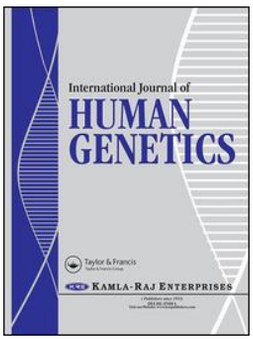

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Genetic Causes of Congenital Malformation in India

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KEYWORDS Congenital malformations; neonates; stillbirths; prenatal detection; prevention

ABSTRACT Congenital malformations are a major cause of death of neonates in India where prenatal detection and treatment are not adequate in many hospitals and health centers. Incidence is specially high in stillbirths. It is not realized that genetic causes - chromosomal, single gene and polygenic - are the main causes of many congenital defects and early detection and prevention should be essential to make the small family norm a success.

INTRODUCTION

Phenotypic changes of genetic diseases at birth include congenital malformations in chromosomes and single gene defects. However the most common defects are usually multifactorial. In India with a large multiethnic population the reports of congenital malformations has usually been sporadic. The fact that 1 in 5 children die within the first 5 months and most of the deaths are still attributed to prematurity, infections and birth trauma suggests that maternal and child care leaves much to be desired. Birth weight is an index of the quality of prenatal care and a predictor of both survival and health of the baby. WHO estimates that 21.6 million infants are born yearly with birth weights less than 2500gm in the world. In India the index is still unfortunately high.

Data in India despite improved care does not yet list genetic diseases as cause of neonatal death, congenital defects or of stillbirths.

Master Notani et al. (1968) studied congenital defects in a Bombay hospital and could find direct correlation to lack of antenatal care. Others have also carried out longitudinal studies giving more or less similar data (Aiyar and Agarwal 1969; Verma 1978; Talukder and Sharma 1979; Mathur et al. 1982; Kulshresta et al. 1983; Verma and Mathur 1983; Ghosh et al. 1985; Singh 1986; Mishra and Banerjee 1989; ICMR 1990; Person 1991) (Table 1).

Verma (1994) listed data from 30987 births from 25 hospitals and incidence was found to be 19.4/1000 births with neural tube defects in 3.5/1000. Incidence of Downs was 1.14/1000 births.

Recently Patel and Adhia (2005) detected major malformations in 7.92% of 17653 births and were able to attribute chromosomal cause to 4%,polygenic to 45.1% and total genetic aetiology to 65.4%.The data from a major hospital in Bombay included stillbirths and only goes to prove the enormity of the problem.

Chromosomal Anomalies as Cause of Congenital Defects

An incidence of 1-2/1000 births of trisomy 21 has been reported (Verma 1978, 1998; Verma and Singh 1975; Talukder 1986). Due to the long reproductive life of Indian women a large number conceive after 34 years and are likely to deliver Down Syndrome babies (Kothare et al. 2002; Dinesh et al. 2003; Kava et al. 2004; Rao et al. 2005).

Some are also associated with repeated abortions which may be detected by advanced cytogenetic techniques including FISH. Jyothi et al. (2000, 2001, 2002) have reported 87.92% as classic trisomy 21, mosaic in 7.69% and translocation in 4.39% with significant contribution of advanced parental age.

The effect of consanguinity on the non-disjunction mechanism was examined in 417 cytogenetically confirmed Down syndrome patients. The incidence of parental and grandparental consanguinity was 17.5% (n=73), while that of only parental consanguinity was 17.2% (n=71). First cousin marriages occurred more frequently, than uncle- niece and 2nd cousin marriages. With regard to parental age, only the mean age difference between consanguineous

couples significantly differed from nonconsanguineous couples. The inbreeding coefficient did not differ between trisomy 21 and translocation Down's families suggesting that consanguinity does not predispose to Down's syndrome.

Few centres exist in India for diagnosis of chromosomal disorders; mostly are being used for female feticide (Verma and Singh 1989; Panchaszadeh 1993).

