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1

Preventive Genetics—Holistic Healthcare

Sharad Gogate

INTRODUCTION

All over the world, particularly in developed and developing countries standard of living and healthcare are improving. As a result nutritional deficiencies, infections and other preventable causes of morbidity and mortality have been controlled to great extent. Hence non-preventable causes like genetic disorders, congenital anomalies, lifestyle disorders like diabetes, cardiac diseases, cancers, etc. have assumed importance as significant cause of morbidity and mortality at all stages of life. With completion of the Human Genome project, whole genome studies and bioinformatics, our understanding of human genome and its role in human body has undergone sea change opening new vistas in medical sciences.

The ancient Indian medical system of ayurveda is the epitome of preventive aspect of healthcare. The definition of health according to this system is given by the following verse from Sushruta (ancient Indian sage),

समदोषः समाग्निश्च समधातु मलःक्रिया।
प्रसन्नात्मेंद्रियमनः स्वस्थ इत्याभिधीयते।।

It means when all three Doshas (proximate principles), Agni (metabolic driving forces), all seven *dhatus* (body tissues) and *malakriya* (body waste disposal systems) are evenly balanced and when *atma* (soul), *indriyas* (body organs) and the *manas* (mind) are happy and contended then one is said to be healthy. This is the most positive and encompassing definition of health!!

It is true that our genetic blue print is beyond our control and comprehensively regulates the development, functioning of human body in health and disease at all stages of life. Contrary to belief, our genetic destiny is not totally preordained!

By implementing multispecialty, holistic, preventive approach at all stages of life we can make a lot of difference in incidence of genetic disorders, their severity, the chances of survival, quality of life of our patients and risk of recurrence in their families. Community health planners are becoming well aware about these facts and a new specialty of preventive genetics and genome based individualized medicine is emerging rapidly to tackle these problems.

Importance of genetic disorders in clinical practice is seen in Table 1.1.

Burden of Genetic Disorders and Congenital Malformations

Various measures reflect the population burden of genetic disorders and congenital anomalies. These include the incidence or prevalence of these disorders, associated

Table 1.1: Importance of genetic disorders in clinical practice

- Increased importance of genetic factors in clinical medicine is very apparent; almost 20–30% disorders seen in day to day practice have some genetic components as a causative / aggravating pathology.
- Definite risk of recurrence in relatives.
- Varied and confusing presentation and inheritance patterns of genetic disorders makes the diagnosis and management more challenging.
- It is more advantageous to prevent occurrence of a genetic disorder, diagnose and treat it at pre-clinical stage than to wait for the birth of a baby with serious genetic disorder.

morbidity and mortality, life expectancy and the economic burden on the family and society. Oocytes and sperms show aneuploidies in 18–19% and 3–5% respectively, as a result 1 in 13 conceptions show chromosomal anomalies. 50% of first trimester abortions are due to chromosomal disorders. Still births and neonatal deaths show chromosomal defects in 5.6 to 11.5% cases.[1]

The exact incidence of various categories of genetic disorders is not known, Table 1.2 shows the incidence of these disorders from a very large study by (Baird et al., 1988).[2]

The incidence of various genetic disorders in India has been found to be 2.3% in a study[3].

Table 1.2: The frequency of genetic disorders in 1,169,873 births

Category	*Rate per million live births*	*% of total births*
Autosomal-recessive	1395.4	0.14
Autosomal-dominant	1665.3	0.17
X-linked	532.4	0.05
Chromosomal	1845.4	0.18
Multi-factorial	46582.6	4.64
Genetic unknown	1164.2	0.12
Total	53175.3	5.32
All congenital anomalies	52808.2	5.28

Source: Baird et al., 1988

Chapter 2: Burden of genetic disorders in India by Dr IC Verma in this book gives more detailed data and analysis.

Preventive Genetics at Macro-level

As a result of this big impact of genetic disorders on community, attention of public health workers has been focused on this problem. As the genetic disorders affect all strata of society irrespective of the social or economic status, it is essential for healthcare policy planners to have a macro-level plan for devising and implementation of preventive genetic program. Only then the full benefit of this program will reach all strata of society in all geographic locations.

Important components of such a program should include are as follows.

Baseline Epidemiological Studies in the Target Population

Incidence of various congenital and genetic disorders varies in different communities, castes and it is essential to study the epidemiology of these disorders in a particular region/community so as to decide the priorities in the program. This will help in identifying specific details of particular disorder like incidence, mutation details, inheritance patterns and clinical presentation and help in finding out information about any high risk sub-population. It is essential to know the natural history of the disorder, impact on morbidity and mortality, epidemiological and cultural effects. Only after this is achieved then appropriate program for efficient screening, diagnosis and management of the target disorders can be finalised.

Increase Awareness about Genetic Disorders

Unfortunately there is very little awareness about the importance of genetic, congenital disorders in healthcare at all levels. There are lots of myths, misconceptions about this in general population in most of the developing countries. High level of awareness in the entire target population about the genetic

program and the target disorder is essential for its success. We require sensitization of the policy makers, administrators, as only then preventive genetics will receive the required importance, funds and support. Over the years there is some positive change in the healthcare policy makers about this. Awareness in the medical, paramedical and other health workers is also far from adequate. This requires due changes in the medical education as well, so as to cover the latest advances in the field of clinical genetics and fetal medicine. *According to latest MCI guidelines, it is now mandatory for faculties of Obstetrics & Gynaecology and Neonatology to have modules on Birth Defects, clinical genetics for postgraduate curriculum.*

Active, co-ordinated participation of government agencies, private practitioners, professional bodies, NGOs, religious and social groups and student bodies will ensure that the program percolates to all regions and communities adequately. It is necessary to inculcate better health seeking behavior in the general population about genetic disorders. Campaign for increased awareness in the populace about the target disorder and the program should also receive top priority. The need for neonatal screening of IEMs has dawned in minds of policy makers with mandatory screening of important metabolic errors being increasingly introduced.

Establish/Strengthen Efficient Two-way Referral System

It is essential to cover the entire population and integrate preventive genetics in healthcare system in the national healthcare programs like Maternal and Child Health. The existing healthcare delivery systems in public as well as private sectors should be fully utilised so as to reach the entire population of the country. This will ensure coverage of the entire target population, better utilization of healthcare facilities at all levels and to provide efficient, patient friendly, easily available quality healthcare at all levels.

Organise Genetic Centers of Excellence

As preventive genetic program requires specialised facilities for counseling, sophisticated laboratories and multispecialty teams for clinical management of these complex disorders, it is essential to develop such well conducted centers of excellence at district levels at least. Such centers should be housed in hospitals affiliated to medical colleges, district level multispecialty hospitals as well as private sector multispecialty hospitals to make utilisation of academic facilities and trained medical and paramedical personnel. Proper conceptualisation, organisation of such centers and multispeciality approach are essential. Components of such a center should include:

1. Clinical facilities (indoor and outdoor) for management of high risk cases,
2. Counselling, social support,
3. Laboratory facilities viz. cytogenetics, molecular genetics, metabolic studies, assisted reproduction and oncogenetics.

Phased manner of development is needed depending upon availability of resources, needs and priorities of the society so as to optimise the utilization of resources. These centers should be used as nodal facilities for starting academic programs to start courses pertaining to the field so as to train personnel to run such facilities, carry out epidemiological studies and research. Proper data collection and compilation at national level, along with periodic reviews of the center's activities with work audits should be done.

Devise and Conduct Appropriate Genetic Screening Programs

Genetic screening tests are very useful as we can cover very large population quickly and cost-effectively so as to identify high risk sub-population from the low risk general population. They help reducing need of costly, potentially harmful diagnostic tests; ensure better utilisation of costly, labour intensive techniques, save costs while helping the down-staging of the target disease. At the same time there are certain disadvantages like

additional costs and efforts to the patients, problem of false positivity, low sensitivity and specificity and ethical, social issues.

Requirements of a good genetic screening program are given in Table 1.3.

Table 1.3: Requirement of a good genetic screening program

- The target disorder should be well defined, have significant incidence and severity to affect the population.
- Screening test should be simple, safe (non-invasive), affordable, easily available and with acceptable false positivity and sensitivity.
- Availability of accurate diagnostic test to confirm the diagnosis in screen positive individuals.
- Follow-up management options should be there for the high risk population identified by the screening test.

Developing countries like India face some major problems in setting-up of genetic screening programs like very large population, lack of awareness, late antenatal registration. Genetic screening is not mandatory even in high risk pregnancies. Cost factor is very important as 40% deliveries are conducted in public sector, where totally free services are provided. The meagre funds are not adequate to cover even higher priorities like malnutrition, prematurity, infectious diseases hence priority for such screening programs is quite low. In recent development a *specific initiative has been launched by the Central Government Maternal Child Health Ministry "Rashtriya Bala Swasthya Karyakram (BSK) with focus on* ***4Ds****,* ***d****iagnosis of genetic* ***d****isorders, childhood* ***d****iseases, deficiency* ***d****isorders*! On the other hand 60% deliveries are conducted by private sector, which is self-funded by the patients as insurance coverage is still very low, due to lack of awareness and high costs the acceptance of screening tests is still quite low. All the same screening programs like NTD, Down's syndrome, Thalassemia/sickle cell disorders have become quite popular in urban and semiurban areas. Though neonatal metabolic screening program has not yet been that well accepted. The author's center was one of the first clinic to set-up second trimester screening for Down's syndrome in Mumbai city almost a decade back. Limitations of genetic screening programs are low positive predictive value, false positivity, confusing risk assessment, need for confirmatory tests and ethical issues which make the implementation of these screening programs quite challenging.

Networking of all Tertiary Level Institutions

It is highly essential to have close networking of all regional, national and global institutions/laboratories involved in preventive genetics program as knowledge and technology in field of clinical genetics is very rapidly expanding. Establishing of such centers of excellence requires very high financial investments, costly equipment and highly skilled personnel. As there are literally thousands of tests needed to diagnose the large number of genetic disorders, all the centers can not perform all the tests as duplication is quite wasteful and un-necessary. It may be advantageous to have genetic centers of excellence for specific disorders which can be regional, state and global reference facilties. Hence it is vital to have close networking of all centers at regional and national level so as to allow free sharing of specialised facilities, training programs, clinical material, information and research data. This will result in proper utilisation of scarce resources and provide better coverage of entire population.

Preventive Genetics at Micro-level
(Individual Patient's Level)

To be really effective in this aspect we have to improve the health seeking behavior of entire family, so as to report to the clinician for timely counseling and investigations for possible genetic disorder. It is also necessary for every family to record details of ethnic back ground, medical, genetic disorders and any unexplained death or deformity and report the same to the clinicians or counsellors. It is also necessary for the clinicians to have

high index of suspicion so as to pick-up more subtle symptoms and signs suggestive of possible genetic causes. Preventive genetic evaluation should begin right from birth till the old age!

Neonatal Period

Along with usual neonatal evaluation for well being of the newborn, we must look for subtle signs and symptoms of chromosomal, monogenic and metabolic disorders. This should follow necessary investigations and management. It is also essential to screen all newborns for Inborn Errors of Metabolism by day three/four of life. It is possible to screen for a large number of such disorders fairly quickly and accurately, which will help in the identification of children at risk so that medical interventions like pharmacotherapy, specific diets, etc. can be instituted so as to avoid deleterious effects on the physical and mental development of the child and preserve quality of life whenever possible. As incidence of many of these disorders is quite low and varies in different ethnic, geographical sub-groups it is necessary to identify the target disorders by epidemiological studies before finalising such screening programs. (*refer to* Chapter 8).

