preclinical period of varying length, during which autoimmune destruction reduces the mass of beta cells in the pancreatic islets to a level at which blood glucose levels can no longer be maintained in a physiologic range. Type 1A is the common immune mediated form whereas type 1B is the nonimmune form. T1D represents approximately 10% of all cases of diabetes with a prevalence of <1% in most populations.[1]

Etiology

The etiology of Type 1 diabetes is complex and arises from the action of many genes and environmental factors. Environmental risk factors such as viral (Coxsackie virus B, mumps, rubella and rotaviruses) and infant nutrition (early exposure to cow's milk protein and short duration of breast feeding) are thought to act as either 'initiators' or 'accelerators' of beta cell autoimmunity, or 'precipitators' of overt symptoms in individuals who already have evidence of beta cell destruction.

First degree relatives of an affected individual have a higher risk of developing T1D than unrelated individuals from the general population (approximately 6% vs ‹1%, respectively).[2] The two primary approaches used to identify the genes for diabetes mellitus have been linkage studies (using pairs of affected relatives, typically siblings) and association studies (using either case–control or family-based designs).[3,4] *Linkage analysis* approach is best suited for discovering genes with strong effects within relatively small family-based studies and involves genotyping affected family members for a set of markers to identify regions that are co-inherited more commonly in affected family members and therefore potentially point to a genomic region containing a susceptibility locus. Although linkage studies have pointed to a number of regions of the genome that contain novel genes that may contribute to the risk of type 1 diabetes, most identifications of actual risk loci have come from studies of candidate genes. Using these approaches, at present, more than 20 regions of the genome may be involved in genetic susceptibility to T1D. However, none of the candidates identified have a greater influence on T1D risk than that conferred by genes in the HLA region of chromosome 6. This region contains several hundred genes known to be involved in immune response. Those most strongly associated with the disease are the HLA class II genes (i.e., HLA-DR, DQ, DP). Two forms of DR, designated DR3 and DR4, are present in 95 percent of Type 1 diabetics, and 30 percent have inherited both DR3 and DR4. This is in contrast with the general population, where only 50 percent of people have DR3 or DR4 and 1 to 3 percent have both. The HLA class II genes, also referred to as IDDM1, contribute approximately 40-50% of the heritable risk for T1D.[3] DRB1*15-DQA1*0602-DQB1*0102 is protective and associated with a reduced risk of T1D in most populations. Genes outside the HLA region also contribute to the risk of type 1 diabetes, but their individual contributions are much smaller than that of HLA.

Association studies look for relative prevalence of an allele at a locus amongst persons with the disease as compared to that in the control population. The particular allele found to be associated with the disease (i.e. significantly more common in the individuals with the disease than in the controls) may be a causative allele or may be in linkage disequilibrium with a specific allele which is an unknown causative variant. Linkage disequilibrium extends over relatively short genomic distances in human populations (typically, tens to hundreds of kilobases) and is dependent on the ethnic background, ancestral history, admixture, and local recombination frequencies. Thus, although a significant result in a genome-wide linkage scan may implicate a region spanning many megabases of DNA it may subsequently require substantial fine-mapping studies. A significant result from an association study may implicate a region of only a few hundred kilobases or less. The associated region may contain either a single gene or a few genes or be located in an apparent "gene desert." *Genome wide association (GWA) studies* take advantage of newly developed, high-throughput SNP genotyping platforms and the development of dense maps of SNPs from the human genome. The high-density genomewide association studies in type 1 diabetes provide confirmatory evidence for previously identified loci such as *INS, PTPN22, CTLA4, and IL2RA*.[3,4]

Type 2 Diabetes mellitus (T2D)

T2D is the most common form of the disease, accounting for approximately 90% of all affected individuals. T2D is caused by relatively impaired insulin secretion and peripheral insulin resistance. Typically, T2D is managed with diet, exercise and oral hypoglycemic agents and exogenous insulin is not required frequently. However, it

is associated with the same long-term complications as T1D. The 'top' three countries in terms of the number of T2D individuals with diabetes are India (31.7 million in 2000; predicted 79.4 million in 2030), China (20.8 million in 2000; predicted 42.3 million in 2030) and the US (17.7 million in 2000; predicted 30.3 million in 2030). The prevalence of T2D increases with the age of the population.[5]

Etiology

The major environmental risk factors for T2D are obesity (>120% ideal body weight or a body mass index >30 kg/sqm), increased waist-to-hip circumference (WHR) and a sedentary lifestyle. Family studies have revealed that first degree relatives of individuals with T2D are about 3 times more likely to develop the disease than individuals without a positive family history of the disease.[6,7] It has also been shown that concordance rates for monozygotic twins, which have ranged from 60-90%, are significantly higher than those for dizygotic twins. Thus, it is clear that T2D also has a strong genetic component.