Women above 34 years should be advised after ultrasonography to avoid amniocetensis with 80% success (Snijders et al. 1998). This could be carried out with the maternal blood levels in three test systems. Use of interphase uncultured amniotic fluids by DNA with three STR markers located on chromosome 21 has also been made (Verma et al. 1998).

Table 1: Burden of genetic disease at birth in India

Disorder	*Incidence*	*Number per year*
Congenital malformations	1 : 49	495096
Down syndrome	1 : 1139	21412
Beta-thalassaemia	1 : 2700	9000
Sickle cell disease	-	5200
Metabolic disorders	1 : 2497	9760

Incidence of Major Congenital Defects

Incidence of congenital malformations has been screened by retrospective and prospective surveys. The latter gives better results (Roychowdhury et al. 1984, 1994). The data has been found to be more accurate in urban than rural hospitals and in areas where post mortem of stillbirths is done (Swain et al 1994; Kumar et al. 1994; Chaturvedi and Banerjee 1993; Ronya et al. 2002).

In another study congenital malformations were studied prospectively from September 1989 to December 1992 covering 12797 consecutive deliveries. The overall incidence of malformations was 3.7% and it was 3.2% among live births and 15.7% among still births. It was significantly higher among male babies ($p < 0.001$), stillbirths ($p < 0.001$), low birth weights ($p < 0.001$) and preterm babies ($p < 0.001$) and more common ($p < 0.001$) in babies born to consanguineus parents. Musculo-skeletal malformations were the commonest (9.69 per 1000) followed by cutaneous (6.33 per 1000), genitourinary (5.47 per 1000), gastrointestinal (5.47 per 1000), central nervous system (3.99 per 1000) and cardiac anomalies (2.03 per 1000) (Bhat and Babu 1998).

In 10100 consecutive births including stillbirths at Shimla, 180 had one or the other congenital malformations (overall incidence 1.78%(Grover 2000). Among the 311 stillborn babies 47 (15.1%) had congenital malformations. Incidence was the highest in mothers over 35 years of age and gravida four and more.

Verma (2001) noted that almost half a million babies were born with malformations and 21000 with Down Syndrome. In a multi-centric study on the cause of referral for genetic counseling the top four disorders were repeated abortions (12.4%), identifiable syndromes (12.1%), chromosomal disorders (11.3%) and mental retardation (11%). In a more recent study in a private hospital the top reasons for referral were reproductive genetics (38.9%) comprising prenatal diagnosis, recurrent abortions, infertility and torch infections mental retardation +/- multiple congenital anomalies (16.1%); Down Syndrome (9.1%), thalassemia or haemophilia (8.8%), and muscle dystrophy, spinal muscular atrophy (8.4%). Recent study carried out in three centers (Mumbai, Delhi and Baroda) on 94610 newborns by using a uniform proforma showed a malformation frequency of 2.03%. The commonest malformations are neural tube defects and musculo-skeletal disorders. The frequency of Down Syndrome among 94610 births was 0.87 per 1000, or 1 per 1150. Screening of 112269 newborns for aminoacid disorder showed four disorders to be the commonest - tyrosinemia, maple syrup urine disease and phenylketonuria. Screening of cases of mental retardation for aminoacid disorder revealed four to be the commonest - hyperglycinemia, homocystinuria, alkaptonuria, and maple syrup urine disease. Metabolic studies of cases of mental retardation in AIIMS, Delhi and KEM Hospital, Mumbai, demonstrated that common disorders were those of mucopolysaccharoidoses, lysosomes, Wilson disease, glycogen storage disease and galactosemia. It is estimated that beta-thalassemia has a frequency at birth of 1:2700, which means that about 9,000 cases of thalassemia major are born every year. Almost 5200 infants with sickle cell disease are born every year. Disorders, which deserve to be screened in the newborn period, are hypothyroidism and G-6-PD deficiency, while screening for amino acid and other metabolic disorders could presently be restricted to symptomatic infants (Table 2).

Table 2: Common single gene disorders. Arranged in the order of frequency.