Adolescent Period

This period is vital as it involves individuals who are more receptive to new ideas and suggestions, who will be the future parents. Inclusion of genetic evaluation and screening along with sex education, nutritional advice and contraception will be helpful in imparting awareness about genetic factors in healthcare, which will help them in seeking timely advice from their clinicians at the appropriate time. Secondary schools, colleges and youth organisations should be encouraged to actively participate in this campaign.

Premarital Stage

Detailed history, thorough examination, follow-up testing done at this stage will certainly go a long way in preventing quite a few genetic disorders. Important areas to be covered are given in Table 1.4.

Table 1.4: Premarital evaluation

- Family/ethnic history of genetic disorder,
- Chromosomal abnormalities in either partners,
- Blood group incompatibility like Rh, hemoglobinopathy
- Familial cancers, coronary heart disease
- Reproductive tract anomalies in either partners,
- Occupational hazards

History of genetic disorders like thalassemia, haemophilia, muscular dystrophy, etc. will immediately prompt the clinician to advice appropriate screening tests to both partners so as to advice them about risk of recurrence, specific tests for prenatal diagnosis and management.

Although most of the conceptions with chromosomal defects are lost during antenatal stage, 0.6–0.8% of live born show chromosomal defects. Of these 0.4% are severe defects diagnosable at birth while 0.3% can be more subtle and have effect on child bearing. It is essential to have appropriate cytogenetic tests to be done in such individuals and counsel them accordingly.[4]

Blood group testing is now universally done in antenatal period but it should be done routinely at premarital stage itself. As it will give timely information in discordant couples so that necessary preventive measures can be taken up.

Certain cancers are caused by specific defective genes like BRCA-1 gene which is responsible for breast cancers. Cancers of breast, ovaries, colon and prostate are known to occur in families with presence of such abnormal genes. Some of the genetic disorders are more prone to cancers like leukaemia in Down's syndrome babies, Fanconi anaemia while gonadal malignancies are more likely in undescended testes and residual gonads in Turner's syndrome (*refer to* Chapter 16 for further details).

Prior to Conception

This is the most vital stage at which proper evaluation and guidance can go a long way in preventing genetic disorders. Unfortunately, majority of conceptions are un-planned and thus a valuable opportunity of preconception evaluation is lost in such couples. Full documentation of medical, obstetric and genetic history, construction of family pedigree and complete medical check-up of both partners is essential. All tests for confirmation of underlying genetic/medical factors should be done at this stage only.

Consanguinity should be investigated and proper counseling offered about the increased risk of genetic diseases. The problem of consanguinity is quite common particularly in Muslims and certain ethnic communities in southern states in India.

Certain genetic disorders and concurrent pregnancy can have mutually deleterious effects. Increased risk of thrombophlebitis, embolic episodes is seen during pregnancy and childbirth in homocystinuria.[5] Ehler-Danlos syndrome and Marfan syndrome have higher risk of aortic/vascular rupture and uterine rupture during pregnancy and childbirth.[6] Sickle cell, epilepsy, SLE and myotonic muscular dystrophy and untreated maternal Phenylketonuria increase risk of pregnancy losses, birth defects considerably. Hence proper control of these prior to conception and close monitoring of maternal and fetal health all through the pregnancy is essential.

Many of the maternal medical disorders like diabetes mellitus, thyroid disorders, epileptic convulsions, psychotic disorders and autoimmune disorders pose a risk of genetic/birth defects due to specific medications, hence proper control of these with use of safer therapeutic options should be achieved prior to planning a pregnancy. It has been shown that strict metabolic control of diabetes prior to conception reduced the risk of congenital malformations in the foetus was 0.8% as compared to 7.55 when the metabolic control achieved after completion of 8th week.[7]

Environmental factors like illicit drugs, smoking, alcohol, exposure to excessive heat and occupational exposure to potential teratogens should be curtailed where ever possible.

Prophylactic immunization against rubella, hepatitis B, E and screening for potentially teratogenic maternal infections like TORCH group, HIV-AIDS and other sexually transmitted infections is equally important prior to conception.

Pre- and peri-conception supplementation of Folic acid, Vit B_{12}, zinc will go a long way in NTD, facial clefting and certain inborn errors of metabolism prophylaxis as well as to reduced risk of pregnancy losses from miscarriages. For maximum benefit the supplementation should be started a menstrual cycle before couple stops contraception and continues till 16–18 weeks of conception. Low dose aspirin prophylaxis is of some benefit in autoimmune disorders like SLE, APL syndrome, unexplained IUGR/stillbirths and higher risk for PIH. Low dose glucocotricoids have been also used for indications like SLE, APL syndrome, unexplained pregnancy wastages with variable results (for more details *refer to* Chapter 21)

Post-conception Stage

Pre-implantation stage evaluation and diagnosis has assumed tremendous importance as more and more women are subjected to assisted reproductive technologies like IVF, ICSI, ZIFT, gamete/embryo donation etc. Many of them or their spouses have high risk factors like advanced maternal age, medical/surgical/genetic co-morbidities. PGS (pre-implantation genetic screening), PGD should be available for them as it improves the success rate of these techniques and ensures birth of a healthy child (*refer to* Chapter 14).

Post-conception stage is the time when majority of women present them selves to the obstetrician. Early enrollment, preferably as soon as pregnancy is diagnosed, is essential

as it gives the clinician adequate time to do various screening tests and offer appropriate diagnostics tests and management options.

I. First–Third Months

Every woman should try and report to the gynaecologist as soon as she misses the menses, confirm pregnancy by urinary/blood beta hCG test. Peri-conceptional folic acid, multi-vitamin supplementation, if not already started, should be given to each pregnant woman. Avoiding very hot baths (hot tub bath/saunas increase the risk of NTDs by several folds).[8] Light diet, small frequent feeds, avoidance of very spicy, unhygienic food is also helpful in ensuring proper health at this stage. As most of the medications, except calcium and multi-vitamins preparations have potential risk of teratogenesis one should avoid any un-necessary/self-medication, prompt consultation with family physician for any medical problem is essential. As women are more likely to be exposed exanthematous infections from the other children in their families they should avoid contact with persons suffering from exanthematous fevers (measles, mumps, etc.). If such exposure is inevitable, it should be reported to the medical personnel immediately.[9] It is also important to avoid exposure to toxic chemicals, and exposure to X-rays, stop alcohol, smoking, etc. as soon as pregnancy is diagnosed. Enquiry about the menstrual history and ruling out pregnancy must be done in all childbearing age women.

Screening for chromosomal and structural anomalies

Neural tube defects are one of the most common birth defects affecting the human foetus with significant morbidity and mortality, also trisomy 21 is the most common aneuploidy with significant impact on the fetal and neonatal wellbeing in form of moderate to severe mental retardation and several genetic deformities. Hence these are the two disorders targeted for developing screening and diagnostic programs in pregnant women.

The emphasis in antenatal screening has been to develop earlier, more reliable, cost effective and safer screening tests so as to cover maximum low risk population to identify the high risk sub-group. As a result diagnostic testing like fetal tissue sampling and confirmatory tests (which are potentially harmful, labour intensive and expensive) can be offered to a smaller sub-population screened positive with maximum pick-up of affected foetuses in a cost effective, efficient manner.

First trimester screening and diagnostic procedures

- 10–14 weeks ultrasonography
- Combined screening with maternal serum and sonographic markers
- Chorion villous sampling for genetic testing.

11–14 weeks NT, first anomaly scan: *With improvement in the resolution of USG equipment and intensive training of operators, 10–14 weeks scan by abdominal and vaginal route has become the first anomaly scan.* Apart from confirming the viability of the pregnancy, almost 70–80% of major structural anomalies can be picked up at this scan. This gives enough time to the clinician to perform any confirmatory tests, offer counseling and start antenatal therapy (where ever feasible) at an early stage. In cases with lethal anomalies an easier and more private option of first trimester can be offered.

Combined first trimester screening (FTS): Use of serum markers for screening for NTD and Down's syndrome started with the advent of triple test in early 1980s. Age as screening parameter is not enough as it can pick-up only one third of Down's babies. To bring forward the screening in the first trimester attempts were started and two molecules viz. free beta hCG and PAPP-A were used by nicolaides and his group in 1995. Together they had detection rate of ~60% at 5% false positive. With combination of maternal age, Nuchal Translucency and these two serum markers the detection rate jumped to almost

90%.[9] For achieving this spectacular success nuchal translucency measurement has to be accurately done on a high resolution scanner by a trained operator and software for risk assessment has to be used as well. With additional USG markers of nasal bone and Doppler flow studies of ductus venosus the detection rate can be further improved.

Recently a valuable addition in first trimester screening at has come 11–14th week, called "Advanced Double Marker" or "Penta Test". IN this there are 5 serum markers, PAPP-A, free beta hCG, placental growth factor (PGLF), AFP, dimeric Inhibin A. Addition of last three markers gives ability to screen for early onset PIH, NTD in addition to aneuploidy screening. Alone, this test has 86% DR at 5%false positivity for Tri 21. This is of significanc in situations where reliable NT measurements may not be available. With addition of NT, NB and DV markers, the DR reaches 98% at 5% FP for Tri 21, this almost reaches the sensitivity of NIPS!!!.[10]

The author set-up combined first trimester screening program in Mumbai city in 2002 analysis of first 300 tests showed a detection rate of 85% at 5% false positivity. Out of these, 22 cases were screen positive. After post-test counseling 18 underwent fetal tissue sampling and karyotyping, ten had normal karyotype while 3 showed aneuploidy (Tri21:2, Tri18:1).[11] To improve the detection rate sequential screening of 11–14 weeks combined testing followed by a quadruple test at 16–18 weeks has been tried with some improvements (DR 92%) (*refer to* chapter "Maternal Serum Screening").

It is now a well-accepted fact that first trimester combine screening (FTS) is a superior and early screening protocol as compared to second trimester screening tests. Early pick up of high risk cases at 11–14 weeks makes corrective measures like low dose aspirin, low molecular heparin therapy to be started when the vascular modulation of spiral arterioles has started beyond 12th week. Hence clinicians must encourage early reporting for first trimester screening. Second trimester screening should be considered only when patient has reported late, after 14 weeks or could not be performed.

Chorion villous sampling for confirmation in screen positive cases has emerged as the logical choice. The chorionic tissue is suitable for cytogenetic tests, DNA testing as well as metabolic studies. Though Amniocentesis is the most commonly performed prenatal diagnostic procedure CVS has the advantage of early and rapid diagnosis in first trimester thus reducing anxiety, keeping the pregnancy private and also to offer the safer first trimester termination option. To achieve the high safety and success of CVS it is essential to have properly trained operator with experience of at least 300–400 tests and should be well-versed in embryology and first trimester USG. Good resolution ultrasound machines also make the procedure quick and safe. Major clinical experiences in first trimester CVS are given in Table 1.5.

Table 1.5: Clinical experience of CVS

Sl. No.	*Author*	*Technique*	*No of cases*	*Gest wk*	*Success%*	*Preg loss%*
1.	Brambati, *et al.*	TC	1305	8–12	99.2	3.9
2.	Brun, *et al.*	TA	10741	8–38	99.9	1.7
3.	Jackson and Wapner	TA	11600	9–12	99.7	1.9
4.	Williams, *et al.*	TC	2949	9–12	99.7	1.9
5.	Brambati, *et al.*	TC/TA	10000	8–32	99.7	2.6
6.	Gogate, *et al.*	TC/TA	10050	9–28	98.8	2.1

(References 12–17)

Doubt about the safety of CVS was raised after the cluster of severe limb reduction defect (LRD) anomalies reported by Firth et al in 1991. WHO statement based on the complete follow-up of 76476 cases by the WHO-CVS registry did not show any increased risk of LRD following CVS performed by well trained operators and performed only after ninth completed week of pregnancy. The risk of bleeding, foetomaternal haemorrhage, infection and pregnancy loss is slightly more than amniocentesis but due to its advantage of early diagnosis, the test is becoming more popular[18] (*refer to* Chapter 10: Invasive procedures for diagnosing genetic disorder').