Candidate genes are previously discovered genes that, based on their inferred physiologic role, are hypothesized to contribute to the disease of interest. In the case of type 2 diabetes, genes related to glucose transport, β-cell function, and insulin secretion would all be considered reasonable candidates for contributing to the genetic basis of disease. Association studies simply compare the relative frequencies of each variant allele in case and control subjects and determine whether one is over-expressed in individuals with the disease. More than 50 candidate genes for T2D have been studied in various populations worldwide. However, results for all candidate genes have been conflicting. To date, only the following genes have been convincingly shown an association with type 2 diabetes.

Gene	Description of disease related allele
PPARG	Missense-Pro12Ala(P12A)
ABCC8	Ser1369Ala
KCNJ11	Missense-Glu23Lys(E23K)
WFS1	Intron exon junction
HNF1B	Intronic

GWA studies among European ancestry populations have identified 18 T2D genetic loci like TCF7L2, KCNJ11, PPARG, HHEX, WFS1, HNF1B and SCL30A8in, CDKAL1, IGF2BP2, CDKN2A/B, FTO, JAZF1, ADAMTS9, CDC123-CAMK1D, THADA, TSPAN8-LGR5,NOTCH2, ,KCNQ1.

Maturity-Onset Diabetes of the Young is an uncommon form of T2D (accounting for <5% of all T2D cases). It generally occurs before age 25 years and is characterized by a slow onset of symptoms, the absence of obesity, no ketosis, and no evidence of beta cell autoimmunity. It is most often managed without the need for exogenous insulin. It displays an autosomal dominant pattern of inheritance. At least six different genes (HNF4A, GCK, HNF1A, IPF1, HNF1B, NEUROD) causing 6 forms of MODY, each associated with a variable severity and phenotype have been identified.[8] All MODY genes are expressed in the islet cells of the pancreas, and play a role in the metabolism of glucose, the regulation of insulin or other genes involved in glucose transport, and/or the development of the fetal pancreas. However, about ~15% of MODY patients do not carry mutations in one of these genes, suggesting involvement of other genes causing MODY.[9]

Clinical Implications of Diabetes Genetic Testing [4,5]

1) Predicting risk of developing diabetes and complications

Type 1 diabetes: Through genetic testing, individuals at high risk for T1D could be identified prior to the onset of the disease – at a time when primary prevention strategies could be safely administered. It is most likely that such predictive genetic testing would be offered to families with an affected individual before it will be made available to the general population. Children who carry both of the highest risk HLA haplotypes (DR3–DQ2 and DR4–DQ8) have a risk of approximately 1 in 20 for development of type 1 diabetes by the age of 15 years. If the child has a sibling who has diabetes and the same haplotypes, the risk is even higher (approximately 55%). Since this haplotype combination occurs in only 2.3% of the white population, it is possible to envision universal screening strategies that pinpoint this highest-risk group.[4]

Type 2 diabetes: Identifying patients in the pre-diabetic stage for intensive lifestyle management or metformin therapy has the potential to significantly reduce the incidence and subsequent morbidity and mortality of type 2 diabetes. Studies have been published regarding the data about aggregated diabetes risk-associated 18 genetic loci to predict diabetes risk (genotype score) in different populations. It was found that the genotype score

provided only a slightly better prediction of risk than knowledge of common risk factors alone.

The rate of progression to cardiovascular disease, renal dysfunction, retinopathy, and other diabetes-related complications is known to differ among patients with similar diabetes duration and glycemic control, raising the possibility that individuals may have a genetic predisposition to specific complications.