Autosomal recessive	
Beta Thalassaemia	113
Primary microcephaly	48
Matachromatic leukodystrophy	15
Congenital adrenal hyperplasia	14
Oculo-cutanoeus albinism	13
Wilson disease	12
Aminoacid disorders	11
Werdnig Hoffman disease	10
Autosomal dominant	
Achondroplasia	16
Marfan syndrome	15
Crouzon disease	11
Apert syndrome	10
X-linked recessive	
G-6-PD deficiency	28
Duchenne musc. Dys.	24
Hemophilia A & B	20
Testicular fem. syndr.	18
Fragile X-syndrome	12

In children between 0-6 years of age from six villages of Ambala District prevalence of congenital malformations was 22/1000. Twenty children had major malformations and six had multiple anomalies. Cardiovascular malformations were the commonest (37%) followed by musculoskeletal (30%), gastrointestinal (23%), central nervous system (13%) and genitourinary anomalies (6.6%). Maternal rubella infection or drug exposure during early pregnancy could be ascertained in only 3 cases. Traditional birth attendents (TBA) and Anganwadi workers (AWW) were helpful in identifying 95% of the cases with externally visible malformations in rural areas. Prospective surveys give better data (Kumar et al. 1994).

In a prospective study (Chaturvedi and Banerjee 1993) of 3000 consecutive deliveries (14 twin deliveries), the rate of congenital malformation was reported to be 27.20 per 1000 births (82 out of 3014). No significant difference was observed in the relative frequency of congenital malformation in urban/rural status, in different religion and caste, and in male/female babies. An increase in frequency was seen in advanced maternal age and in primi and fourth gravida mothers. A number of environmental factors studied, such as use of different tooth powders, type of drinking water, different cooking vessels, associated vitamin deficiencies did not seem to influence the prevalence of birth defects significantly. The factors which significantly increased the rate of congenital malformation were consanguinity in parents, heredofamilial history of malformations, presence of hydramnios, maternal febrile illness in first trimester, past history of abortion and history of progesterone intake during pregnancy.

In a later prospective study in a rural hospital in Maharashtra of a total of 3000 consecutive births over a 9-month period the frequency of congenital malformations was 21.1 per 1000 births. Stillbirths were associated with a higher incidence of malformations (14.5%) as compared to live births (1.8%). Gastro-intestinal tract and the genito-urinary tract (20.4% each) and the central nervous system (17.3%) were affected. Higher incidence of congenital malformations was associated with increasing maternal age (> 35 years), higher gravida mothers (> G4), parental consanguineous marriages, previous history of abortions, maternal hypertension, etc. (Ronya et al. 2002).

INDIVIDUAL CONGENITAL DEFECTS

When discussing individual congenital malformations the data available is mainly on skeletal gastrointestinal and neurological defects affecting newborn.

Skeletal Defects

The conditions like Aperts Syndrome, Crouzons Syndrome and achondroplasia are mostly autosomal dominant and reported as new mutants (Mukundan et al. 2000; Rajesh et al. 2004).

Split hand and legs, tibial and radial aplasia and other defects have been sporadically reported (Shenoy and Kamath 2004; Varma and Yadu 2003; Thami and Kaur 2002).

Jain (1994) in 200 patients with congenital limb deficiency at the Artificial Limb Centre, Pune from January 1984 to April 1990 as representative of the congenital limb deficient population of the country reported transverse phalangeal total/ partial deficiency and transverse forearm partial deficiency (below elbow) in upper limbs as the most common, whereas transverse metatarsal total/partial deficiency and transverse leg partial deficiency (below knee) were commonest in lower limbs. Transverse forearm partial deficiency was more common in female, while transverse leg partial deficiency was more common in male

children. No definitive cause for the deformities could be isolated; however, many parents believed that possible exposure to the eclipse during pregnancy was the cause of the deficiency. The eldest child was most affected. Some skeletal defects could also by caused by intrauterine bands.

