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Medical Genetics in Israel

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Abstract
The state of Israel was founded in 1948 and includes approximately 4.5 million Jews and 1 million of non-Jews, mainly Muslim Arabs. Subgroups can be distinguished within each of these two groups: among the Jews according to their country of origin and among the non-Jews according to their religion or even their village of origin. The precise origin of each patient is particularly important for the medical geneticists since in each subgroup some hereditary disorders have been reported with an increased frequency. This knowledge also allows in some cases for preventive genetic screening. The reasons for the relatively high frequency of mendelian disorders in the different communities in Israel are numerous including mainly a founder effect with genetic drift and selection. In Israel, medical genetics is a recognized medical speciality and there are eleven clinical genetic centers in the country. These centers are in close contact with the individuals active in the different fields of human genetics in Israel both for service and research.

Characterization of the Country and Populations

Israel is a very small country in the Middle East. Even though some 70% of its land is desert, agriculture has always been one of the major resources. The majority of the population is clustered along the Mediterranean shore and the center of the country. It includes two major groups: Jews (approximately 4.5 million) and non-Jews (approximately 1 million), mainly Muslim Arabs [1]. Most of the employed persons are in public services (28.7%), industry (21.3%) and commerce (14.8%). Today only 3.6% of the employed persons are in agriculture, however, it still

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represents one of the major goods for exportation together with the industrial products.

The *Jewish population* includes: (1) the Ashkenazi Jews which originated from central and eastern Europe and comprise some 40% of the Jewish population and (2) non-Ashkenazi Jews divided into Sephardic (originating from the Mediterranean basin) and Oriental Jews (originating from Asia). Most of the Jewish population immigrated to Israel after its independence in 1948 and the immigration has continued practically uninterrupted since then. Consanguineous marriages have been relatively frequent among Jews particularly in non-Ashkenazi Jews [2]. A survey on congenital malformations in Israel between 1966 and 1975 showed an overall consanguinity rate of 9.4% (16.8% in Oriental Jews, 12.2% in Sephardic Jews and 0.7% in Ashkenazi Jews) [3]. We are not aware of more recent estimates; however, the impression is that intrafamilial marriages are becoming less frequent in all the Jewish communities, even though they still occur, particularly among Oriental Jews. Whereas Jews have a tendency to marry within their community, in the years following their immigration to Israel, this trend declines thereafter and 'mixed' marriages are more frequent.

The *non-Jewish population.* The non-Jewish citizens of Israel include mostly Muslim (751,400 in 1993), Christian Arabs (151,700) and Druze (approximately 80,000) [1]. The Muslim community includes the bedouins who still recently lived as nomad tribes. The non-Jewish population in Israel lives in larger cities like Jerusalem or Nazareth but mostly in small towns and villages of 5,000–15,000 inhabitants. The majority of smaller villages is constituted of large kindreds originating from a few founders. In these communities the marriages are within the family by preference. Consanguineous matings are very frequent and represent about 44% of the marriages [4]. Half of the consanguineous marriages are between first cousins and the mean coefficient of inbreeding in this population is 0.0192 [4].

Genetic Epidemiology: Relatively Frequent Mendelian Disorders in Israel Jew

Frequent Disorders among Jews

An increased frequency for many disorders has been reported to be found among Jews (table 1); however, there appear to be different reasons for this phenomenon.

In most of the relatively frequent disorders among Ashkenazi Jews in which mutations shave been reported, the high incidence is due to more than one frequent mutation. The best known examples are the three lysosomal storage diseases: Tay-Sachs, Gaucher and Niemann-Pick [5]. Similar observations have also been made for the Canavan disease [6], glycogenesis VII [7] and factor XI deficiency [8]. These results may support the possibility of some selective advantage for heterozygotes [5]. In other disorders, the cause of the high frequency may be a founder effect since only one mutation has been identified. An example is familial hypercholesterolemia in Lithuanian Jews, a small community within the Ashkenazi Jews [9].

