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Review

Global burden of genetic disease and the role of genetic screening

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SUMMARY

It is estimated that 5.3% of newborns will suffer from a genetic disorder, when followed up until the age of 25 years. In developing, as compared to western countries, hemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency have a higher incidence due to severe falciparum malaria in the distant past, and autosomal recessive disorders have a higher frequency due to greater proportion of consanguineous marriages. Chromosomal disorders have a combined frequency of 1 in 153 births, therefore screening for chromosomal disorders is essential, using biochemical markers, ultrasonography, and recently by non-invasive prenatal diagnosis based on cell-free fetal DNA in maternal plasma. Pre-conceptional counseling should be encouraged. For genetic disorders screening should be carried out, ideally after marriage, but before pregnancy. The disorders to be screened depend upon ethnicity. Metabolic disorders have a high incidence in developing countries due to greater rate of consanguineous marriages. Newborn screening is recommended to reduce the burden of these disorders, as many metabolic disorders can be treated. Hearing and critical congenital heart disease should both be screened in the newborn period.

1. Introduction

The key studies that have served as the basis for the calculations of the global burden of genetic disorders are presented. The variables that affect this are briefly discussed. This is followed by a description of screening at different stages of the life cycle: before marriage, before conception, during pregnancy, and after birth.

2. Global burden of genetic disease

Most of the estimates of the global burden are derived from the landmark study by Baird et al. [1] in Vancouver (Table 1). The authors examined the data base of the population-based British Columbia Health Surveillance Registry, with more than 60 sources of registration, to estimate the population load of genetic disease in more than 1 million consecutive live births, followed up to the age of 25 years. The births were divided into three decades (1952–1963, 1964–1973, and 1974 to 1983). The decade showing the highest rate was selected, because it was expected that there was an underascertainment, rather than overestimation in the study. Particular care was taken to avoid multiple entries. The incidence of genetic disorders was documented as 5.32% in births followed up to 25 years, if the congenital anomalies that have significant genetic component only are included, and 7.94% if all congenital anomalies are included.

Christianson et al. [2] pointed out that the dominant and X-linked disorders would be similar in developed and developing countries, except for disorders due to genes that carry founder mutations, e.g. spino-cerebellar ataxia type 12 among the Aggarwal community in North India [3]. Among X-linked diseases, glucose-6-phosphate dehydrogenase (G6PD) deficiency is more prevalent in developing countries in the equatorial regions. The distribution of the various disorders in these categories documented by Baird et al. is similar to what is observed in India. However, the frequency of autosomal recessive disorders is higher in developing countries, because of consanguineous marriages in many communities, and the high prevalence of hemoglobinopathies. For example, thalassemia, sickle cell, and spinal muscular atrophy would have a greater frequency in India. Phenylketonuria has a lower frequency in North compared to South India, due to more consanguineous marriages in the latter. Cystic fibrosis, which formerly was considered to have a very low prevalence in India, is now more frequently identified because of better molecular diagnostic facilities. Studies in North India have shown a greater frequency of autosomal recessive disorders among the Aggarwal community, with founder mutations. They do not marry consanguineously but do practice endogamy [4].

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Table 1
Frequencies of genetic disorders in 1,169,873 births, 1952–1983.

Category	Rate per 1 million births	% of total births
Dominant	1,395.4	0.14
Recessive	1,655.3	0.17
X-linked	532.4	0.05
Chromosomal, numerical	1,845.4	0.18
Multifactorial[a]	46,582.6	4.64
Genetics unknown	1,164.2	0.11
Total	53,175.3	5.32
Including all congenital anomalies	79,399.3	79.8

[a] Includes congenital anomalies that have a significant genetic component, such as cleft lip and palate, talipes, spina bifida, etc.

The most prevalent single gene disorders are listed in Table 2 , according to the pattern of inheritance.

There has been a change in the pattern of diseases in the past 20 years. The Global Burden of Disease Study [5] analyzed the global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010. Deaths from non-communicable diseases rose by about 8 million in this period, accounting for two of every three deaths (34.5 million) worldwide. The most frequently occurring non-communicable disorders were of adult onset: cancer, cerebrovascular and circulatory disorders, stroke, diabetes mellitus, Parkinson disease, etc. Deaths due to epilepsy increased by 36.4%, while those due to hemoglobinopathies remained almost the same, although there was an increase in deaths from sickle cell disease, as this has a higher prevalence in Africa with higher mortality rates. Deaths due to congenital anomalies decreased, perhaps due to the effect of folic acid supplementation around the world, as well as deaths from Down syndrome (the latter perhaps due to screening and terminations during pregnancy).