Jain and Lakhtaria (2000) found congenital amputation in 36 cases among the physically handicapped individuals in a district level hospital during the period from 1 January 1999 to 31 December 2000. Out of 3550 individuals, 612(17.2%) had congenital orthopaedic anomalies, 36cases had congenital amputation (amputation through digits and toes were not included). Both unilateral and bilateral congenital amputations were much more common in the upper extremity as compared to lower extremity. Not a single case of simultaneous upper and lower extremity involvement was seen. The most common transverse deficiency in the upper limb was through the forearm, and in the lower limb it was through the foot. Congenital amputation was common in males with a gender ratio of 3.5:1. Left limb involvement was twice as much as right limb involvement, and it was common in both sexes. Bilateral limb involvement was seen only in males.

Molecular studies of polydactyly syndromes have not so far yielded specific results. Mutations in the human GLI3 gene have been identified in Greig cepalopolysyndactyly, Pallister-Hall syndrome (PHS), and postaxial polydactyly type-A (PAP-A). The involvement of GLI3 in additional phenotypes of digital abnormalities in one family (UR003) with preaxial polydactyly type-IV (PPD-IV), three families (UR014, UR015, and UR016) with dominant PAP-A/B (with PPD-A and -B in the same family), and one family with PHS. Linkage analysis showed no recombination with GLI3-linked polymorphisms. Family UR003 had a 1-nt frameshift insertion, resulting in a truncated protein of 1,245 amino acids. A frameshift mutation due to a 1-nt deletion was found in family UR014, resulting in a truncated protein of 1,280 amino acids. Family UR015 had a nonsense mutation, R643X, and family UR016 had a missense mutation, G727R, in a highly conserved amino acid of domain 3. The patient with PHS had a nonsense mutation, E1147X. These results add two phenotypes to the phenotypic spectrum caused by GLI3 mutations: the combined PAP-A/B and PPD-IV. These mutations do not support the suggested association between the mutations in GLI3 and the resulting phenotypes.

Neurological Defects

Neural tube defects were the first to be reported due to early diagnosis and high mortality and recurrence in future pregnancies is also common. Talukder (1985) in study of 33950 births over 5 years in Calcutta reported incidence of 1.28/1000 and 1.15/1000 births. The incidence was lower 0.015/1000 and 0,84/1000 in two rural hospitals during the same period out of 32339 births In another study over a 10 yr period (1982-91), in four major maternity hospitals of Lucknow, overall incidence was 3.9/1000. It was significantly higher in the teaching hospital compared to non-teaching hospitals. But there was no significant difference in the incidence of NTD between the Government and Private hospitals. During the decade (1982-91) under study there was no decline in NTD births. (Sharma et al. 1994).

Sikhs of British Columbia were found to have an increased incidence of NTD (2.85 / 1000) compared to others (1.26 /1000) (Baird 1983).

With improvement in diagnostic methods and supply of folic acid and vitamin B to mothers the incidence has now decreased (Karmarker1997; Bajpai 1997; Verma 1997).

The diagnosis of other inherited neurological diseases like muscular dystrophies, fragile X syndrome also are available by molecular analysis of the amniotic fluid. Unusual conditions have also been reported like congenital hypomyelinating neuropathies (Chandra et al. 2003) and Acrocallosal syndrome (Gulati et al. 2003).

In a detailed study the condition of spinal dysraphism in North India 155 patients were studied prospectively (143) or retrospectively (12). The male to female ratio was 1.5:1. Mean age at presentation was 5.7 years. Out of 155 cases of spinal dysraphism, 119 had open spina bifida [meningomyelocele (MMC) in 113 (72%), meningocele in 3 (2%) and myelocystocele in 3 (2%)] and 36 had occult spina bifida [split cord malformation (SCM) without overt MMC sac (pure SCM) in 29 (19%) and midline dermal sinus in 7 (4.5%)]. Lipomeningomyelocele constituted 73 of the 113 cases of MMC (65%). Twenty cases of MMC (18%) had associated SCM (complex spina bifida) (Kumar and Singh 2003).