II. Fourth–Sixth Months

This is a very vital period when the organo-genesis is complete and growth phase has started. Comprehensive antenatal care with adequate and balanced diet, regular antenatal exercises and multi-vitamin, iron and calcium supplementation should be provided to ensure proper fetal development. Those women who enroll late should be evaluated and counseled for risk of any genetic/birth defects.

Second trimester screening for NTD and aneuploidies

Although maternal serum screening for NTD and Down's syndrome should be offered to all women at 16–18 weeks, we in developing country like India face some vexing problem in prenatal screening for NTD and Down's syndrome. Significant percentage of women deliver at home and do not receive comprehensive antenatal care, the time of enrollment is also late (mostly by 5–7th months) thus missing the chance for such screening. In Mumbai city 40% deliveries take place in public sector hospitals at almost free of charge, due to resource limitations such screening cannot be provided. Remaining 60% deliveries take place in private nursing homes and hospitals most of these are paid for by patients themselves, which adds to the cost. Low demand for these tests keeps the cost per test high which has a negative effect on the acceptance of the tests and coverage of entire population. The incidence of NTD in India varies from 1.7 to 12.2/1000 live births. There is no national data on incidence of Down's syndrome but it varies from 1:800–1000 live births.[19] With the annual deliveries of over 25 million the load of these anomalies is really quite huge. In spite of these difficulties attempts have been made to offer this screening program to antenatal patients and over last 5–7 years the acceptance has improved and more and more obstetricians are including second trimester (for last couple of years even the first trimester test) in their antenatal program. The performance of our center in Mumbai for second trimester test is given in Table 1.6.

Anomaly scan at 18–20 weeks is vital as it should be able to pick-up most of the structural anomalies, except some of the anomalies like renal, Musculoskeletal and growth related defects which appear later. Study of various ultrasonography markers associated with chromosomal anomalies like Nuchal thickness, duodenal atresia, choroid

Table 1.6: Second trimester screening for Down's syndrome and NTD

	99–00	*01–02*	*02–03*	*03–04*	*Total*
Screen +ve	46 (5.1%)	50 (5.7%)	71 (4.7%)	134(5.6%)	301
Screen –ve	826	936	1500	2240	5502
NTD +ve	17(1.8%)	24(2.3%)	36(2.2%)	59(2.45%)	136
Trisomy 18	11	7	6	15	39
Un-evaluable	14	9	12	17	52
Total	**914**	**1026**	**1625**	**2465**	**6030**

Source: Ref. 20

plexus cysts, etc. is equally vital to pick-up the high risk cases and offer prenatal diagnostic testing to them. In view of this, some workers are shifting the anomaly scan to 22 weeks (for more details *refer to* Chapters 9 and 11).

Fetal tissue sampling in second trimester: In spite of the screening tests, ultrasonography and other non-invasive tests certain high risk patients have to undergo fetal tissue sampling for confirmation and prognostication of the fetal disorders like chromosomal anomalies, single gene disorders, IEM, fetal infections, etc. To carry out these interventional tests reliably and safely we have to have genetic centers of excellence with well trained clinical and laboratory facilities, multispecialty fetal medicine program.

Amniocentesis is the most prevalent test and is considered as a gold standard. Genetic amniocentesis is conventionally done between 15–24 weeks of pregnancy. The amniotic fluid is tested for chromosomal evaluation by study of cultured/uncultured amniocytes (conventional karyotyping, FISH/QF-PCR), study of single gene disorders by DNA diagnostic tests and evaluating errors of metabolism by study of supernatant fluid or amniocytes. Fetal involvement in maternal infections can be verified by DNA testing, immunological work-up. The clinical safety and success of amniocentesis depends upon:

1. Experience of the operator performing the procedure,
2. Characteristics of the amniotic fluid (blood staining/discolored fluid)
3. Direct ultrasonography supervision and
4. Indication for the procedure.[21]

The clinical efficacy of this test performed in over 500 cases last year by our center was success rate of 99.6% and pregnancy loss rate of 0.4%. The efficacy of the laboratory testing was over 99% with failure to grow AF culture in less than 1%.[22]

Fetal blood sampling for prenatal diagnosis is most likely to be done for rapid fetal karyotyping, evaluation of fetal hematological disorders and fetal infections, DNA diagnosis. Therapeutic procedures like intrauterine transfusions, drug therapy and stem cell transfer are also performed through cordocentesis. Direct ultrasound guided cord blood sampling is the most commonly preferred technique. Safety of the procedure is acceptable with uncorrected pregnancy loss rate of 1.6% in a large collaborative data from 14 North American centers.[23] In a similar multi-centric study by the author, 1216 cordocentesis were evaluated from seven centers in India with success rate of 93.2% and uncorrected pregnancy loss of 2.3%.[24]

The extension of transabdominal CVS in second and third trimester is a very convenient, safe alternative to amniocentesis and fetal blood sampling particularly as an alternative to early amniocentesis, when patient presents late or an anomaly diagnosed beyond 26 weeks or when amniocentesis or cordocentesis is confounded by unfavorable conditions like severe oligohydramnios.[25,26] We have also been using late CVS in second and third trimesters as an alternative to fetal blood sampling and amniocentesis with gratifying results.

Antenatal learning: This is a new concept which has been pursued by many workers. The human foetus is aware about its surrounding milieu and can interact with it, this can be appreciated after 16 weeks of pregnancy. Based on the ancient Hindu concept of prenatal education, an on-going study has been going on in an educational community near Mumbai, India for last three decades. In this study positive inputs like better dialogue with mother (of course the father as well) and the foetus, welcome the baby with good thoughts, use of Vedic chants and music were given to the pregnant woman. Efforts were made to improve the physical and emotional status of the mother during pregnancy and delivery. The impact of these on the foetus was studied by stroboscope tests, fetal Doppler and ultrasound. This study showed there was statistically significant difference in the study group in the form of better emotional bonding, alertness, receptivity and more stable temperament.[27] Attempts are on

to test this concept on fetuses diagnosed to have physical/mental disorders and evaluate the impact on fetal development in these affected babies (*refer to* Chapter 24: Antenatal learning—ancient concept and modern science).

III. Seventh–Ninth Months

Problems encountered during last three months of pregnancy are:

1. Certain congenital defects which can manifest/are diagnosed in third trimester or follow-up of anomalies detected earlier and pregnancy continued.
2. Intrauterine Growth Restriction due to various genetic and environmental causes
3. Premature rupture of membranes and preterm labour with risk of lethal pulmonary hypoplasia.

Diagnosis, management of fetal anomalies

Anomaly scan done in first and second trimester can detect most of the anomalies, but some times patients present late or certain anomalies like obstructive uropathies like PUJ obstruction/posterior urethral valve, congenital diaphragmatic hernia, non-immune hydrops due to cardiac anomalies or rhythm disturbances, certain CNS anomalies like late onset hydrocephalus or agenesis of corpus callosum and amniotic fluid volume problems appear quite late. Hence indication based ultrasound examination is needed with joint consultation with paediatric surgeons, cardiologist and neonatologist so as to arrive at correct diagnosis and prognostication. In many of these problems it is worth while doing invasive testing in third trimester by amniocentesis or fetal blood sampling so as to look for associated chromosomal/single gene disorders.

The whole exercise is worth as it gives the woman range of options like intrauterine therapy, postnatal therapy, medical termination (when ever feasible and possible) and plan the place, time and mode of delivery so as to give best chance to the high risk foetus. We have been conducting a Multispecialty Fetal Medicine Consultancy Services in Mumbai for last three years. We have managed over 350 high risk pregnancies with good results.[28]

Intrauterine growth restriction

This is an important problem as it is associated with increased pregnancy wastage, increased risk of acute and chronic fetal distress, impaired neurologic development and long term complications like obesity, type-2 diabetes, coronary artery disease and certain genetically determined malignancies (*refer* Chapter 26: Adult diseases of fetal origin for further details). By definition IUGR is suboptimal hyperplasia and hypertrophy in second and third trimesters of pregnancy with deficient fetal growth, weight gain, size and maturation of the foetus.[29] The aetiology of IUGR is very varied and includes genetic factors like placental confined mosaicism involving chromosomes 4 and 7, uniparental disomy involving chromosome 16. Many of the structural anomalies like cardiac defects, musculoskeletal anomalies and aneuploidies like Down's syndrome are also associated with moderate to severe IUGR.[30] Chronic/acute malnutrition in pregnant mother is also an important cause particularly in developing country like India with more than 50% population below poverty line, lack of comprehensive antenatal care and unsupervised home delivaries in significant sections of pregnant women in rural areas.. The incidence of IUGR/LBW babies in India ranges from 22 to 40% with resultant impact on child survival, development and long term complications like hypertension, diabetes and coronary heart diseases.[31] Prevention of such nutritionally caused IUGR is a major concern in public health workers and obstetricians from India.

Diagnosis of IUGR depends upon,

- Detailed history elicitation and examination for any of the underlying causes as well as appropriate investigations,

- Accurate dating of the pregnancy by history and early scan in first trimester
- Regular antenatal check-up with meticulous record of maternal weight gain, fundal hight,
- Ultrasonography parameters like upper abdominal circumference, cerebellar diameter, amniotic fluid index (AFI) and Doppler studies.

Management of IUGR is far from satisfactory, particularly when ever it is idiopathic. In spite of many claims there is no effective treatment for such cases. Early diagnosis and amelioration of causative pathology, improving maternal nutrition (especially pre-conceptional stage onwards), and close monitoring of high risk cases by a team approach so as to decide the optimum time, place and mode of delivery yield best results. These fetuses require close neonatal and long term follow-up so as to manage various problems in a preventive manner.

Premature rupture of membranes/preterm labor

Causes of these problems are quite varied and not well understood. Infections like STIs, chorio-amnionitis play important role, certain genetic/structural birth anomalies are more prone to preterm labor and rupture of membranes. The high perinatal mortality is mainly due to pulmonary hypoplasia with resulting respiratory distress though infections, other organ immaturity with metabolic disturbances also play important role. The treatment depends on the timely diagnosis and management of underlying causative factors. Prenatal prediction of pulmonary hypoplasia is highly desirable as it can influence the antenatal, postnatal management and give valuable help in deciding place and mode of delivery. The best prediction is achieved by combination of clinical, ultrasonography and biometry parameters, MRI, biochemical (L/S ratio) and Doppler flow studies of pulmonary circulation.[32]

Amniotic fluid volume disorders: Amniotic fluid is essential for proper development of fetal respiratory, gastrointestinal tract, urinary and musculoskeletal systems as well as for proper fetal growth. Amniotic fluid is formed from various sources like fetal urine, tracheal secretions and transfer of fluid from the maternal blood across the placental surface as well as across fetal membranes. While fetal swallowing removes the amniotic fluid. Any change in the amniotic fluid volume can be because of any of these factors.[33] Hence careful assessment of amniotic fluid volume is vital part of anomalies scan. **Oligohydramnios** is caused mainly by fetal anomalies involving urinary tract, premature rupture of membranes and intrauterine growth restriction. Moderate to severe oligohydramnios causes lung hypoplasia, compression of fetal body as well as interfere in proper fetal anomalies scan. There is appreciable increase of fetal losses, morbidity. **Polyhydramnios** is caused by a variety of pathologies, both maternal and fetal, like maternal diabetes, iso-immunisation, fetal anomalies (mainly gastrointestinal, central nervous system and urinary), chromosomal disorders, multiple gestations, hemoglobinopathy like alpha thalassemia and infection by parvovirus. It poses the risks of preterm labor, accidental hemorrhage, PIH, etc. In idiopathic moderate polyhydramnios judicious use of anti-prostaglandin indomethacin with USG monitoring for premature ductal closure can help inprolongation of pregnancy with better survival.