It appears that among the non-Ashkenazi Jews, the relatively high frequency of many of the disorders may be attributed to the isolation in which the respective communities used to live. A single mutation was found to be responsible for the high frequency of phenylketonuria [10] and metachromatic leukodystrophy (MLD) among Yemenite Jews [11], corticosterone methyloxidase II deficiency among the Iranian Jews [12] or Creutzfeldt-Jakob disease in Libyan Jews [13]. Multiple mutations have been identified for β-thalassemia among Jews from Kurdistan [14], most

Table 1. Relatively frequent Mendelian disorders among Jews

	McKusick	Inheritance	Frequency[1]
Ashkenazi Jews			
Abetalipoproteinemia	200100	AR	?
Adrenal hyperplasia III (nonclassical 21 OH deficiency)	201910	AR	1:27
Bloom syndrome	210900	AR	1:100,000
Canavan disease (spongy degeneration of central nervous system)	271900	AR	1:15,000
Dysautonomia, familial	223900	AR	1:3,700
Dystonia musculorum deformans	128100	AD	1:4,000
Factor XI deficiency (PTA deficiency)	264900	AR	1:450
Familial hyperinsulinism (nesidioblastosis)	256450	AR	?
Gaucher disease type I	230800	AR	1:1,000
Glycogenosis VII	232800	AR	?
Hypercholesterolemia, familial (Lithuanian Jews)	143890	AD	1:69
Mucolipidosis IV	252650	AR	1:30,000
Niemann-Pick disease A,B	257200	AR	1:60,000
Pentosuria	260800	AR	1:5,000
Tay-Sachs disease			
Infantile	272800	AR	1:4,000
Adult	272800	AR	1:67,000
Non-Ashkenazi Jews			
Factor V, VIII combined deficiency	227300	AR	1:100,000
Algeria			
Familial mediterranean fever	249100	AR	1:700
Egypt (Karaites)			
Huntington disease	143100	AD	?
Spinal muscular atrophy I	253300	AR	1:400
Ethiopia			
Neutropenia, chronic familial	162700	AD	1:3
Iran			
Achromatopsia	216900	AR	?
Anencephaly	206500	AR	?
Corticosterone methyl oxidase II deficiency	203410	AR	1:4,000
G6PD deficiency	305900	XLR	1:7 males
Hyperbilirubinemia II (Dubin-Johnson syndrome)	237500	AR	1:1,300
Microphthalmia/anophthalmia	251600	AR	?
Myasthenia gravis, infantile	254210	AR	?
Myopathy, rimmed vacuole	–	AR	?
Pituitary dwarfism II (Laron)	262500	AR	?
Polyglandular deficiency syndrome	263620	AR	?
Pseudocholinesterase deficiency (E1)	177400	AD	1:9
Iraq			
Achromatopsia	216900	AR	?
Factor XI deficiency (PTA deficiency)	264900	AR	1:3,670
Familial mediterranean fever	249100	AR	1:1,000
G6PD deficiency	305900	XLR	1:4 males
3-Methyl glutaconic aciduria	250950	AR	1:10,000
Microphthalmia/anophthalmia	251600	AR	?
Myasthenia gravis, infantile	254210	AR	?
Pituitary dwarfism II (Laron)	262500	AR	?
Pseudocholinesterase deficiency (E1)	177400	AD	1:11
Thrombasthenia (Glanzmann)	273800	AR	1:7,700
Xeroderma pigmentosum, unclassified	–	AR	?