Disorders of the Eye

Axenfeld-Rieger anomaly (ARA) is a form of anterior segment dysgenesis of the eye, mainly

caused by mutations in the FOXC1 gene mutation in the wing region of FOXC1 were studied in an autosomal dominant family (Panicker et al. 2002). Two new autosomal dominant families and seven sporadic cases of ARA from different ethnic backgrounds were screened for mutations by direct sequencing of the coding region of the FOXC1 gene. Another autosomal dominant ARA family that was previously reported was also included for comparative analysis of clinical genetic parameters. The segregation of the mutations in the autosomal dominant families was analyzed by haplotype and restriction analysis. Genotype-phenotype correlation were also undertaken to study the role of FOXC1 in phenotypic manifestation in the patient cohort. Three of the nine ARA cases harbored mutations in FOXC1, of which two novel nonsense mutations Q2X and Q123X, resulted in haploinsufficiency of the gene product. The missense mutation (M161K) that was previously reported in an autosomal dominant family was also found in another family. Haplotype analysis of these two families suggested multiple founders in the same ethnic group. The mutations resulted in variable expressions of phenotype among the patients as assessed from their prognosis based on visual outcomes. The different visual outcome seen in the patients suggest a variable expression of FOXC1 and also provide some insight for understanding the gene functions in this population. (Komatireddy et al. 2003; Panicker et al. 2002). Non syndromic ocular defects have also been reported. (Hornby et al. 2003).

In children with ocular coloboma without systemic features in Andhra Pradesh, 56 probands, 25 females (44.6%) and 31 males (57.4%) with a colobomatous malformation were identified. In 12 cases (21.4%) another family member was affected. The risk to siblings was 3.8%. The parents were consanguineous in 25 cases (44.6%). 21.4% of cases of isolated ocular coloboma in this highly consanguineous population of south India were familial, with both autosomal dominant and autosomal recessive mechanisms likely in different families.

Hornby et al. (2001) in an earlier study in children with clinical anophthalmos and remnant microphthalmos in either eye in Andhra Pradesh observed that 15 had anophthalmos and 9 had remnant microphthalmos in one or both eyes. Twelve children had associated systemic findings, of which 6 were major and 6 minor abnormalities. Consanguinity was present in 19 children, 12 of whom had consanguineous parents. Five children had a positive family history. Two mothers had a history of night blindness, and one had a history of pesticide exposure during pregnancy. High rates of consanguinity suggest a genetic recessive aetiology.

Gastroentrointestinal Malformations

Sporadic high incidence has been reported among non-resident Indian groups like Gujaratis of Leicestershire of Meckel's diverticulum (Young et al. 1985).

During a 25-year period (1972-1996), 585 patients with esophageal atresia with or without tracheoesophageal fistula were treated at the Department of Pediatric Surgery, SMS Medical College, Jaipur, India. Increasing awareness of the anomaly has led to early detection and referral with fewer pulmonary complications (Sharma et al. 2000).

In 1999, eleven babies were born with gastrointestinal malformations, one a still birth, 9 associated malformations of other systems, two had trisomy 21 (Dadhwal et al. 2001).

Mittal et al (2004) in 140 patients (80 males and 60 females) reported high and low type of anorectal malformations(ARM) in 52.14% and 47.86%. Associated anomalies were more common with high type of ARM (78.08%) than in patients with low type of ARM (37.31%). 58.57% patients had associated anomalies which included those of urinary system (37.14%), vertebral system (34.28%), skeletal system other than vertebral (15.17%), genital system (14.29%), cardiovascular system (12.14%), gastrointestinal tract (10.7%) and spinal cord (10%). 37.43% patients had 3 or more than 3 components of VACTERL association. Two patients had all six components of VACTERL. Most common association was vertebral, anal and renal anomalies seen in 16 patients (Deka et al. 1999).

Molecular Studies

Cleft lip and palate normally considered multifactorial are also found in families suggesting Mendelian inheritance. With improved methodology of gene scan these studies are being carried out in increasing number (Field et al. 2004).