IV. During and after Delivery

It is vital to evaluate the high risk pregnancies with suspected genetic/birth defects prior to the delivery. It is better to have a multi-specialty team approach to evaluate the condition of the foetus, its maturity, any high risk factors about the neonatal resuscitation and any need for specialized facilities required soon agter birth, so that the place, time and mode of delivery can be decided. *It is always better to transfer a high risk foetus*

in situ to a appropriately equipped and staffed facility rather than transferring a critically ill foetus after delivery. The couple as well as the family should be properly counseled about the natural history of the disorder, special facilities like special diet/medication needed and the nature of post-delivery management.

In case of sad outcomes like termination of an affected pregnancy, stillbirths/ neonatal death it is utmost important for the treating physicians to put across the need for confirmatory tests like postmortem, genetic/metabolic tests in a sympathetic but firm manner, this should be done before the process of delivery/MTP is initiated. The couple and the family are in a state of grief and shock and are unable to grasp the importance of such studies from future pre-conception counseling and evaluation. Properly conducted studies like these can be very valuable for confirmation of antenatal diagnosis, risk assessment, preconception evaluation and appropriate tests to be done in future pregnancies (*refer to* Chapter 25: Role of perinatal pathologist in preventive genetics). Virtual postmortem evaluation by non-invasive imaging modalities like MRI, skeletal X-ray study can be used in cases where the request for postmortem is refused, to get better idea about the details of structural anomalies diagnosed antenataly.

Presymptomatic and predictive genetic diagnosis

After the advancements in laboratory technologies, better understanding of the structure and functioning of human genome achieved by the completion of human genome project, we are able to diagnose or do screening of asymptomatic carriers in a large number of medical disorders at molecular level. With the availability of targeted Micro-Array panels for specific dosorders, EXHOME studies, NGS it is possible to pick-up the disorder at an overt stage, so that early preemptive treatment can be started so as to increase chances of survival and preserve quality of life. Identification of carriers in other family members can enable required surveillance tests which will permit timely diagnosis and appropriate therapy. Several familial cancers (familial adenomatous polyposis, breast cancers, retinoblastoma, von Hippel-Lindau disease, etc.), adult polycystic kidney disease and Huntington's disease are some of such disorders.[34]

Of course such testing has its own ethical dilemmas like confidentiality of the client versus right of relatives to know the lab results, misuse of such information by third parties like insurers, employees governments with discrimination against the individual and prolonged period of anxiety when there is no clinical disease as yet (*refer to* Chapter 27 on ethical and medicolegal problems for more details).

CONCLUSIONS

The twenty second century will be dominated by genetics, bio-informatics, its second decade is already getting over! With vast knowledge generated, by the recently completed Human Genome Project, about the structure and function of human genome in health and disease we are on the threshold of a revolution in field of screening, diagnosis and management of a large number of genetic anomalies. As most of the genetic disorders/ birth anomalies are not curable once they are manifested fully, only preventive genetics initiative will be more effective in alleviation of the significant pregnancy wastage, morbidity and mortality due to such genetic disorders. .

It will take a shift in the mind set of general population and medical and paramedical workers and a concerted, multispecialty approach spanning all streams and branches of medicine and other related faculties that will yield the desired results. The spectacular advances in the fields of biotechnology, genetic engineering and pharmacogenetics are double edged weapons and should be handled in a responsible and far sighted manner to avoid problems of eugenics, discrimination, ethical and religious insensitivity. The clash of maternal and fetal interests will also

pose significant problems requiring adroit handling.

In spite of all these problems it is necessary for all of us to move ahead in making preventive genetics as an essential part of healthcare. The rewards will be worth the efforts!!

REFERENCES

1. Milunsky A, Milunsky J. Genetic counseling: preconception, prenatal and Perinatal: population study, Genetic disorders and the Fetus. Editor: Milunsky A; John Hopkins. Fifth edition page 1, 2004.
2. Baird PA, Anderson TW, Newcomb HB, et al. Genetic disorders in children and young adults: Am J Hum Genet 1988; 42:677.
3. Verma IC. Burden of genetic disorders in India. Indian J Paediatr 2001; 67:893.
4. Benn PA, Hsu LYF. Prenatal diagnosis of chromosomal abnormalities through amniocentesis: Genetic disorders and the foetus. Editor: Milunsky A; John Hopkins, fifth edition 2004; 214–5.
5. Parris WCV, Quimby CW. Anaesthetic considerations for the patient with Homocystinuria. Anaesth Analg 1982; 61:708.
6. Lipscomb KJ, Smith JC, Clarke B, et al. Outcome of pregnancies in women with Marfan's syndrome. Br J Obstet Gynaecol 1997; 104:201.
7. Fuhrmann K, Reiher H, Semmler K, et al. Prevention of malformations in infants of insulin dependant diabetic mothers. Diabetic care 2001; 24:1904.
8. Milunsky A, Ulcickas M, Rothman KJ, et al. Maternal heat exposure and neural tube defects. JAMA 1992; 268:882.
9. Nicolaides KH, Sebire Nj, Snijders JM. Nuchal translucency and maternal serum biochemistry. The 11–14 weeks scan. Parthenon Publishing. 1999; 38–41.
10. Carmichael J B, Liu Hasio-Pin, Janok D, Hallahan T W, Nicolaides KH, Krantz DA. Expanded first trimester screening; Prenatal Diagnosis, 37, 802–7, 2017.
11. Gogate SG, Purandarey HM, Talwalkar SC, Phadke AA, et al. First trimester combined screening for Down's syndrome. Un-published data presented at International Foetoscopy group meeting in Greece. 2005.
12. Brambati B, Lanzani A, Tului L. Trans-abdominal and transcervical chorionic villous sampling: efficiency and risk evaluation. Am J Med Genet 1990; 35:160.
13. Brun JL, Mangione RGangho F, et al. Feasibility, accuracy and safety of chorionic villus sampling: a report of 10741 cases. Prenat diagn 2003; 23:295.
14. Jackson L, Wapner RJ. Chorionic villus sampling. In: Simpson JL, Elias S. eds. Essentials of prenatal diagnosis. New York: Churchil Livingston. 1993:45.
15. Williams III J, Wang BB, Rubin CH, et al. Chorionic villus sampling: experience with 3016 cases performed by single operator. Obstet Gynaecol 1992; 80:1023.
16. Brambati B, Tului L, Cislaghi C, et al. First 10000 chorionic villus samplings performed on singleton pregnancies by a single operator. Prenat Diagn 1997; 18:255.
17. Gogate SG, et al. Fetal tissue sampling for diagnostic and therapeutic purposes: an Indian experience. In: Chakravarty A, Purandarey HM, Gogate SG. Eds. Prenatal diagnosis and therapy. New Delhi: Jaypee Brothers. 1998:80–3.
18. Brambati B, Tului L. Prenatal Genetic diagnosis through chorionic villus sampling. In: Milunsky A. ed. Genetic disorders and the foetus. Baltimore: Johns Hopkins University Press. 2004:179–213.
19. Proceedings of the BDR meeting. BDR News. Ed. Fetal Care Research Foundation; Chennai, India. 2005; 5:1.
20. Gogate SG, Talwalkar SC, Purandarey HM, Phadke AA. Second trimester screening for Down's and NTD in Mumbai city.Un-published data presented at the International Foetoscopy group meeting in France, 2003.
21. Elias S, Simpson JL. Amniocentesis and Fetal blood sampling. In: Milusky A. ed. Genetic disorders and the Fetus. Baltimore: John Hopkins University Press. 2004:81.
22. Gogate SG, Purandarey HM, Shah PS, et al. Amniocentesis for prenatal diagnosis: experience of over 500 cases. Un-published data presented at the annual meeting of International Foetoscopy Group meeting in Greece:2005.
23. Weiner CP, Okamura K. Diagnostic fetal blood sampling related fetal losses. Fetal Diagn Ther 1996; 11:169.

24. Gogate SG, et al. Fetal tissue sampling for diagnostic and therapeutic purposes: an Indian experience. In: Chakravarty A, Purandarey HM, Gogate SG. (eds.) Prenatal Diagnosis and Therapy. New Delhi: Jaypee Brothers: 1998:80–3.
25. Holzgreve W, Miny P, Schloo R, et al. Late CVS Registry: compilation of data from 24 centers. Prenat Diagn 1990; 10:159.
26. Podobnik M, Ciglar S, Singer Z, et al. Transabdominal chorionic villus sampling in the second and third trimesters of high risk pregnancies. Prenat Diagn 1997; 17:125.
27. Kelkar.GS A Prenatal project in India, J. of Prenatal and Perinatal Psychology and Health. 2002; 16(4): 331–9.
28. Gogate SG, Rege V, Utture A, et al. Multi-specialty fetal medicine program in Mumbai, first year's experience. Un-published data presented at International Foetoscopy Group meeting in France. 2002.
29. Gogate SG. Intrauterine growth restriction: obstetrician's perspective. International J of Diabetes in developing countries 2001; 21(1):51–4.
30. Wladimiroff JW. Prenatal diagnosis and management of abnormal fetal development in third trimester of pregnancy. In Milunsky A. ed. Genetic disorders and the foetus. Baltimore: John Hopkins University Press. 2004:901–43.
31. Sachdev HPS. Low birth weight in South Asia. International J of Diabetes in developing countries 2001; 21(1):13–27.
32. Laudy JAM, Tibboel DG, Robben SGF, et al. Prenatal prediction of fetal lung hypoplasia: clinical biometric and Doppler velocity correlates. Paediatrics 2002; 109:259.
33. Brace RA. Physiology of amniotic fluid regulation. Clin obstet Gynaecol 1997; 40:280.
34. Milunsky A. Presymptomatic and predictive genetic diagnosis. In Milunsky A ed. Perseus Publishing: Your genetic destiny 2001:309–22.

Chapter

2

Burden of Genetic Disorders in India

IC Verma, Sunita Bijarnia-Mahay and Ratna D Puri

INTRODUCTION

India has a population of more than a billion people, with almost 25 millions annual births. Combine this with high rates of consanguinity in many communities, endogamous marriages in various ethnic groups, poor nutritional status (low folate levels) of the mothers and high incidence of infections, and the stage is set for a high frequency of genetic disorders and birth defects. We review the burden of genetic and genetically related disorders that are relevant for preventive intervention.

Genetic diseases occur in two waves—one at birth and one later on in adult life. In the current paper we discuss the disorders that occur in early life, and do not discuss the disorders in adult life like coronary artery disease, hypertension, diabetes mellitus, and mental illness, although they have a significant genetic component.

Table 2.1 summarizes the frequency of genetic disorders/related disorders observed at birth in India. These data are collated from various published sources.[1, 2]

CONGENITAL MALFORMATIONS

It is intriguing that the malformation rate varies little in different parts of the world. It is possible that Homo sapiens can only tolerate a certain load of malformations, say around 2–4%. In India, a meta-analysis of almost all published studies on congenital malformations showed the frequency to be 19.4 per 1000 on analysis of 301,987 births[3]. A more recent study[4] carried out in three centers (Bombay, Delhi and Baroda) on 94,610 newborns by using a uniform proforma showed a frequency of 2.03%. Expectedly, the malformation rate among stillbirths is much higher (13.6%).