Table 1 (continued)

	McKusick	Inheritance	Frequency[1]
Kurdistan			
G6PD deficiency	305900	XLR	1:1.6 males
Thalassemia, alpha	273500	AR	1:80 carriers
Thalassemia, beta	273500	AR	1:160
Libya			
Familial mediterranean fever	249100	AR	1:250
Cystinuria	220100	AR	1:2,500
Creutzfeldt-Jakob disease	123400	AD	1:24,000
Morocco			
Adrenal hyperplasia IV (11β-hydroxylase deficiency)	202010	AR	1:5,000
Ataxia telangiectasia	208900	AR	1:8,000
Cystinosis	219800	AR	1:20,000
Cerebrotendinous xanthomatosis	213700	AR	1:10,000
Familial mediterranean fever	249100	AR	1:700
Glycogen storage disease III	232400	AR	1:5,000
Tay-Sachs disease	271800	AR	1:10,000
Uzbekistan (Bukhara)			
Oculopharyngeal muscular dystrophy	164300	AD	1:700
Tunisia			
Brittle cornea syndrome	229200	AR	?
Familial mediterranean fever	249100	AR	1:700
Pernicious anemia, juvenile, due to selective intestinal malabsorption of vitamin B_{12} with proteinuria	261100	AR	?
Turkey			
Familial mediterranean fever	249100	AR	1:1,000
Yemen			
Neutropenia, chronic familial	162700	AD	1:4
MLD, late infantile (Habbanite Jews)	250100	AR	1:75
Phenylketonuria	261600	AR	1:5,000
Pituitary dwarfism II (Laron)	262500	AR	?
Thalassemia, alpha	273500	AR	1:5 carriers

Most of the relevant references can be found in McKusick [27] and/or are available from the authors.
AR = Autosomal recessive; AD = autosomal dominant; XLR = X-linked recessive; G6PD = glucose 6-phosphate dehydrogenase.
[1] Estimated frequency according to published figures.

probably as a result of a selective advantage against malaria. However, many of these mutations are novel, an observation which may be attributed to the isolation in which the Kurdish Jews were living. Multiple mutations were also identified in other diseases such as cerebrotendinous xanthomatosis and Tay-Sachs disease among Moroccan Jews but the reason is unknown [15, 16].

Frequent Disorders among Non-Jews (table 2)

From the structure of the non-Jewish population and its marriage habits, as described above, the expected cause for the high frequency of Mendelian disorders are multiple founder effects. In most of the disorders studied up to now a single mutation is indeed responsible for the high frequency of the respective disease. One common mutation was

Table 2. Relatively frequent Mendelian disorders among non-Jews in Israel (incomplete list)

	McKusick	Inheritance	Reference No.
Muslim Arabs			
Arthrogryposis[1]		AR	28
Cystic fibrosis[1]	219600	AR	(a)
Deafness[1]		Mi	29
Gaucher disease, neuronopathic	230800	AR	(a)
Glutaric aciduria I	231670	AR	(b)
Hydrocephalus, congenital	236600	AR	30
Krabbe disease[1]	255200	AR	31
Meckel syndrome	249000	AR	(a)
Metachromatic leukodystrophy	250100	AR	17
Methylmalonic aciduria	251000	AR	(b)
Non-ketotic hyperglycinemia	238000	AR	(c)
Nephrosis, congenital, Finnish type[1]	256300	AR	(a)
Niemann-Pick disease type A	273500	AR	(a)
Osteopetrosis	259700	AR	(a)
Thalassemia, beta	273500	AR	21
Tyrosinemia[1]	276700	AR	(b)
Bedouins			
Bardet-Biedl syndrome	209900	AR	24
Niemann-Pick disease type C[1]	257220	AR	(a)
Druzes			
Ataxia telangiectasia	208900	AR	(a)
Cerebrotendinous xanthomatosis[1]	213700	AR	18
Familial mediterranean fever	249100	AR	(a)
Hurler syndrome	252800	AR	22
Krabbe disease[1]	255200	AR	20
Mucolipidosis III[1]	252600	AR	(a)
Samaritans			
Usher syndrome type I	276900	AR	19

AR = Autosomal recessive; Mi = mitochondrial; (a) = personal observations; (b) = Dr. Orly El Peleg, personal communication; (c) = Dr. Avihu Bonneh, personal communication.