Patients with primary microcephaly, an

autosomal recessive trait, have mild to severe mental retardation without any other neurological deficits. It is a genetically heterogeneous disorder with six known loci: MCPH1 to MCPH6. Only the genes for MCPH1 and MCPH5 have been identified so far. In nine consanguineous families with primary microcephaly from India, to establish linkage to known MCPH loci, microsatellite markers were selected from the candidate regions of each of the six known MCPH loci and used to genotype the families. The results were suggestive of linkage of three families to the MCPH5 locus and one family to the MCPH2 locus. The remaining five families were not linked to any of the known loci. DNA-sequence analysis identified one known (Arg117X) and two novel (Trp1326X and Gln3060X) mutations in the three MCPH5-linked families in a homozygous state. Three novel normal population variants (i.e., c.7605G > A, c.4449G > A, and c.5961 A > G) were also detected in the ASPM gene (Kumar et al. 2004).

Some data are available from other countries working on Indians (Field et al. 2004). In order to identify genes or regions involved in nonsyndromic cleft lip with or without cleft palate (CL/P) in families from India, we analyzed 38 multiplex families (DNA from 272 individuals, 82 affected with CL/P, 190 unaffected) for 285 genome-wide markers (average spacing 12.6 cM), including markers in six candidate loci or regions on chromosomes 2, 4, 6, 14, 17, and 19 that have been implicated in other studies of CL/P. LOD scores (two-point and multipoint), and model-free association (TDT) and linkage (NPL) statistics, were calculated between each of the markers and a hypothetical CL/P susceptibility locus. The most statistically significant two-point linkage results were with markers on chromosome 7 (LOD = 1.89 with D7S435, 7p15, 47 cM), chromosome 5 (LOD = 1.76 with D5S407, 5q11, 65 cM), chromosome 15 (LOD = 1.55 with D15S652, 15q26, 90 cM), and chromosome 20 (LOD = 1.46 with STS155130, 20q13, 54 cM). The most significant multipoint linkage result was on chromosome 5q, again near D5S407 (HLOD = 1.40). Regions on chromosomes 1p, 1q, 7q, 12q, 16q, 18q, and Xp also had a LOD or HLOD > or = 1.0. Of seven candidate markers and regions with previous positive reports in the literature (TGFA, MSX1, D4S175, F13A1, TGFB3, D17S250, and APOC2), none had a significant linkage result, but one (the APOC2 region) had a significant association result and three others (TGFA, MSX1, F13A1) had suggestive results. The results are consistent with the involvement of multiple loci in CL/P expression in this West Bengal population, which concurs with results found in other CL/P study populations.

Novel Mutations Causing Eye Defects

Mutations in the transcription factor gene PAX6 have been shown to be the cause of the aniridia phenotype of 28 members of 6 clinically diagnosed aniridia families and 60 normal healthy controls. The coding exons of the human PAX6 gene were amplified by PCR and allele specific variations were detected by single strand conformation polymorphism (SSCP) followed by automated sequencing. The sequencing results revealed novel PAX6 mutations in three patients with sporadic aniridia: c.715ins5, [c.1201delA; c.1239A>G] and c.901delA. Two previously reported nonsense mutations were also found: c.482C>A, c.830G>A. A neutral polymorphism was detected (IVS9-12C>T) at the boundary of intron 9 and exon 10. The two nonsense mutations found in the coding region of human PAX6 gene are reported for the first time in the south Indian population. The genetic analysis confirms that haploinsuffiency of the PAX6 gene causes the classic aniridia phenotype due to stop codons and correlates with expression of aniridia (Neethirajan et al. 2003, 2004).

Congenital Heart Disease

Of 10964 consecutive live births weighing more than 500 g and more than 28 weeks of gestation 43 had CHD (3.9/1000 live births). Incidence of CHD was higher in preterms as compared to full term live births (22.69 vs 2.36/ 1000 live births). 28% had other associated somatic anomalies, Down syndrome being the commonest (9.3%). Patent ductus arteriosus (41.9%) and ventricular septal defects (VSD) (34.9%), were the commonest lesions with an incidence of 1.6 and 1.4/1000 live births (Ashok et al. 2003).