2) Response to treatment based on genotype (pharmacogenomics)

In addition to predicting risk for diabetes or related complications, a more detailed understanding of an individual's genetic background may help guide treatment for T2D so that one can choose "right" treatment for the "right" patient, based on both expected response and propensity for adverse side effects. Since PPARγ, ABCC8 and KCNJ11 are the targets of drugs used routinely in the treatment of T2D, there are pharmacogenetic implications for maintaining good glycemic control.

a) PPARγ P12A variant - Recent evidence suggests that knowledge of allelic variation at this locus does not yet offer a rationale for therapeutic choices.[5]

b) KCNJ11- Neonatal diabetes carriers of specific mutations at *KCNJ11* can be safely transitioned from insulin to sulfonylurea therapy.[10] However, impact of genetic variation on sulfonylurea therapy in common type 2 diabetes is unclear. In contrast to UK Prospective Diabetes Study, [11] results by Sesti et al.[12] showed that carriers of E23K had a relative risk of failure to respond to sulfonylureas of 1.45 as compared with E23E homozygotes.

c) ABCC8- A recent trial by Feng et al. showed that Ser/Ser homozygotes at *ABCC8* A1369S had a 26.1% decrease in fasting plasma glucose compared with a 31.6% decrease in Ala/Ala homozygotes (which translates into a significant difference of 12.6 mg/dl between genotypic groups).[13]

d) TCF7L2- To investigate potential interaction of *TCF7L2* with drug therapy, the recently published Go-DARTS (Genetics of Diabetes Audit and Research Tayside) study genotyped 6,516 U.K. participants for *TCF7L2* and found that the T allele was overrepresented in individuals requiring insulin treatment and underrepresented in the patients managed by diet alone. The authors concluded that *TCF7L2* variants may be associated with increased disease severity and therapeutic failure.[14] Also the carriers of the risk *TCF7L2* variants were more likely to fail with sulfonylurea but not metformin therapy as measured by A1C >7% within 3–12 months after treatment initiation.

3) Behavioral response based on genetic risk of T2D -

It is not known to what extent individual genetic risk information can be applied to patients with prediabetes to motivate significant behavior change but studies from the DPP (Diabetes preventive program) on participants with impaired glucose tolerance and elevated fasting glucose reveal that the lifestyle preventive intervention was effective in reducing the genetic risk conferred by the high-risk homozygous genotype to the level of their wild-type counterparts.

Conclusions

Understanding the complex interactions among genetic profiles, individual lifestyles, and environmental factors lies at the core of effective diabetes management. Attempts to integrate such knowledge into clinical practice are still in the early stages. Nevertheless, current research is directed towards developing diagnostic tests to identify the high risk individuals and to develop novel preventive and therapeutic strategies for these complex diseases.

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Recurrent Pregnancy Loss: From Chromosomes to Genes

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Recurrent pregnancy loss (RPL), also known as recurrent spontaneous abortions, habitual abortions, or recurrent miscarriages are traditionally defined as 3 or more consecutive pregnancy losses at less than 20 weeks of gestation. Two to 5 percent of couples experience RPL.[1] The cause of RPL is difficult to assess and in fact, no cause can be determined in half of the cases in spite of a battery of investigations. This suggests the presence of unidentified genetic causes.[1]

Chromosomal abnormalities

In 3-5% of couples with RPL, one partner is found to carry a balanced chromosomal rearrangement.[2] Approximately 50% of these chromosomal rearrangements are balanced reciprocal translocations, 24% are Robertsonian translocations, and 12% are sex chromosomal mosaicism. The remainders are chromosomal inversions and other sporadic abnormalities[2]. In these couples RPL occurs due to abnormal segregation of gametes at the time of meiosis. The balanced chromosomal rearrangement carrier is phenotypically normal; however, the separation of chromosomes during meiosis results in an aberrant copy number of chromosome segments in the conceptus resulting in pregnancy loss. If one of the spouses has a balanced translocation, the risk of a live born child with chromosomal imbalance is about 4 % and depends upon the particular chromosomal segments involved[1]. Preimplantation genetic diagnosis or fetal karyotyping by amniocentesis is an options for these couples to select fetuses with normal chromosomal content. Some chromosomal variations like pericentric inversion of 9, small or large heterochromatin on the q arm of Y chromosome and inversion Y are seen in many normal individuals and not known to be associated with poor reproductive outcome. Formation of gametes with unbalanced chromosomal constitution is shown in figure 1, in which one of the partners is a carrier of a reciprocal translocation between chromosomes 2 and 9. In addition to the gametes shown in the figure, 3:1 and 4:0 segregations are possible and will always be unbalanced.