[1] The high frequency of the disorder is limited to one large pedigree or to a small geographic region.

identified for MLD in the Jerusalem area [17]. Cerebrotendinous xanthomatosis which is frequent in a Druze village is caused by a common mutation [18] and one frequent mutation was found to be responsible for the high frequency of cystic fibrosis in an Arab village [Abeliovich, pers. commun.]. A similar phenomenon appears to be true for the Usher syndrome in Samaritans [19] and for Krabbe disease in the Druze [20] since in each community a single common haplotype has been identified in all the carriers.

As expected from studies of other populations the high frequency of β-thalassemia is

due to many different mutations [21]. However, unexpectedly many different mutations caused diseases such as Hurler's disease or MLD in Galilee [22, 23]. In addition, haplotype studies indicate that three different mutations are responsible for ataxia telangiectasia which is frequent in Druze from Galilee [Shiloh, pers. commun.]. In the case of the Bardet-Biedel syndrome in the bedouins from the Negev the high frequency of the disease is caused by mutations in different genes [24]. These observations are very difficult to explain and further studies are needed for their clarification.

Screening for Genetic Disorders

The Ministry of Health sponsors a national program for the detection and the prevention of birth defects. This program includes newborn screening for phenylketonuria and hypothyroidism and screening of high risk populations. It comprises screening for Tay-Sachs disease carriers among Ashkenazi Jews (carrier frequency 1/30) and Moroccan Jews (carrier frequency 1/60) as well as prenatal diagnosis for chromosomal aberrations in women above the age of 35 years. In addition the triple test (α-fetoprotein, β-HCG and estriol) is offered to every pregnant woman and partly paid for by their health insurance. Molecular screening for fragile X is available to women on a private basis in some of the genetics centers.

Five mutations represent 97% of the mutations causing cystic fibrosis among the Ashkenazi Jews, therefore allowing for carrier screening in this population [25]. Up to now this screening has been paid by the individuals screened. Mutations causing cystic fibrosis in other communities are being studied and this will allow for carrier screening in those communities in the future.

The ultraorthodox Jewish Ashkenazi community does not see prenatal diagnosis as an acceptable means of prevention because of religious beliefs. Therefore, a special program for carrier screening prior to marriage has been started including the Tay-Sachs disease [26] and more recently cystic fibrosis. The purpose of this approach is to prevent mating of two heterozygotes.

Human Genetics in Israel

The Clinical Genetic Centers

Ten clinical genetic centers are located in the major hospitals affiliated to one of the four medical schools in the country, and there exists an additional center in a private hospital. All these centers include a genetic clinic and have laboratory facilities for tissue culture and cytogenetics and are able to perform routine cytogenetic examinations and prenatal diagnosis. Biochemical and molecular tests are usually carried out in specialized laboratories according to the type of the tests. Relatively common disorders are investigated in several laboratories (cystic fibrosis, fragile X syndrome) while for other disorders one specific laboratory is responsible for all tests performed in Israel (Duchenne muscular dystrophy, hemophilia, lysosomal storage disorders, phenylketonuria).

In addition to the clinical genetics centers, there are research units on specific areas of human genetics in all the universities as well as the Weizmann Institute for Sciences. All are in close contact with the genetics centers for diagnostic purposes and for research. Individuals active in the different fields of human genetics are grouped in the Israeli Society of Human Genetics, and many are members of the European Society of Human Genetics and the American Society of Human Genetics. A list of the members of the society as well as their research interests may be obtained upon request from the authors.

Training and Education in Medical Genetics

Since 1986 medical genetics is a medical specialty recognized by the Israeli Medical Association and the Ministry of Health. The 2 years' training program for medical genetics in an approved clinical genetic center is available for physicians certified in either internal medicine, pediatrics or obstetrics and gynecology. Board examinations are required to obtain the degree. In 1994, there were 23 board-certified medical geneticists in the Association of Medical Geneticists (14 pediatricians, 7 gynecologists and 2 internal medicine specialists) which is part of the Israel Medical Association. They are also members of the Israeli Society of Human Genetics, which comprises medical and nonmedical professionals in human genetics.

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