The frequency of other-cardiac, extracardiac and chromosomal-anomalies in fetuses with A VSD diagnosed in a prenatal diagnosis center was analysed from the database during the 54-month period (November 1997 to May 2002). 103 fetuses were diagnosed with A VSD. Among them

other-cardiac and extra cardiac anomalies - were present in 56 and 75 cases respectively. Of the 22 fetuses that had undergone karyotyping, no metaphase was seen in one case. In the remaining 21, 15 (71.4%) were normal, 3 (14.2%) trisomy 18, 2 (9.5%) trisomy 13 and one trisomy 21 (4.8%).

Causes of Congenital Malformation

Conditions like prematurity, infections like rubella are well known causes of congenital malformations specially sporadic ones. They need to be excluded before assigning an inherited cause. Higher incidence of congenital defects has been reported due to consanguinity (Appaji Rao 1991; Jain et al. 1993; Badaruddozah et al.1998; Hornby et al. 2001). In another report mean coefficient of inbreeding was 0.056. Consanguinity had no significant effect on average pregnancy rate and reproductive wastage. The frequency of consanguinity was significantly higher especially with autosomal recessive disorders ($p < 0.001$), congenital heart diseases ($p < 0.001$), multiple malformations ($p < 0.001$), neurological malformations ($p < 0.005$), chromosomal disorders ($p < 0.01$), genitourinary disorders ($p < 0.02$) and mental retardation-developmental disorders ($p < 0.02$) (Jain et al. 1993).

Study of Environmental Effects on Genetic Load

Mulvihill and Czeizel (1983) suggested the surveillance of birth defects which could be easily recognized as "sentinel phenotypes" as an index of genetic load. The underlying theory is the assumption that systematic observation of a few well marked phenotypes including some autosomal dominant conditions at birth could well be undertaken by trained assistants to establish baseline data which could be utilized for determining environmental genotoxicity. One such suerveillance data over a seven year period was carried out in South America by Castilla and Lopez Camillo (1990) and 13 Mendelian dominant inherited phenotypes are given in Table 3. Any non inherited mutant could be taken as a new mutant in a family or population .

Other studies include congenital malformations seen in babies of mothers living around hazardous landfill sites in Europe (EUROHAZON study, Dolk et al. 1998). Here mothers living within 3.5km of landfill sites had significantly higher incidence of babies with NTD (odds on ration 1.86:1.24-2.79) malformations of cardiac septa (1.49:1.09,2.04), malformations of great arteries and veins (1.91:1.02-3.20). Other congenital defects also showed a raised risk and this data from highly developed countries with excellent healthcare system is disquieting. It is well known that congenital heart disease and NTD are common in India.

Other environmental hazards studied have been the effect of background radiation first reported in increase of Down syndrome in

Table 3: Single gene disorders causing congenital malformations Sentinel phenotypes

Diagnosis	*MIM*[a]	*Smith*[b] *pg*	*ECLAMC*[c] *code*	*Expected*[d] *Rate*	*Observed*		
					No	*No*	*Rate*
Achondroplasia	10080	188	98506	1.08	94	21	0.24
Thanatophoric	18760	180	98527	0.04	3	19	0.22
Osteogenesis imperfecta-I	16620	286	98532*	0.22	19	1	0.01
Apert	10120	242	98505	0.07	6	4	0.05
Crouzon	12350	234	98521	0.11	10	11	0.13
Treacher-Collins	15450	134	98520	0.04	3	10	0.11
EEC	12990	162	98559	0.04	3	3	0.03
Holt-Oram	14290	172	98507*	0.07	6	4	0.05
Polysyndactyly IV	17470	-	98035	0.22	19	0	0
Lobster claw	18360	-	755/7*	0.15	13	13	0.15
OFD-I	31120	144	98523	0.02	2	0	0
Aniridia	10620	-	7445-	0.11	10	1	0.01
Incontinentia pigmenti	30830	298	75725*	0.11	10	1	0.01
All 13 diagnoses	-	-	-	2.28	198	88	1.02

[a] MIM : in Mendelian Inheritance in Man number.
[b] Smith.pg : Page in Recognizable Patterns of Human Malformation
[c] ECLAMC code : If* : code its not specific, and original forms have to be examined for proper diagnosis
[d] Expected rate : Rates per 10000 births.
After Mulvihill and Czeizel 1983

mothers exposed to radiation from monazite sand in Kerala (Jaikishan et al. 1999).