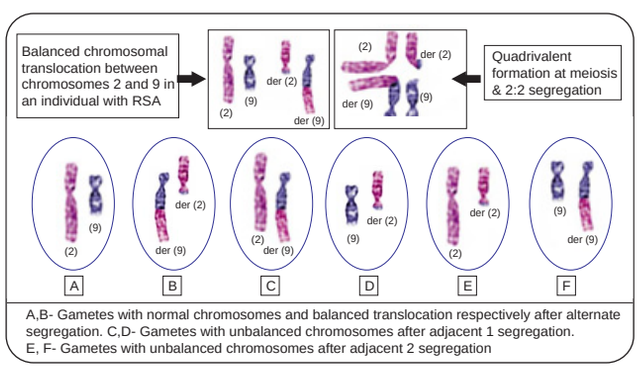

Fig 1: Gamete formation in an individual with a balanced translocation between chromosomes 2 and 9

Non genetic causes

Anatomical anomalies of the uterus such as Mullerian anomalies, uterine fibroids, Asherman syndrome and cervical incompetence are the cause of RPL in 10-15% of the affected couples. Several endocrinological factors like diabetes mellitus, untreated thyroid disease, hyperprolactinemia, luteal phase defect, high serum androgen and polycystic ovaries might be associated with RPL but convincing evidence for their role in RPL is lacking. Luteal phase deficiency has been found in 10-28% of couples with RPL and there seems to be evidence of benefit by progesterone therapy in women with a history of RPL.[3,4]

Thrombophilia

Congenital or acquired thrombophilia is another important cause in couples with RPL. Mechanisms which have been proposed are placental thrombosis, placental infarction, inhibition of thrombolytic system and abnormal prostacyclin metabolism. Apart from RPL, other obstetric complications that have been associated with thrombophilia are still birth, early onset of preeclampsia, intrauterine growth retardation and placental abruption. Histopathological examination of placental vasculature in pregnancy with thrombophilia also show increased fibrin deposition and thrombus formation.[5] The most common inherited thrombophilic disorders are the factor V Leiden

mutation and the prothrombin G20210A mutation. There is sufficient evidence to recommend factor V Leiden and prothrombin gene mutation testing in patients with RPL after excluding more common causes. Mutations in genes of protein C, protein S and antithrombin have also been shown to be associated with RPL but as compared to Factor V Leiden mutation and prothrombin gene mutation, they are far less common and studies are not consistent enough to recommend routine testing for these mutations in all couples with RPL. These tests can be considered if there is a strong family history of thrombosis and tests for other causes of thrombophilia are negative. Some mutations in genes of the fibrinolytic pathway such as the 675 4G/ 5G and A844G polymorphisms in the promoter region of the plasminogen activator inhibitor-1 (PAI) gene, have been hypothesized to be associated with RPL. However, the available data is not adequate to provide a convincing association between the PAI gene and RPL.[2,5]

Autoimmune disorders

Many autoantibodies have been studied in association with RPL, but most of the studies have focused on antiphospholipid antibodies consisting of anticardiolipin antibodies (ACA) and lupus anticoagulant (LAC) directed against negatively charged molecules present in the cell membrane. One or the other of these is found to be present in 5% - 15% of women with recurrent pregnancy loss and therefore testing for these antibodies is recommended in couples with RPL. Many mechanisms have been postulated for the role of these autoantibodies in the causation of RPL including thrombosis of placental vessels and infarction, inhibiting the implantation process, impaired trophoblast function or complement activation. Combined therapy with unfractionated heparin and low dose aspirin may reduce pregnancy loss by 54% in couples with RPL showing presence of antiphospholipid antibodies. Some recent studies also show beneficial effects of this combination therapy in couples with unexplained RPL with no demonstrable evidence of thrombophilia. Other autoantibodies like antinuclear and antithyroid antibodies can be found in increased frequency in couples with RPL but most studies do not show any significant relationship with RPL.[6] Studies from India have reported a significant contribution of genetic and acquired thrombophilias in recurrent early and late fetal losses.[7]