Table 2.1: Burden of genetic diseases at birth in India

Disorder	*Incidence*	*Number per year*
Congenital malformations	1 in 50	595,096
G-6-PD deficiency	1 in 10–30 (M)	390,000
Down syndrome	1: 1139	21,412
Congenital hypothyroidism	1: 2500	10,400
Beta-thalassemia	1: 2700	9,000
Sickle cell disease		5,200
Amino acid disorders	1:2347	9,760
Other metabolic disorders	1:2500	9,000
Duchenne muscular dystrophy	1:5000 (M)	2,250
Spinal muscular atrophy	1:10,000	2,250

However, the type of malformations seen in different regions is variable.[5] For example, neural tube defects predominate in North India, being very high in Punjab, Rajasthan and Delhi (about 1 in 250 births); while it is lower in Tamil Nadu (1 in 330 births), Mumbai (1 in 450 births), and Kolkatta[6]. From the published studies it is apparent that defects of the musculoskeletal system are the commonest defects in areas where neural tube defects occur with less frequency. Defects of gastrointestinal system including cleft lip/cleft palate are frequent. It has become clear, especially after ultrasonography during pregnancy became wide spread, that congenital heart diseases are also common, occurring with a frequency of 8 per 1000 births.

What about consanguinity and malformations? The highest coefficients of inbreeding in the world are observed in India. It is generally agreed that the incidence of malformations is higher among offspring of consanguineous as compared with non-consanguineous marriages. In the WHO sponsored study of congenital malformations[7], the rate of malformations was higher in the offspring of consanguineous as compared with the non-consanguineous (15.5 vs 9.6 per 1000) in Alexandria, Egypt. In Japan studies showed a malformation rate of 2.49% among the consanguineous as compared with 1.13% among the non-consanguineous. An analysis of the data from India did not show an increase in malformations among the consanguineous in studies in Pondicherry and Vellore.[5] Studies in Mumbai[7] and Chennai[8] showed a higher rate of malformations among the offspring of consanguineous as compared with the non-consanguineous (13.6 vs 8.1 per 1000 respectively in Mumbai and 22.4 vs 16.4 per 1000 respectively in Chennai).

NEWBORN SURVEYS FOR CHROMOSOMAL DISEASES

In the multicentric study[4] 83 infants with Down syndrome were born among 94610 births, giving a frequency of 0.87 per 1000, or 1 per 1150. In this study every newborn was not tested cytogenetically, but in all clinically suspected cases the diagnosis was confirmed by cytogenetic analysis. A meta-analysis of other published studies on newborns[9] showed there were 82 cases of Down syndrome among 75,103 births (one per 916 births). The incidence seems to be similar to the western figures, if one keeps in mind that all the Indian studies are based on clinical examination with chromosomal studies only in selected infants, while the Western data are based on cytogenetic studies in consecutive newborns. The Indian data is therefore, an underestimate. The increasing incidence of Down syndrome with advanced maternal age at conception is evident also in the Indian data, and thus is similar to that observed in the West. In recent years there has been an increase in the number of pregnancies among older women, due to women increasingly going into higher education and employment, with delay in having children due to their careers. This has been matched to some extent with increasing awareness of Down syndrome among women and the obstetricians so that triple tests and ultrasonography are increasingly being utilized to screen pregnancies for Down syndrome.

NEWBORN SCREENING FOR METABOLIC DISORDERS

Screening of 112,269 newborns by Appaji Rao and colleagues[10] for amino acid disorders showed three disorders to be the commonest—tyrosinemia, maple syrup urine disease and phenylketonuria (combined frequency of amino acid disorders 1:2495, with frequency of generalized aminoaciduria 1:1605). In another hospital-based study[11] biochemical screening of 4400 cases of mental retardation revealed abnormalities of amino acids in 256 (5.7%). Four amino acid disorders were the commonest—hyperglycinemia, homocystinuria, alkaptonuria, and maple syrup urine disease. Generally phenylketonuria has a lower frequency than in the West, while the incidence is definitely

higher in South India as compared to North India. Our recent experience at Sir Ganga Ram Hospital using GC/MS studies and tandem mass spectrometry has demonstrated that organic acidurias and urea cycle disorders are not uncommon in the neonatal period.[12]

There are a number of studies on the frequency of various metabolic disorders among subjects with mental retardation. In the collaborative study conducted by the Indian Council of Medical Research[13] in five centers to determine genetic etiology of mental retardation 65 (4.3%) of 1314 cases had metabolic disorders. Of these 7 (0.5%) were found to have amino acid disorders. Studies in Delhi, AIIMS and Bombay, KEM Hospital[14, 15] revealed that common metabolic disorders were mucopolysaccharide disorders (24–37% of cases), lysosomal disorders (13–24%), Wilson disease (9–14%), glycogen storage disease (4%) and galactosemia (3–5%).

The incidence of congenital hypothyroidism (CH) is higher than in the West, due to increased prevalence of iodine deficiency in many parts of India. The frequency at birth varies from 1 in 500 in a study in Delhi to about 1: 2500 in Mumbai.[16, 17] The recent study by A. Radha Rama Devi showed a frequency of CH to be 1 in 1700 births, among 10300 newborns.[18] The incidence of CH in areas of iodine deficiency is much higher. Although the Government has taken up iodination of salt as a priority mission, but the use of non-iodised salt continues in some parts.

Currently there is no government-sponsored newborn screening program in India. A critical analysis of the above data, and considering cost-effectiveness, disorders that deserve to be screened in the newborn period are hypothyroidism and G-6-PD deficiency, even if the parents pay for these tests. Screening for amino acid and other metabolic disorders should ideally be taken up as a research study to obtain frequency data from different parts of India. This would lead to rational decisions regarding which disorders to screen. Presently, it is being restricted to testing of symptomatic infants.

DATA FROM GENETIC COUNSELLING CLINICS

Table 2.2 lists the results of an ICMR-sponsored multicentric study[19] on the causes of referral for genetic counseling. The top four disorders for which referrals were made were repeated abortions (12.4%), identifiable syndromes (12.1%), chromosomal disorders (11.3%) and mental retardation (11%).

Table 2.2: Categories of patients provided genetic counseling in multi-centric study in India (n = 6396)

Category	*No.*	*%*
Repeated abortions	795	12.4
Identifiable syndromes	774	12.1
Chromosomal disorders	722	11.3
Mental retardation	705	11.0
Intersex, amenorrhea, hypogonadism	609	9.5
High risk pregnancy	584	9.1
Hematologic disorders	475	7.4
Neural tube defects	280	4.4
Multiple congenital anomalies	271	4.2
Metabolic disorders	144	2.2
Primary microcephaly	133	2.1
Skeletal dysplasias	81	1.3

The data from a more recent study in a private hospital[20] are summarized in Table 2.3. The top reasons for referral were reproductive problems (38.9%)—comprising prenatal diagnosis, recurrent abortions, infertility and torch infections; mental retardation ± multiple congenital anomalies (16.1%), Down syndrome (9.1%), thalassemia/hemophilia (8.8%), and muscle dystrophy/spinal muscular atrophy (8.4%). It is thus seen that prenatal diagnosis is an important part of genetic counseling in India. The burden of managing a child or adult with genetic disease is very high in India, as the support facilities from the government are very poor. Therefore, every couple earnestly desires to have a normal child, and would not wish to continue a pregnancy with an abnormal child.

Information on the common single gene disorders encountered in the Indian population is available from the ICMR multicentric study, summarized in Table 2.4.

Table 2.3: Genetic counseling at Ganga Ram Hospital ($n = 1370$)

Disorder		*No.*	*%*
Reproductive genetics		525	38.9
⋆ Prenatal diagnosis	288		
⋆ Recurrent abortions	119		
⋆ Infertility	63		
⋆ Torch infections	30		
⋆ Teratogenic drugs	25		
Mental retardation + Multiple congenital anomalies		220	16.1
Down syndrome		125	9.1
Thalassemia, hemophilia, leukemia		120	8.8
Muscle dystrophy, spinal muscular atrophy		115	8.4
Malformations		90	6.6
Metabolic disorders		75	5.5
Spina bifida, anencephaly, hydrocephalus		60	4.4
Short stature, skeletal dysplasia, craniosynostosis		40	2.8

PRENATAL DIAGNOSIS

The recent data from the Sir Ganga Ram Hospital shows that the commonest application of genetic testing is for reproductive events. The severe burden of genetic disease impels couples to seek antenatal diagnosis to make sure that the fetus is not abnormal. In fact many couples having a child with a birth defect would seek genetic counseling only when the wife is pregnant, so as to avoid the birth of another affected child.

Table 2.5 shows the distribution of women who sought prenatal diagnosis over an 8-year period. The advent of molecular testing has been a great boon for the people, as this has enabled antenatal diagnosis of many burdensome disorders, which were earlier not identifiable in the fetus.

PRIORITIES FOR INTERVENTION

For control of non-communicable and genetic disorders WHO has enunciated steps, using the paradigm of beta thalassemia, that is based on experiences the world over. These are appropriate for India, with some modifications.

Table 2.4: Common single gene disorders (more than 10) observed in the ICMR national study[19], arranged in the order of frequency

Autosomal recessive		*X-linked recessive*	
Beta Thalassemia	113	G-6-PD deficiency	28
Primary microcephaly	48	Duchenne musc. Dys.	24
Mucopolysaccharidoses	22	Hemophilia A and B	20
Metachromatic leukodystrophy	15	Testicular fem. syndr.	18
Congenital adrenal hyperplasia	14	Fragile X syndrome	12
Oculocutanoeus albinism	13		
Wilson disease	12		
Amino acid disorders	11		
Werdnig-Hoffmann disease	10		
Autosomal dominant			
Achondroplasia	16		
Marfan syndrome	15		
Crouzon disease	11		
Apert syndrome	10		

Table 2.5: Prenatal diagnosis at Sir Ganga Ram Hospital (n = 10750)

Indication	*Disorder(s) identified*	*No.*
Triple test/1st trimester screening for Down syndrome (DS)		7294
Amniotic fluid cultures (chromosomes)		1358
+ve triple test (DS, NTD)	1198	
Advanced maternal age	126	
Previous child with DS	69	
NTD in previous child	63	
Products of conception (chromosomes)	788	
Chorionic villus samples (chromosomes)	129	
Thalassemia / other hemoglobin disorders		796
Spinal muscular atrophy		172
Duchenne muscular dystrophy		85
Intrauterine infection		70
Hemophilia, Dwarfism		30
Cystic fibrosis		12
Fragile X syndrome		10
Spinocerebellar ataxias, Huntington's disease		6

These principles are as follows:

1. Provide the best possible treatment to the affected children.
2. Sensitise the community to the problem,
3. Establish the technologies for screening of the population.
4. Provide facilities for prenatal diagnosis,
5. Obtain financial and political backing for these activities,
6. Have all components in place before starting the program.

These issues can be examined in greater detail, using the example of beta thalassemia, which is the commonest single gene disorder in India. It is an autosomal recessive disorder, with a carrier frequency of 5–8% in many states, e.g. Maharashtra, Delhi, Punjab, Rajasthan, Haryana, Madhya Pradesh, Gujarat, West Bengal and north-eastern states. The disease is very burdensome as frequent blood transfusions are required and expensive chelating agents have to be used to remove the excess iron in the body. In order to provide optimal treatment to those who are affected, it is essential to initiate a program for the control of beta thalassemia in India to reduce/prevent the birth of children affected with the disease.