Subsequently studies in the same area noted natural radiation dose rates range from 1.0 to over 35.0 mGy per year. From August 1995 to December 1998, a total of 36,805 newborns were screened, including 212 (0.58%) stillbirths. There were 36,263 singletons, 536 (1.45%) twins, and 6 born as triplets. The overall incidence of malformations was 1.46% and was dependent on maternal age. The stillborns exhibited a very high malformation rate of 20.75% compared to 1.35% among the live births. Likewise, twins also had a higher malformation rate (2.99%) compared to singletons (1.44%). About 3.5% of the newborns originated from consanguineous marriages. Consanguinity also led to a relatively higher rate of malformations (1.97%) as well as of stillbirths (1.18%). About 92% of the deliveries took place by the maternal age of 29 years and only 1.2% among women above 34 years old. The stratification of newborns with malformations, stillbirths or twinning showed no correlation with the natural radiation levels in the different areas.

In a later genetic epidemiological and fertility survey among 70,000 inhabitants in a high-background radiation region (HBRR) and normal radiation region (NRR) in Kerala, 985 persons were found to have heritable anomalies. Suggested etiologies for the anomalies were chromosomal and Mendelian, 15 percent; multifactorial, 60 percent; and congenital, 25 percent. There was a statistically significant increase of Down syndrome, autosomal dominant anomalies, and multifactorial diseases and an insignificant increase of autosomal recessive and X-linked recessive anomalies in the HBRR. The total fertility rate was 3.85 per couple; 9 percent of live-born children were reported dead. The rate of untoward pregnancy outcome—death of the offspring or presence of an anomaly in a living child—was 6.4 percent among the unrelated couples in the NRR, with one spouse born outside the area of current residence (migrant) RR (nonmigrant) showed 35% HBRR (nonmigrant), 9% NRR consan-guineous76%; and NBRR-consanguineous 157%. Ionizing radiation, consan-guinity, and nearness of birthplace of the spouse are risk factors for the death of offspring and for anomalies. The higher risk among the nonmigrant couples may be due to geographic inbreeding. The findings are suggestive of an autosomal recessive etiology for the majority of the multi-factorial anomalies (Padmanabhan et al. 2004).

An International WHO workshop (1991) on the impact of the environment on reproductive health discussed the nature of environmental factors affecting reproductive health, Environmental factors were blamed for declining sperm quantity and quality, and natural and man-made disasters for reproductive health including chemical pollutants, research is needed using more recent methodologies and surveillance data. Recommendations were made to promote international research collaboration with an emphasis on consistency of methodological approaches for assessing developmental and reproductive toxicity, on development of improved surveillance systems and databases, and strengthening international disaster alert and evaluation systems; also to promote research capabilities for multidisciplinary studies, for interactive studies of the environment and cellular processes, and for expansion of training and education; and take action on priority problems of exposure to chemical, physical, and biological agents, pesticides among specific populations. Vitamin A and toxic chemicals are cited as agents probably having serious effects on malformations. postnatal death, functional learning deficits, and premature aging.

Fetal factors associated with low weight births include fetal infection and congenital abnormalities (Tibrewala et al. 1980; Deka et al. 1989). The cause of low weight births varies in different populations and the first step in any preventive program is to determine the major causes of low weight births in the target population. Preventive measures include improving socioeconomic and public health conditions; upgrading maternal diets and maternal and prenatal health care; expanding health education programs; and preventing premature births (ICMR 1990; International workshop 1991). The necessity for increasing the detection of genetic diseases in populations based at the family welfare planning levels cannot be overemphasized. An extensive data is present on the incidence of genetic diseases in India and the large population with high birth rate has little or no access to detection of genetic causes of prematurity, stillbirth and congenital defects. For the small family norm to take off genetic counseling centers are required in large numbers.

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