Immune mechanisms

Immunological mechanisms have also been proposed to be related with RPL due to the break down of the normal maternal immune system and rejection of the fetus. Some studies show that specific immune cells like CD56+ Natural Killer (NK) cells may have an abnormal distribution in the peripheral blood and endometrium of women with RPL as compared with controls. The total number of T cells is not altered but T cell expression may be altered in the peri-implantational endometrium or peripheral blood. In some recent studies, multiple cytokine polymorphisms have been reported to be associated with RSA. However these results have not been consistent and have not been confirmed in other studies. This might be related to differences in the ethnic background. The contribution of HLA genes to the etiology of RPL is still under discussion. Some prospective studies in the past have shown that sharing of HLA-B and HLA-C alleles between the husband and the wife may significantly increase fetal loss rates but convincing evidence for this hypothesis is still lacking. Human Leukocyte Antigen (HLA)-G is a nonclassical protein that is expressed on the surface of invading cytotrophoblasts and may play a role in immunoprotection of the developing pregnancy. There have been several reports linking HLA-G deficiency and some polymorphisms in this gene have been associated with increased miscarriage rates in selected populations. Further investigation is needed to determine the role of HLA-G in normal and abnormal pregnancy.[2, 6]

Immunotherapy

A number of clinical trials have now been carried out for inducing immunological tolerance in the wife for paternal antigens. This includes administering repeated infusions of the husband's peripheral blood mononuclear cells to the wife. A Cochrane review, concluded that paternal cell immunization, as well as other immunologic treatments, such as third party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin provide no significant beneficial effect over placebo in preventing further miscarriages.[4]

Other possible genetic causes

It is likely that many other single gene polymorphisms may cause or contribute to pregnancy loss but these genetic mechanisms remain poorly understood. The likely candidate genes are the genes involved in immune pathways or in the control of placental and fetal development. Carolyn et al have suggested that multiple mutations in many genes rather than specific gene mutations may be risk factors for RPL, supporting the multifactorial model. The genes which have been shown to have association with RPL in the recent past are listed in table 1. Further studies of these polymorphisms in larger number of patients from different populations and search for the pathogenetic mechanisms involved are necessary before any definite conclusions can be drawn. At present, study of these polymorphisms is not included in routine patient care investigations, but it may open up new strategies for treatment in the future.

Recurrent pregnancy loss in clinic

Recurrent pregnancy loss is a common clinical problem disturbing equally to the patient and the doctor. Usually investigations are recommended after three pregnancy losses. If the patient is in her thirties, the family may wish to get investigations done after two pregnancy losses. However after a single spontaneous abortion, reassurance to the family is needed rather than order expensive list of investigations. All the investigations including karyotypes of the husband and wife may be done in one go rather than doing investigations one after the other. Karyotypes of the couple give more information regarding the possibility of recurrence of chromosomal abnormality in the next pregnancy and must be done in all cases. Karyotype of the products of conceptions may not be done if there are cost constraints. The chromosomal analysis of each spontaneous abortion is not indicated. The culture and karyotype of products of conception obtained after curettage is not only costly, but has a high failure rate even in a good laboratory. TORCH group of infections do not cause recurrent pregnancy losses and serological investigations for TORCH are not indicated in evaluation of a case of recurrent pregnancy losses.

The abnormal test results need to be discussed with the family regarding the availability of treatment. Detection of a thrombophilia needs appropriate treatment. The most important counseling is for balanced chromosomal rearrangement. If one of the partners is found to be a carrier of a balance chromosomal rearrangement then there is 30 to 50% chance of each pregnancy ending in a spontaneous abortion. This may depend on the chromosomes involved and the size of translocated segment. Some translocations are likely to lead to unbalanced gametes in higher proportions and the risk of spontaneous abortions may be higher. It also means there is a good chance of a normal live born child in the couple though there is no treatment for a chromosomal abnormality. However there is also an increased possibility (5 to 10% and depends on the chromosomal abnormality) of birth of a child with chromosomal imbalance and hence malformations and / or mental retardation. In such a family karyotyping from amniotic fluid should be offered if the pregnancy continues beyond first trimester. In vitro fertilization followed by preimplantation diagnosis and implanting only chrmosomally balanced embryos is a good option for the families with chromosomal abnormality. However, in absence of chromosomal abnormality in one of the partners, in vitro fertilization is not an option for RPL.