1. The best management of affected children, which the country can afford, should be provided—safe blood transfusions and adequate chelation either with deferral or oral chelator.
2. For sensitising the community three messages have to be conveyed—beta thalassemia is a burdensome disease, heterozygote state does not disadvantage the person (who is a carrier), and the risk arises only when both the partners in marriage are carriers giving a risk of 25% that their child can suffer from beta thalassemia major.
3. The message for families with an affected child is clear—they should have prenatal diagnosis in the next pregnancy. This ought to be supported by the government, because there are many parents who cannot afford the cost of prenatal diagnosis.
4. However, to reduce the burden in the community to a significant extent, and prevent the birth of the 'first' affected child prospective genetic testing is essential. The approach that yields the quickest returns is to test every pregnant woman for carrier status in early pregnancy, along with the husband, in all states with a high carrier frequency. We favour testing the husband at the same

time, rather than testing the wife first, and then the husband if she is a carrier. This approach saves time in arriving at the final decision whether prenatal diagnosis is necessary, and allows for slight inaccuracies in carrier testing, because if one of the partners is clearly not a carrier then prenatal diagnosis is not be required.

5. Other approaches suggested are screening school children and college students, or the population. Screening high school children and college students and combining the activity with blood donations is good, and we have tried this successfully in association with the "Thalassemics India"—an association of parents of children with thalassemia. It is very helpful to create awareness but will produce results many years later.
6. The strategy giving high yields is to screen relatives of the affected families, as many carriers would be detected, and birth of affected children would be prevented. The relatives are usually well motivated, as they have seen the suffering of the child.
7. A suggestion is often made that vigorous campaigns should be mounted so that carriers should not marry carriers. It has been assumed that this would be highly successful in India with many arranged marriages. But it is often forgotten that this course of action has been available to us for decades, without much success. In arranged marriages many characteristics in the family of the boy and the girl are matched making it a complex process. Therefore, adding another feature for matching is likely to create social problems, unless the public is well enlightened about the genetics of thalassemia. We should advocate that people should know their carrier status as regards thalassemia gene, and if both husband and wife are carriers, then carry out prenatal diagnosis. Our experience in the project on sickle cell disease in Kerala revealed that the tribals, contrary to all expectations, were willing to have testing for carrier status after marriage, but not before. They were also willing for prenatal diagnosis, without much persuasion.
8. Providing facilities for prenatal diagnosis is also important, as without this reducing the burden of this disorder is not easy.
9. Obtaining financial and political backing for these activities is crucial.
10. One should have all components in place before starting the program. If this is not done, then it may bring discredit to the program.

Neural Tube Defects

A recent study carried out in three centers (Bombay, Delhi and Baroda) on 94,610 newborns, by using a uniform proforma, showed a malformation frequency of 2.03%, the commonest malformations being neural tube defects and musculoskeletal disorders. The discovery that folic acid given during the periconceptional period prevents the recurrence or the occurrence of this disorder in the offspring is an important milestone in the control of neural tube defects. In India we need to work out a strategy on how best to utilize this information for the benefit of our people. Fortification of food with folic acid seems to be the best option to increase folic acid content of diet of all women likely to become pregnant.

Down Syndrome

The frequency of Down syndrome is about one per 1000. The risk is especially high if the maternal age is more than 35 years. However, the screening should aim to include women of all ages, and not only older women. One should screen women using first trimester or second trimester markers combined with ultrasound studies to prevent the birth of affected children.

Newborn Screening

Currently there is no government-sponsored newborn screening program in India.

However, there is a need to introduce screening for hypothyroidism, both during newborn period. Screening for G-6-PD deficiency is also cost-effective, while screening for amino acid and other metabolic disorders should be taken up as a research study to obtain frequency data from different parts of India.

Establishing Intervention Programs

For single gene disorders the Indian Council of Medical Research, and more recently the Department of Biotechnology have invested heavily to develop centers for carrying out molecular based diagnostic tests. Currently there are about 20 such centers in the country and networking and collaboration among them would hasten the introduction of control programs for genetic disorders. Twenty genetic centers for a vast country like India are too few in number. It is therefore essential to introduce genetics and genetic counseling in a big way in the medical schools and open more departments of medical genetics. These genetic centers should establish links with the district hospitals and through them with the primary health centers and the general population in the rural areas.

Due to the lack of facilities in the Government sector, it is apparent that the private sector has an important role to play for putting in place the intervention strategies to bring the benefits of modern genetic knowledge and technologies to the people in India. The obstetricians are the most crucial for an effective intervention program, by screening pregnant women to identify those at high risk, and to carry out the definitive tests to confirm normality of the fetus.

It may also be worthwhile to empower women directly through mass media approaches. Once the women recognize the risks they would ensure that their obstetricians offer them the tests that are essential to reduce the burden of genetic disease among the offspring.

REFERENCES

1. Verma IC. Genetic disorders need more attention in developing countries. World Health Forum. 1986; 7:69–70.
2. Verma IC, Bijarnia S. The burden of genetic disorders in India and a framework for community control. Community Genetics 2002; 5: 192–6.
3. Verma IC, Elango R, Mehta L. Monitoring reproductive and developmental effects of environmental factors in India–a review. Program and Abstracts. Indo-US Symposium "Effects of Environmental and Genetic Factors on Pregnancy Outcome." All India Institute of Medical Sciences, 1990; pp 63–73.
4. Verma IC, Anand NK, Modi UJ, Bharucha BA. Study of malformations and Down syndrome in India—a multicentric study. Department of Atomic Energy, Bhabha Atomic Research Center. Trombay, Mumbai. 1998.
5. Verma IC. A new perspective for congenital malformations in India. In: Genetic Research in India. Verma IC (Ed). Sagar Printers and Publishers, New Delhi.1986, pp 178–87.
6. Verma IC. High frequency of neural tube defects in North India. Lancet 1: 879, 1978.
7. Stevenson AC, Johnston HA, Stewart MIP, and Golding DR. Congenital malformations—report of a study of series of consecutive births in 24 centers. Bull WHO 34 suppl. 1986.
8. Kesavan P, Nataraja U, Murugesan W and Ramakrishnan MS. Congenital malformations and consanguinity. In: Medical Genetics in India. Verma IC (Ed). Vol 1. Auroma Enterprises, Pondicherry. 1978, p.65.
9. Verma IC: Genetics causes of mental retardation. In: M.Niermeijer and E. Hicks (eds) "Mental Retardation, Genetics and Ethical Considerations". Bishop Bekkers Foundation, International Symposium. Reidel Publishing Co. Amsterdam 1988. pp 99–106.
10. Appaji Rao N. Genetic consequences of inbreeding in a large human population. Proc Indian Nat Sci Acad B. 1991; 57:361–8.
11. Kaur M, Das GP, Verma IC. Inborn errors of aminoacid metabolism in North India. J Inh Metabol Dis 1994; 17:230–3.
12. Verma IC, Bijarnia S, Puri RD. Screening for inborn errors of metabolism. Journal of Neonatology 2005; 19: 107–16.

13. ICMR Collaborating centers and central coordinating unit. Multicentric study on genetic causes of mental retardation in India. Indian J Med Res (B) 1991; 94:161–9.
14. Bharucha BA, Kher AS, Naik GG, et al. Spectrum of inherited metabolic disease in India – a 15 year experience. In: Chaudhry P, Sachdev HPS, Puri RK et al (eds). Abstracts 8th Asian Congress of Pediatrics. Jaypee Publishers, New Delhi. 1994. p 98.
15. Kumta NB. Inborn errors of metabolism – an Indian perspective. Indian J Pediatr. 2005; 72: 325–32.
16. Desai MP, Colaco AR, Ajgaonkar AR, et al. Neonatal screening for congenital hypothyroidism in a developing country-problems and strategies. Indian J Pedatr 1987; 54:571–81.
17. Menon PSN, Mathews AR, and Verma IC: Screening for hypothyroidism in AIIMS. In: Genetic Research in India. Edited by I.C. Verma, Sagar Printers and Publishers, New Delhi 1986. pp 171.
18. Devi AR, Naushad SM. Newborn screening in India. Indian J Pediatr. 2004.
19. Genetic Counselling and Antenatal. Diagnosis of Common Genetic Disorders , Report of an ICMR Task Force Study. Indian Council of Medical Research. New Delhi. 1996.
20. Verma IC, Saxena R, Lall M, Bijarnia S, Sharma R. Genetic counseling and prenatal diagnosis in India—experience at Sir Ganga Ram Hospital. Ind J Pediatr. 2003; 4: 293–7.

Chapter

3

Genetic Disorders—Impending Public Health Challenge

Anita G Shenoy and Shantha Sankaranarayanan

The world today is seeing a reduction in morbidity and mortality associated with communicable diseases but the quality of life of our citizens cannot be ensured unless we reduce the morbidity and mortality caused by genetic disorders. By controlling communicable diseases, we are able to reduce the mortality and morbidity. So far priority was given to infectious disease prevention, immunization and prevention of malnutrition. These areas were given greater focus that contributed hugely to the implementation of several kinds of programmes in this field. Though communicable diseases are controlled, an upward trend was seen in the occurrence of non-communicable diseases and inherited abnormalities. With decreasing trend of infant mortality rates in India, genetic disorders are emerging as an important group of medical ailments requiring attention at a priority level. These diseases are assuming proportionately greater importance in medical practice today. According to the World Development Report 1993, congenital malformations constitute 6.5% of the total disease burden for children under 5 years of age in developing countries and 4% of all deaths during 0–4 years of age.[1] In developed countries, genetic predispositions to various diseases are recognized and are addressed in great detail. Genetic counseling and facilities for prevention of hereditary and congenital diseases are available in these countries whereas in developing countries these services are still rare and are absent in some countries.

Globally, at least 7.6 million children are born annually with severe genetic or congenital malformations; 90% of these are born in mid and low income countries. Precise prevalence data are difficult to collect, especially in developing countries, owing to great diversity of conditions and also because many cases remain undiagnosed. The genetic and congenital disorder is the second most common cause of infant and childhood mortality and occurs with a prevalence of 25–60 per 1000 births.[21]

Genetics is the science of heredity. It deals with the transfer of biological information from cell to cell, from parents to offspring and thus from generation to generation. Genetic diseases make up a large proportion of the total disease burden in the population.[2]

Genetics recognizes a relationship of the organism with its various biological functions and the numerous environmental forces acting upon it whereas medicine emphasizes the importance of extrinsic events in the origin of the disease. Both extrinsic and intrinsic factors interact with each other and destabilize the equilibrium leading to diseases.[3]

The first version of the database has been published online. It has been divided into 19 disease categories in the 1st version of the database. It includes:

- Blood related disorders
- Bone and joints related growth disorders
- Eye disorders
- Gastrointestinal disorders
- Hearing disorders
- Lysosomal disorders
- Multi-system disorders
- Muscle related disorders
- Neurological disorders
- Pigmentary disorders
- Skin related disorders.

India is a country with many communities where there is high load of genetic disorders. It is due to consanguineous marriage or marriages between close relatives practiced in the community. This database keeps track of mutations in the causal genes for the genetic diseases common in India. The database will be helpful to the Physicians, Geneticists and other professionals in India and abroad related to genetic disorders to retrieve and use the information for the benefit of mankind.

THE HUMAN GENOME PROJECT[18]

The Human Genome Project is a coordinated international program to sequence the entire human genome. The draft DNA sequence of 3 billion base pairs was successfully completed in 2000 and the complete sequence was announced ahead of schedule amid considerable anticipation and excitement. The immediate benefits of the sequence data are being realized in research that is leading to better diagnosis and counseling for families with a genetic disease.

Factors Influencing Gene Frequencies[4]

a. **Mutation:** According to geneticists the entire body structure of man and other animals are being built through hundreds of millions of years by means of a long succession of mutation. It is well known that external influences like ionizing radiations and certain chemicals are capable of producing mutations.
b. **Population movement:** Because of industrialization, people are moving from one place to other. This population movement will lead to changes in the distribution of the genes. The inter-mixing of people makes new genetic combinations possible.
c. **Public health measures:** Advances in medical care services do affect the genetic endowment of the people as a whole. More lives are saved and the life expectancy has increased. The carriers of hereditary diseases are able to survive for a long time and pass on their genes to their progeny.