Table 2
Prevalence of single gene disorders.

Disorder	Frequency per million births
Autosomal dominant disorders	
Neurofibromatosis	84.6
Chondrodystrophies	76.1
Osteodystrophies	70.1
Tuberous sclerosis	49.6
Hereditary spherocytosis	42.7
Congenital cataract and lens anomalies	30.8
Retinoblastoma	30.8
Retinal dystrophies	29.7
Myotonias	23.9
Congenital disorders of skin	18.8
Autosomal recessive disorders	
Cystic fibrosis	232.5
Phenylketonuria	64.1
Other amino acidurias	48.7
Hereditary retinal disorders	48.0
Muscular dystrophies	43.4
Myoneural disorders	41.1
Thalassemia	32.5
Werdning–Hoffman disease	34.2
Deafness	24.8
Cystic kidney disease	23.9
Adrenogenital disorders	21.4
Hyperaldosteronism	18.0
Mucopolysaccharidoses	18.0
Glycogenosis	19.7
Cerebral lipidosis	15.4
Lipidosis	15.4
X-linked recessive disorders	
Progressive muscular dystrophies	76.9
Color vision deficiencies	64.1
Factor VIII deficiency	56.4
Mental retardation	19.7
G6PD deficiency	16.2
Factor IX deficiency	15.4
Multifactorial disorders	
Strabismus	10,424.6
Inguinal hernia	6,167.1
Clubfoot	5,114.7
Congenital heart disease	5,016.5
Congenital dislocation of hip	3,418.2
Congenital hypertrophic pyloric stenosis	2,365.2
Epilepsy	1,933.7
Epispadias	1,822.1
Cleft lip and cleft palate	1,421.7
Diabetes mellitus	1,286.8

G6PD, glucose-6-phosphate dehydrogenase.

3. Chromosomal disorders

The burden of chromosomal disorders starts from birth, and continues throughout pregnancy, being highest in the early part of pregnancy (50% of miscarriages in the first trimester are due to chromosomal disease). Therefore, the frequency of chromosomal disorders is highest at the time of chorionic villus sampling, decreasing in the period when amniocentesis is done (Table 3), leading to a smaller burden at birth [6]. The well-known association of chromosomal aneuploidies with maternal age is well illustrated in Table 3.

The chromosomal abnormalities among live-born infants are shown in Table 4 . These were derived by combining the data from a number of studies among newborns [6]. The incidence of all chromosomal disorders among live-born infants is 1 per 153 births. Most autosomal chromosomal disorders lead to mental retardation and malformations, whereas the sex chromosomal disorders often lead to infertility; thus the burden of chromosomal disorders is high. This underlies the need to screen for chromosomal disorders during pregnancy.

Down syndrome deserves a special mention. Chromosomal disorders are related to the maternal age at conception; therefore, their frequency will be high in those countries with a larger group of women conceiving at advanced maternal ages (>35 years). Second, the method of ascertainment is critical, such as active case-finding. For example, in the USA during the period 2004–2006 the prevalence of Down syndrome was 1 in 691 births [7]. The increase was due to active ascertainment, and the inclusion of stillbirths and termination of pregnancies. In recent years the number of fetuses conceived with Down syndrome has increased as the mean age of pregnant women has increased in the USA, but the number of terminated pregnancies with Down syndrome has also increased, so that the current prevalence has decreased to about 1 in 1000. On the other hand, extremely high frequencies have been recorded in the Middle Eastern countries, varying from 1.8 to 3.5 per 1000 [8]. The reasons for this are that conceptions continue until women are in their late 40s, and abortion is not allowed. In India, in a three-center study of 94,600 births, the incidence of Down syndrome was 1 per 1,150 births [9]. In this study, the diagnosis of Down syndrome was confirmed by cytogenetic analysis. Since this was lower than the usually quoted statistics globally, the authors estimated the frequency of Down syndrome in India, based on the data provided by Baird et al. [10] from Vancouver, and the maternal age distribution at birth in 2010 in Delhi, to be 1 in 1,200. The reason for this low frequency, therefore, is that conceptions at maternal age >35 years occur in only about 5% of women in Delhi [11].

The introduction of new advanced technologies, such as micorarrays, has revealed the considerable burden of copy number variations (CNVs) – microdeletions and microduplications. These