If no cause is detected after all the investigative work up, the family should be counseled about inability to detect the cause of RPL and lack of availability of any definitive treatment. Even after three RPL the chance of a live birth in the next pregnancy is around 70% without any treatment and it decreases with higher number of losses. Possibilities of good outcome should be presented with caution in families with many spontaneous losses. Conveying the truth about inability to detect cause and definitive treatment must be shared with the family. It may help in accepting the situation and take appropriate decisions about taking chances and other options like adoption.

Tests for genes and treatment modalities currently under research should not be offered unless it is a part of research program cleared by ethics committee.

Author and year of publication	No of cases	No. of controls	Gene studied	Polymorphism or mutation or allele having significant association	P value	Odds ratio
Karvela et al, 2008 [8]	131		Androgen receptor	G1733A polymorphism	0.0004	2.12
Goodman et al, 2009 [9]	69	37	Apo E	ApoE4 allele	0.036	-
Bolor et al, 2009 [10]	26	150	SYCP3	1)c.IVS7 16_19delACTT in intron7 2) c.657T/C in exon 8	Mutation found in 2/26 affected women but in none of the controls	
Zammiti et al, 2009 [11]	372	274	TNFa	1) -238A/G, 2) -308G/A	.019-0.455 .013-0.184	0.57- 0.85 1.52-1.32
Faridi et al, 2009 [12]	205	224	KIR	BB genotype	<0.0001	4.4
Prigoshin et al, 2004 [13]	40	53	IFN-gamma	+874A?T polymorphism	0.01	-
Coulam et al, 2009 [14]	152	65	VEGF	-1154AA genotype	< 0.05	-
Firouzabadi et al, 2009 [15]	97	32	p53	Codon 72 polymorphism	0.041	-
Kaare et al, 2009 [16]	46	191	p53	C11992A polymorphism	0.0414	2.08

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Medical Genetics in India – What needs to be done?

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Genetics in India has come a long way, but it still has a long way to go. All that we have been able to achieve so far is some demonstration of its utility, some creation of demand and some generation of interest in medical students and trainee doctors[1]. But a large mass of medical profession, public at large and government remain indifferent to the potential of medical genetics for public good [2,3]. One of the major limiting factors is high cost of genetic tests and lack of their accessibility. *It needs to be appreciated that at present the strength of genetics lies in prevention of disease and not its cure. Therefore, it needs to be taken up as a public health measure for prevention of physical and mental handicap, cancers and other debilitating disorders rather than just a clinical superspeciality.* More than 50% of clinical services of genetic centers abroad are occupied by newborn screening for inborn errors of metabolism [4-6], screening of pregnancies for birth defects and chromosomal disorders[7,8] and screening of adult population for various genetic markers including those for cancer [9], coronary artery disease [10], and more recently for drug/xenobiotic metabolizing enzymes. One national program that can transform the scenario of Medical Genetics in India could be control of Thalassemias and Hemoglobinopathies[11-15]; but such a decision is to be taken at a political level rather than the scientific or professional one. Other major applications of genetics are in fields of reproductive medicine and cancer[16]. These disciplines need to take up genetics in a much bigger way.

As mentioned above, the Achilles heel in Medical Genetics is the laboratory infrastructure for genetic tests. This need to cover 3 distinct areas viz., Cytogenetics, Biochemical genetics and Molecular genetics; each requiring *specially trained manpower,* highly specialized and sophisticated instrumentation and a blend of research and clinical service culture to provide prompt and reliable results of ever increasing number of tests. Now sequencing and microarray are becoming a part of routine clinical genetics laboratory rather just research. There is also a need for strong quality control of genetic tests, requiring accreditation and monitoring of test results[17, 18]. In addition, *there should be a statutory requirement of pre-test and post-test counseling* to discuss the need and utility of testing, interpretation of test results and action/s to be taken in response to them[19,20]. Both the clinical and laboratory components need to be developed as a composite unit for efficient functioning. It is a new paradigm for the medicine of tomorrow. The testing needs to be covered by health insurance to make access equitable, and by confidentiality/privacy laws to protect individuals and families from discrimination.