Most of the common congenital malformations (e.g. cleft lip, cleft palate, neural tube defects) and common diseases of adult life (e.g. diabetes mellitus, hypertension, obesity, coronary heart disease, schizophrenia) have a significant genetic component in the etiology, in addition to environmental risk factors which are responsible for their development.[5]

Treatment of Genetic Disorders

As there is no definitive cure with acceptable risk, these disorders are a significant burden on the health care delivery system. This is because the chronic nature of genetic diseases requires lifelong medical attention, expensive, supportive and symptomatic therapy and specialist care.[5]

The goal of treatment of genetic disorders is to modify or prevent the natural history of expression of genetic traits so that affected individuals can develop skills optimally with his/her inherent potential.[6] This is not only costly but also does not cure the diseases in many instances. Moreover genetic disorders have longstanding effects on the patients' morbidity and mortality and there is always greater risk of recurrence. The problems experienced after the birth of a child with genetic disorder are immense. The parents and the other family members face lot of emotional as well as financial problems along with the other problems from the society. Hence it is ideal to focus on more cost effective

preventive programmes than just relying on the cost intensive treatment.

Gene Therapy[4]

Gene therapy is the introduction of a gene sequence into a cell with the aim of modifying the cell's behavior in a clinically relevant fashion. It may be used in several ways, e.g. to correct a genetic mutation (as for cystic fibrosis), to kill a cell (as for cancer) or to modify susceptibility (as for coronary heart disease).

The gene may be introduced using a virus (usually a retrovirus or adenovirus) or by means of lipid or receptor targeting. There is now almost universal agreement that gene delivery to somatic cell to treat disease is ethical, and that gene therapy should take its place alongside other forms of medical treatment.

BENEFITS OF PREVENTION OF GENETIC DISORDERS

It is customary to study the frequency of diseases to assess the health status of the community. The fallacy in this method is that, these figures do not give information on innumerous deleterious effect on various organs caused by the disease. They also do not highlight the irreversible damage leading to impairment of normal physical, psychological function of body as well as emotional and economic damages done to the individuals and families. Measuring the benefit of preventing the prenatal defects is a formidable task because of highly inadequate database and several conceptually unresolved problems.[7]

Moreover, it is not possible at present to estimate all the benefits of prevention. Heavy expenditure may be incurred for providing special schools to the affected children. Additionally they may require cardiac, orthopedic, abdominal and other surgeries which cause physical, mental and economic burden to the families. Prevention will definitely save all these expenditure. Apart from this prevention will also reduce the stress, frustration and other psychological problems faced by the parents and other family members.

Social benefits take many forms. Amongst them, the important ones are:

1. Increase in productive capacity (earnings, home making, other unpaid work at home and away from home, etc.)
2. Decrease in medical expenditure (clinical, laboratory and other services)
3. Decrease in institutional care
4. Decrease in special educational classes and other similar training programmes
5. Increase in life expectancy
6. Improvement in mobility and quality of life.

In short, by undertaking prevention programmes, we are estimating increased productivity with reduced institutional and medial costs for each case in the community. These activities will also increase the social well being tremendously.

There is no single road to prevention. Many separate avenues must be sought and each will contribute its bit to reduce the problem. Collectively they will have a major effect on the social well-being.

PREVENTION AND CONTROL OF GENETIC DISORDERS

Implementation of prevention and control programmes can prevent the birth of an affected child, thus achieving primary prevention. These programmes can also reduce the homozygous and double heterozygous states, morbidity and psychosocial trauma.[16]

Steps towards prevention and control of genetic disorders.

A. Prevention

1. **Primary prevention:** Early detection and interaction to prevent the birth of an affected child. Examples of primary prevention are genetic counseling in carriers, immunizing girls with rubella vaccines, folic acid prophylaxis before and during pregnancy.

2. **Secondary prevention:** To prevent clinical manifestations in affected individuals by appropriate interventions. Early and appropriate intervention plays a key role in either preventing the genetic disease or reducing the severity of its clinical manifestations
3. **Tertiary prevention:** Provision of adequate care and rehabilitation in affected individuals.

B. Screening

Preimplantation genetic diagnosis (PGD) for single gene disorders[17] is a powerful genetic test that may be performed during IVF treatment to screen embryos that are at risk to develop a serious genetic disorder. Preimplantation genetic diagnosis (PGD) is used for embryos during *in vitro* fertilization (IVF). The goal of PGD testing is to help couples build a healthy family. PGD is done before the pregnancy is established and helps avoid difficult decisions and situations.

Preventive Screening

- The preclinical diagnosis of genetic disorders can lead to early intervention measures, thereby help in the correction and prevention of disabilities and reduce the expression and severity of disability.
- The carriers and high risk groups detected can be given genetic counseling which will help to prevent and control genetic disorders in the future.
- Population, premarital and preconception screening are carried out with the objectives of identifying carriers for a particular gene defect or to identify individuals with a genetic predisposition to a disease. Genetic counseling will then help these individuals to prevent the birth of an affected child or to prevent or delay disease development.
- In several countries newborn screening is carried out for: Phenylketonuria, congenital hypothyroidism, sickle cell disease, congenital adrenal hyperplasia, galactosemia, biotinidase deficiency, maple syrup urine disease.

C. Counselling

Educational processes by which patients or at risk individuals are given information to understand the nature of the genetic disease, its transmission and the options available to them in management and family planning.

Genetic counseling is a communication process of providing information about the risks of occurrence and recurrence of genetic disorders within a family. Counselors will provide fullest comprehension of all the implications of the disease to the families at risk. Further objective and intrinsic aim of counseling is to help the families through their problems, facilitate their decision-making and their adjustments.

The beneficiaries of genetic counseling are individuals or couples seeking counseling for the following reasons:[16]

- Having an affected child
- Are carriers
- History of genetic disease in family
- Have recurrent abortions
- High maternal/paternal age
- Exposed to a mutagen
- Consanguineous marriage

Prospective Genetic Counseling

This approach requires identifying heterozygous individuals for any particular defect by screening procedures and explaining to them the risk of having affected children if they marry another heterozygote for the same gene.

Retrospective Genetic Counseling

Most genetic counseling at present are retrospective i.e. the hereditary disorder has already occurred within the family. The couples and family members seek genetic counseling in connection with congenital abnormalities, mental retardation, etc. and only a few seek premarital advice.

D. Increase Awareness

- Patients, families and community
- Clinical staff and paramedical personnel

- Health policy makers and administration
- Awareness can be increased through:
  - Public lectures
  - Pre-requisite for prevention programs
  - Articles in newspapers
  - Doctor–patient meetings
  - Inclusion in curriculum
  - Publications, booklets, pamphlets, posters
  - Radio, TV, video documentation

EUGENICS AND EUTHENICS

Eugenics

Eugenics has both negative and positive aspects.

- **Negative eugenics:** The aim of negative eugenics is to reduce the frequency of hereditary diseases and disability in the community to be as low as possible. This is done by debarring the people who are suffering from serious hereditary diseases from producing children.
- **Positive eugenics:** It seeks to improve the genetic composition of the population by encouraging the carriers of desirable genotypes to assume parenthood.

Euthenics

Studies with mentally retarded children indicated that exposure to environmental stimulation improved their IQ. Thus the solution of improving the human race lies with the mutual interaction of hereditary and environmental factors. This environmental manipulation is called euthenics and has considerable broader prospects for success.

For the prevention of genetic disorders effective action can be taken at two levels.[8]

- General population
- Families and individuals at risk

General Population

- Population education
- Genetic screening
- Preconception vitamin therapy

Population Education

Population education can be of great help in decreasing the incidence of genetic diseases. People must be informed about various risk factors which are responsible for the occurrence of genetic disorders in the families so that they may take necessary precautions with this knowledge.

Risk Factors

- **Consanguinity:** Consanguineous marriages/unions pose the risk of having children with congenital malformation and other abnormalities in the offspring.
- **Advanced maternal age:** Relation between advanced maternal age and the occurrence of chromosomal abnormalities is present in all ethnic groups.

Awareness should be created for general population especially for elected representatives, policy makers and community influencers. Necessary scientific information should be made available to the school and college students as well as for non-student youth. This will facilitate them to take responsible decisions. Training of medical/paramedical and other health care providers will help in not only preventing the disorders but also will help in the management of the cases.

Genetic Screening

Genetic screening is the method to identify a person within a population who is at the risk of transmitting the disease to themselves or to their descendants by virtue of their genetic constitution. The primary objectives of the screening are:

- To enumerate the frequency of variation in a population and to investigate biological significance and genetic epidemiology of the variation.
- To detect those at risk for their own health and for whom medical intervention may decrease the harmful effects of the gene expression.
- To detect those at risk of transmitting the harmful genes to their offspring. They may

benefit from genetic counseling regarding their reproductive options.

Preconception Vitamin Therapy[2,9]

Cleft lip and/or palate and neural tube defects are caused by a deficiency in folic acid and its receptors in the mother. The neural tube closes by 23rd day in an embryo. Any defect in this closure gives rise to the neural tube defect. These defects can be prevented by preconception vitamin therapy in which the prospective mother consumes 4 mg of folic acid 4 weeks prior to her conception and continue for 12 weeks after she conceives during the organogenesis period. This prevents the occurrence of these birth defects in the population and will reduce the incidence by 70%.

Families and Individuals at Risk[8]

Families with cases of congenital or inherited disease:

In this situation the aim is to educate the family members about the occurrence of genetic disorders. The close relatives are to be convinced to seek genetic counseling and take appropriate decisions.

- Genetic counseling
- Carrier screening
- Neonatal screening
- Early detection and treatment of inborn errors of metabolism of single gene disorders.

Genetic Counseling

Genetic counseling helps the family members in clearly understanding their reproductive options thus enriching their decision making process. A large amount of factual knowledge must be considered a vital prerequisite for counseling. This includes information on how to confirm the diagnosis, the recurrence risks, the mode of inheritance, the tests available for carrier detection, the natural history of the disease and the prognosis for survival. The counselors should have required knowledge, necessary skills, for providing efficient and effective counseling. They also should have proper attitude, behavior and sufficient training.

Carrier Screening

Screening for the carrier state of recessive traits would identify carriers who have a 25% risk of getting affected children. Screening of certain genetic carrier states can be recommended in selective situations.

The following criteria must be met:

1. Disease presentation is severe.
2. Screening is directed towards high risk population
3. Availability of an inexpensive sensitive and specific test.
4. Reproduction options are available to couples found to be at risk.
5. Genetic counseling is available.

Neonatal Screening[8]

Neonatal screening is done for some metabolic disorders (PKU and hypothyroidism), sickle cell anaemia, thalassemia, congenital adrenal hyperplasia in most developed countries. Such programmes remain limited to some regions or to small size populations in developing countries.

Early Detection and Treatment of Inborn Errors of Metabolism of Single Gene Disorders[2]

Newborn screening methods for inborn errors of metabolism can be incorporated in community health care. A drop of blood that is collected from 3 or 4 days old babies onto a filter paper can be mailed to the reference laboratories and thus the metabolic disorders can be detected. This test will definitely help in early detection and for providing prompt treatment to reduce morbidity and mortality due to the metabolic disorder.

Rationale for Providing Genetic Health Services

A community based programme started in the city of Havana, Cuba in 1981 was very effective and was extended to the whole country

in 1988. Between 1982 and 2002, 2.8 million pregnant women were tested for sickle cell carrier status, 96,000 carriers and 4,786 couples at risk were detected and offered genetic counseling and prenatal diagnosis. The accessibility to legal abortion and the autonomous decisions by the majority of couples to terminate abnormal pregnancies reduced the prevalence of neural tube defects and sickle cell disease at birth by 90 and 65% respectively by 2002.[10]

A screening at the population level and premarital level, followed by genetic counseling to prevent the conception of a child with a genetic abnormality in a high-risk group is one of the most effective strategies in primary prevention. The best example of the application of this strategy is the control of thalassemia by carrier screening. In Cyprus, Sardinia and the Ferrara district of North-east Italy, almost no thalassemia major births have been reported since 1982, although the incidence was very high during the 1970s. Counselling to reduce consanguineous marriages in high-risk families is also beneficial; to prevent the birth of a child with recessively inherited disorders.[11]

Breast cancer education programs may be of greater service to women if they incorporate information about genetic mutations associated with breast cancer and are able to make referrals to appropriate genetic services. In future, it is foreseeable that our understanding of gene-environment interactions will provide more information on disease risk. Eventually, it may be appropriate to recommend avoidance of certain behaviors or environments based on one's genetic profile.

Principles for the Prevention of Genetic Diseases[12]

1. The mode of inheritance and natural history of the disease should be understood.
2. Cost effectiveness should be established and total justification in relation to expenditure can be proved.
3. Public heath education should precede all testing.
4. Programme effectiveness should be evaluated against all predetermined goals.
5. The privacy and confidentiality of the participants should be assured.
6. The tests should be acceptable to the individuals, families and communities. The right to participate should be recognised and safe guarded.
7. Facilities should be made available within the reach of the community.
8. The tests should be accurate, reproducible, valid, inexpensive and simple. They should be performed by skilled and trained personnel.
9. Legal and ethical standards are mandatory.

COMMUNITY GENETIC HEALTH SERVICES

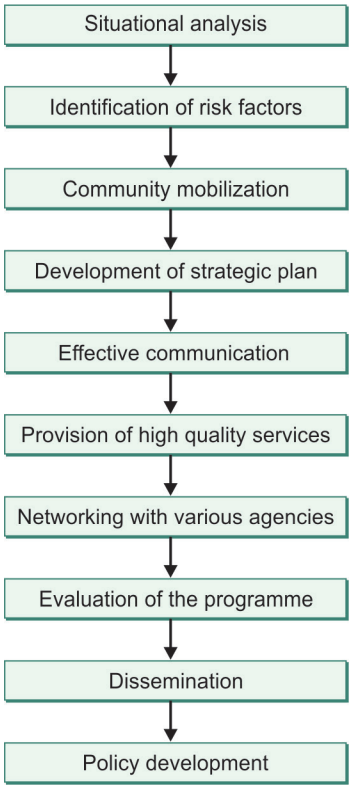
There are 10 essential steps involved in providing community genetic health services (Flowchart 3.1).

1. Situational Analysis

The development and maintenance of a strong health data base with the capacity to monitor genetic factors that may lead to health problems is very valuable. This includes the database of genetic information linked to diseases and pertinent information regarding monitoring the incidence and prevalence of diseases. Data collected in these systems could include genetic variants, health status, demographics, interventions, environmental triggers, and safety and efficacy of genetics technologies. The ability of population-based data collection systems to capture associations between genetic and environmental factors and resultant clinical manifestations will expand our understanding of the relationships between these factors and provide new insights into prevention.[13]

The genetic variables which may become subjects for public health surveillance include:

Flowchart 3.1: Steps for community genetic health services



1. The population frequency of genetic variants that predispose people to specific diseases
2. The population frequency of morbidity and mortality associated with such diseases; and
3. The prevalence and effects of environmental factors known to interact with given genotypes in producing disease.[14]

Other important factors include the availability of resources in the community. This includes the availability of appropriate genetic technologies, accessibility of clinical and genetic services, the cost-benefit of using genetic technology and the community's knowledge of the use of genetics to improve health status.

Data collection systems for genetics should be integrated with existing data systems (e.g., birth defects registries, vital statistics, birth and death certificates, cancer registries, laboratory reporting).

2. Identification of Risk Factors

Various genetic risk factors which are responsible for the morbidity and mortality of the community should be identified. This is necessary to increase the opportunities for early intervention, reduction of disease burden, and primary prevention of disease throughout the life span.

3. Community Mobilization

The mobilization of various public and private agencies and partners who are interested in working collaboratively will promote effective and efficient delivery of health services. This provides greater understanding about genetics and its contribution to disease prevention and health promotion.

4. Development of Strategic Plan

A health promotional strategic plan should be developed. This will help the citizens to use genetic information appropriately and reduce the risks of disease. The community needs for genetic information and services should be assessed and considered. The policymakers and other stake holders should be involved in preparing the plan. Training and skill development of the personnel is necessary to meet the challenges.

This plan should envisage the integration of genetics into public health practice and policies.

5. Effective Communication

Effective communication with community members regarding genetics services will improve their efficient utilization. Materials used to educate the public should be culturally relevant and should be easily available to all populations including underserved populations.

Key community and peer leader members of these partnerships also serve as excellent

community informants and can disseminate beneficial genetic information.

6. Provision of High Quality Services

High-quality, culturally competent genetics services should be available for those who need or desire them. Assure the availability and accessibility of up-to-date genetics programs, services, tests and treatment. Current and future health professionals including counselors will need training and skills development in the appropriate use of genetic information to promote health and prevent diseases. They should be encouraged to incorporate advances in genetic medicine in their practices.

7. Networking with Various Agencies

Effective networking of services which are community-based and culturally sensitive is very necessary to mainstream the genetic services to the existing health care service.

8. Evaluation of the Programme

A system is needed to provide ongoing evaluation of the impact of genetic information and the effectiveness, accessibility, and quality of genetic tests and population-based health services. Quality of services, personnel, cultural competency, and use of surveillance and population-based epidemiological studies are important components of evaluation.

9. Dissemination

Communication and information dissemination will be necessary to provide timely and accurate information to the general public and professionals in order to enhance their basic knowledge about genetics, genetic screening, counseling, and comprehensive services. The elected representatives, community influencers and policy makers should be addressed effectively with relevant data and documents.

10. Policy Development

Population-based genetic information should be applied to state policies and programs to improve individual and community health. Legislation, statutes, and regulations should be developed which will provide optimal use of genetic information to improve health, while protecting clients and consumers from misuse.

Clinical utility and validity of genetic tests should be done from time to time. There are numerous studies that examine the link between genes and disease and provide insight into reducing the occurrence, morbidity, and mortality of disease. The findings must be analyzed through a public health lens to determine when they should be incorporated into public health practice.

Future strategies[16] for control of genetic disorders:

- Determine the frequency and distribution of genetic disorders in the population.
- Construct data bases of genetic disorders.
- Establish care and counseling facilities.
- Establish programs for carrier detection.
- Provision of appropriate counseling.
- Increase awareness of the genetic defects.
- Better understanding of molecular pathology of genetic defects.
- Update information.

CONCLUSION

The developing countries lack sufficient understanding of the critical demographic factors that affect gene frequency, the incidence of chromosomal abnormalities, and the opportunity for selection in human populations. Thus, we do not know with reasonable certainty whether the current genetic status of the populations (as it is affected by shifts in demographic variables) is undergoing a dysgenic trend, or whether it is stabilizing in terms of the genetic load.[15]

In the decades to come, molecular genetic insights and techniques will have great influence on prevention and health care. General communication about hereditary

issues can be dealt with by well-informed health care workers along with appropriate computerized support. But in order to address specific risks and disorders, consultation at a genetic center is preferred. Long-term follow-up to evaluate predictions and interventions needs more attention and can easily be integrated into primary care. With respect to counseling and clinical practice, many ethical issues have to be considered in the domains of both reproductive medicine and clinical practice. Doctors, patients and society, traditionally battling to reduce diagnostic and prognostic uncertainties, must now realize that they are provided with necessary skills to cope with newer challenges.

The complex genetic architecture, the vast numbers, the high rates of consanguinity, all position India as a Pandora's Box in the field of genetics.[20] The number of geneticists and laboratories are too scarce to cater to the huge population of India. Improved health budget allocations, sensitization of the health authorities and policy makers toward the burden of genetic diseases, inclusion of genetics in medical curriculum and creating awareness amongst medical practitioners from other fields are important steps required for this purpose. Screening programs like newborn screening, thalassemia prevention and Down syndrome screening need to be implemented.

REFERENCES

1. Guidelines for the study of genetic effects in human populations. Geneva, World Health Organization (Environmental Health Criteria, no.46), 1985.
2. Sridevi Hegde, Integration of genetic counseling into Multi-disability community based rehabilitation programmes, www.dinf.ne.jp/doc/english/asia/resource/apdrj.
3. Human genetics: possibilities and realities, CIBA Foundation, Symposium 66, new series, June 1979.
4. K. Park: Textbook of Preventive and Social Medicine, 24th Edition (2017).
5. MAF El-Hazmi, Spectrum of genetic disorders and the impact on health care delivery: an introduction. Community Genetics, Vol.5, Issue 6, Pg. 1104–1113, 1999.
6. Yujen Edward Hsia, Treatment in Genetic Diseases. Ch.11, The Prevention of Genetic Disease and Mental Retardation, 277–305, 1975.
7. Ronald Conley: The Economics of Prenatal Genetic Diagnosis, The Prevention of Genetic disease and mental retardation, 440–455, (1975).
8. Habiba Chaabouni, Genetic counseling and Prevention of genetic disorders: A myth or reality in developing countries. www.charite.de/ch/medgen/eumedis/consanguinity04/geneticcounseling. html.
9. Czeizel. AE. Prevention of congenital abnormalities by periconceptional multivitamin supplementation. British Medical Journal, 306:1645–1648 (1993).
10. Luis Heredero-Baute, Community-Based Program for the Diagnosis and Prevention of Genetic Disorders in Cuba, Twenty years of experience. Community Genetics; 7:130–136; 2004.
11. Angastiniotis MA, Hadjiminas MG, Prevalence of thalassaemia in Cyprus, Lancet, 1:1369–80, 1981.
12. Aubrey Milunsky, The Prevention of Genetic disease and mental retardation, 1–18, (1975).
13. Integrating Genetic Services into Public Health, genes-r-us.thscsa.edu/nnsgrc genetic.
14. Muin J. Khoury, Wylie Burke and Elizabeth J. Thomson, Genetics and Public Health in the 21st Century using genetic information to improve health and prevent disease, New England Journal of Medicine. Volume 343, 1580, No.1 (November 23–2000).
15. Mark Lappe, Can Eugenic Policy Be Just? The Prevention of Genetic Disease and Mental Retardation. Pg. 456–74, 1975.
16. Control and prevention of genetic disorders. faculty.ksu.edu.sa/52876/Presentations.pdf
17. Preimplantation Genetic Diagnosis. www.igenomix.com/tests/prevent-genetic-diseases-pgd
18. Peter D. Turnpenny, Sian Ellard. Emery's Elements of Medical Genetics. Twelfth Edition, Elsevier Churchill Livingstone
19. Sanchari Pradhan, Mainak Sengupta, Anirban Dutta, Kausik Bhattacharyya, Sumit K. Bag,

Chitra Dutta, Kunal Ray; Indian genetic disease database, Nucleic Acids Research, Volume 39, Issue suppl_1, 1 January 2011, Pages D933–D938, https://doi.org/10.1093/nar/gkq1025

20. Shagun Aggarwal and Shubha R Phadke. Genetics and genomic medicine around the world Medical genetics and genomic medicine in India: current status and opportunities ahead. Open access article. http://onlinelibrary.wiley.com. Volume 3, Issue 3, Version of Record online: 14 May 2015
21. Anupam Kaur and Jai Rup Singh. Chromosomal Abnormalities: Genetic Disease Burden in India. Int J Hum Genet, 10(1–3): 1–14 (2010).