The uniqueness of genetic disorders is variety and rarity. In medicine, proficiency comes by numbers, whereas most individual genetic disorders are rare having the prevalence of 1:5000-15000 births, or even more. At the same time there are several thousand genetic disorders, affecting all systems of the body. So, how to achieve proficiency in Genetics? If we wish to achieve competency there must be pooling of clinical and laboratory resources – in a collaborative network. Fortunately DNA is a hardy material and can be easily transported. Regarding clinical material we should make use of the internet. We should evolve standardized clinical databases and be benefited by the clinical expertise wherever it exists. The interest and expertise in genetics must percolate to all specialties and super-specialties. Since the variety is so immense, we must restrict specialized laboratory investigations, area wise, to different laboratories according to their interest and expertise so that greater expertise is developed and more and more areas are covered. There is need to develop medical genetics in an organized manner as a medical school/hospital activity rather than as research tool.

The most important need for improving the standards of medical education across the country is to give prominence to modern medical biology, which is largely an offshoot of advances in genetics, in undergraduate and postgraduate medical curriculum. It now constitutes a major part of articles published even in hard core medical journals like NEJM, BMJ and Lancet etc. Although the Medical Council of India has incorporated quite a bit of genetics in medical curriculum most medical colleges are ill prepared for it.[21, 22]The Council should seriously consider prescribing establishment of medical genetics unit as an integral component of Medical Colleges. It can be a part of any of the major clinical departments, viz., Medicine, Pediatrics or Obstetrics and Gynecology. It should also see that evaluation of knowledge of Medical genetics and its application are incorporated in the final certifying examination. It would not be trite to say that without the knowledge of genetics, the practitioner of modern medicine of tomorrow would be practically illiterate.

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Fetal loss due to Thrombophilia AND others : Feto-materno-paternal unit shares the onus

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Fetal loss due to Thrombophilia: Feto-materno-paternal unit shares the onus[1]

Thrombophilia has extensively been studied in obstetric complications particularly with intrauterine fetal demise. Majority of studies done till now have focused on genetic contribution by mother. Tranquilli, et al have tried to correlate the fetal genotype in placental samples in third trimester fetal loss. Fetal genotype in 86 primiparous women with unexplained fetal death was compared with 100 age matched primiparous healthy pregnant women without any obstetric complications. Genes which were studied were methylenetetrahydrofolate reductase (MTHFR C677 T), Prothrombin (FII G20210A), Factor V (FV G1691A), and Plasminogen activator inhibitor-1 (PAI-1 4 G/5 G). Simultaneous presence of 2 or 3 mutations in single fetus was significantly associated with fetal loss (Odd's Ratio 7.4 and 8.7 respectively). Study highlights the importance of analyzing the mother–fetus–father triad DNA to screen the thrombophilic mutations in the evaluation of the risk of intrauterian fetal death.

Predicting eclampsia in the first trimester: Role of the 'Whistle-blower' genes[2]

Preeclampsia (PE) is an important cause of maternal and fetal mortality and morbidity. The etiology and predictive markers have not been elucidated until now. In a prospective cohort study Farina et al analyzed gene expression profile by microarray hybridization in the chorionic villus tissue (taken for fetal karyotype) in women who subsequently developed PE. The differentially expressed genes were confirmed by RT-PCR in peripheral blood in pregnant women at term and compared with normal control women. The genes which were found to be upregulated in preeclampsia patients included Biotinidase, Adducin 1, Claudin 6, Titin, vasoinhibin, lactotransferrin and HLA class II DR4. The authors have also suggested pathophysiologic pathways in development of PE involving these genes i.e. including inflammatory stress, angiogenesis, blood pressure control and endothelial aberration. These mRNA may further be used as screening method for preeclampsia.

Capturing the pulse of the ART[3]

Worldwide there is an increase in use of artificial reproductive procedures. Definitions used in medically assisted reproduction within different countries are frequently the result of adaptations to particular medical, cultural and religious settings. Standardization of these definitions is necessary to monitor efficacy, safety and quality of procedures and international data collection. WHO in collaboration with The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and health professionals from different organizations have reviewed the existing ART glossary and have introduced new glossary having 87 terminology including 34 new terms.

Uterine transplantation: The inside story[4]

Gestational surrogacy is the only option to achieve the genetic parenthood for the women that either lack or have a non-functional uterus. Uterine transplantation is another option for these women. Brannstrom et al have published a review based on all studies about uterus transplantation (in animals and humans) and identified aspects related to surgery, cold-ischemia/reperfusion, rejection, immunosuppression, pregnancy, ethics and institutional requirements. Till date one human uterus transplantation attempt has been performed in the year 2000 which became necrosed after 3 months due to acute vascular occlusion. The authors have suggested that longer vascular pedicles during uterus retrieval, increase in the uterine fixation by multiple attachment and reconstructions of the uterosacral ligaments and cardinal ligaments will be valuable in future attempts of human transplantation. Animal studies suggest that uterus is resistant to ischemic perfusion injury and after transplantation it exhibits normal function and ability to carry out pregnancies if not rejected.

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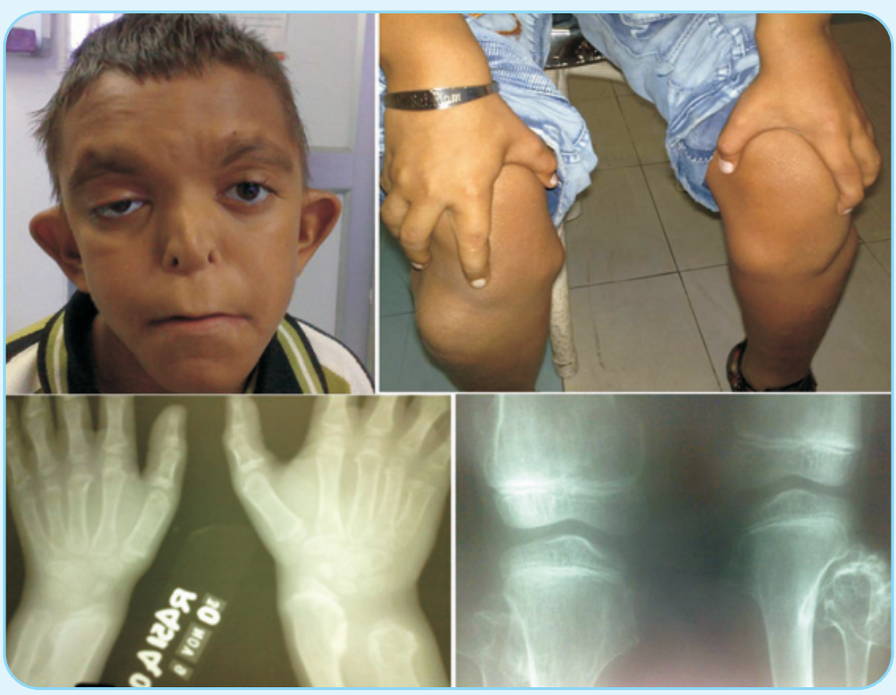
A 12 year old boy came to us with the complaints of multiple bony swellings over the ends of all four limbs. See the facial features and radiographs. What is the diagnosis?



Answer to the PhotoQuiz 7 of the previous issue:

Dyskeratosis Congenita (OMIM 305000, 127550, 224230)

Dyskeratosis Congenita (DKC or DC): DC is a monogenic disorder characterized by cutaneous pigmentation, dystrophy of the nails, leukoplakia of the oral mucosa, continuous lacrimation due to atresia of the lacrimal ducts, often thrombocytopenia, anemia, and in most cases testicular atrophy. The common mode of inheritance is X –linked recessive (also known as Zinsser-Cole-Engman Syndrome) and is caused by mutations in the gene encoding dyskerin (DKC1). An autosomal recessive form of dyskeratosis congenita can be caused by mutation in the NOLA3 gene on chromosome 15, or by mutation in the NOLA2 gene on chromosome 5. Bone marrow failure and cancer which develops in the leukoplakia of the anus or mouth or in the skin, are important complications.

Correct responses were given by:

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Jayaprakash KP (Kottayam), Anju Aggarwal (New Delhi), Narendra Chaudhary (Manipal)
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