Application of medical genetics in Turkey

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Turkey is among the most populous countries of the world, and has a young population structure. The rate of consanguinity has been approximately 20-25% for the last 25 years. Various studies have shown that high consanguinity can be a contributing factor to the high incidence of some rare autosomal recessive diseases. Hemoglobinopathies are an important health problem, and Turkey also has one of the highest incidences of phenylketonuria in the world.

Training and education in medical genetics, established as a specialty since 1972, play an important role in the setting of genetic services and meeting public health problems.

Prenatal and preimplantation diagnosis is available for a variety of fetal diseases.

Key words: consanguinity, congenital malformations, population genetics, genetic services, medical genetics, population structure genetic, testing, genetic training.

Introduction

Turkey, with a population of about 70 million, lies at the crossroads between Europe and Asia. Inhabited since prehistoric times and experiencing massive migration throughout the land, the population is quite heterogeneous and is a challenge for genetic studies. There has been a strong emphasis on the eradication of infectious diseases and now inherited diseases have emerged as a public health issue. The field of medical genetics plays an important role in medical school curricula and in hospital practice. In this context, this paper intends to give an overview of the genetic diseases prevalent in Turkey and the organization of available genetic services and training in medical genetics.

Population Structure

Anatolia was dominated by Seljuqs for almost two centuries (1071-1243) and later became the core of the Ottoman Empire, which ruled in Europe, the Middle East and Africa for almost six centuries. At the end of the First World War, the Ottoman Empire dissolved and in 1923 the Turkish Republic was proclaimed to give the State a democratic and secular status.

Turkey has an area of 774,815 square kilometers and borders with Greece and Bulgaria in the Thrace and with Syria, Iraq, Iran, Georgia, Armenia and Nahcivan (Azerbaijan) in the Anatolian part.

According to the census of 2000, the population was 67.8 million[1]; it is estimated around 73.7 million for 2006[2]. Citizens of Turkey are predominantly Muslim (98%). Turks predominate ethnically. Kurdish, Arabic, Greek, Circassian, Georgian, Armenian and Jewish communities of varying sizes complete the mosaic of the rich and complex culture of the Turkish society. The official language is Turkish. Some general facts about the population are given in Table I.

Turkey has a young population structure as a result of the high fertility and growth rate. Nearly one-third (29.1%) of the population is under 15 years of age, whilst the proportion of 65+ years accounts for only 6.9% according to the Turkish Demographic and Health Survey (TDHS) 2003[3]. Recent decades have witnessed dramatic declines in fertility rates. In the early 1970's, the total fertility rate (TFR) was around five children per woman, versus TDHS 2003 which shows a decline in TFR to 2.23 per woman[3].

Table I. Facts about Turkey[3]

Population under 15 years	29.1%	
above 65 years	6.9%	
Total Fertility Rate (TFR)	2.23	
Antenatal care visit	81%	
Delivery at a health facility	78%	
Median age at first birth (years)	22	
Teenage (15-19) pregnancy	8%	
Children born to women over 35	11.7%	
Infant mortality rate	(per thousand)	29
Child mortality rate	" "	9
Under 5 mortality rate	" "	37
Perinatal mortality rate	" "	24
Median no of years of schooling (years)		
Males	4.8	
Females	4.3	
Life expectancy (years)[4]		
Males	66	
Females	71	

There is a lack of accurate information about adult mortality. According to reported causes of death, the main causes are cardiovascular diseases, cerebrovascular accidents, malignancies and accidents[4]. In contrast to adult mortality, data on child mortality has been available for a long time from a series of fertility surveys. The infant mortality rate in the late 1950's was around 200 per thousand live births. It declined to 29 per thousand live births according to the TDHS 2003. Fifty-nine percent of infant deaths occur during the neonatal period. Child mortality and under-five mortality are 9 and 37 per thousand, respectively. The perinatal mortality rate is estimated as 24 per thousand in TDHS 2003[3]. Life expectancy in Turkey has been estimated as 69 years for males and 74 years for females[4].

Primary education in Turkey starts at age six and continues for eight years. Although basic education has been compulsory, there is a gap in educational attainment between males and females. The median number of years of schooling for men is 4.8 and for women is 4.3. Nevertheless, there has been a substantial increase over time in educational attainment of both men and women. For example, the median number of years of schooling is 9 years for males aged 20-24 years compared with 4.9 years in the 40-44 years of age group[3].

Overall, 81% of mothers had at least one antenatal care visit with trained health personnel and 78% of all babies were delivered at a facility, according to TDHS 2003. Public sector health facilities were preferred (65%) to private sector (13%), and one-fifth of the births were home deliveries[3]. The median age at first birth was 22 years and the teenage (15-19) childbearing was around 8%. The percentage of children born to women over 35 years of age was 11.7%[3].

Consanguineous Marriages

Turkey has a high rate of consanguineous marriages. Quinquennial TDHS showed that the rate of consanguinity has been stable at 20-25% since 1983. Approximately 70% of all consanguineous marriages are first-cousin marriages, and usually between the uncle's children[5].

Although it is generally observed that infant mortality is high in consanguineous families, this high mortality rate can not solely be explained by recessive disease, since there are many socio-economic factors that affect infant mortality. In a study where 1988 TDHS data was used, when factors such as educational level and settlement place were controlled, it was shown that consanguinity plays a role in high infant mortality and fertility in Turkey[6].

Various studies in Turkey revealed that parental consanguinity in autosomal recessive diseases shows a spectrum from 100% to near Turkey's average rate of consanguinity. The highest figures belong to propionic acidemia (100%) and Friedreich's ataxia (96.4%) and the lowest to familial Mediterranean fever (FMF), which is one of the more common autosomal recessive diseases in Turkey. This shows that high consanguinity can be a contributing factor to high incidence of some rare autosomal recessive diseases[7].

Health Care System in Turkey

The Ministry of Health (MOH) is officially responsible for designing and implementing health policies and delivering health care services nationwide. In addition, other public sector institutions and non-governmental and private organizations contribute to providing mostly curative health services.

The present network of Health Centers and Health Houses was formed on the basis of "Legislation for the Socialization of Health Services". The simplest element of the socialized health services is the Health House, which

serves a population of 5,000-10,000. Health Centers mainly offer integrated, polyvalent primary health-care services.

Abortion is legal on request by women up to the tenth week of pregnancy. In addition, in cases at risk for fetal diseases and anomalies, abortion is legally permitted and has been carried out up to 25 weeks of pregnancy. Prenatal diagnosis has been available for a variety of fetal diseases and preimplantation genetics is newly emerging.

Education and Training in Genetics

The first genetic units in Turkey were established in 1964 at Hacettepe Medical Faculty, Ankara, and Cerrahpaşa Medical Faculty, İstanbul. In the beginning, all genetic units were located in Departments of Pediatrics and the focus was mainly on clinical and cytogenetics. After the 1980's, establishment of Medical Biology Departments in Medical Faculties led to the development of molecular genetics.

Since 1972, the discipline of medical genetics has been recognized as a two-year medical specialty. In 2003, because of the insufficiencies of this two-year program, the duration was increased to four years. Now this specialty is organized under the clinical sciences, at the same time being a subspecialty of pediatrics with a training period of three years.

All medical school curricula contain undergraduate courses in basic genetics, either specific or as a part of biology lecture. PhD programs in Medical Genetics are available at some universities in the Departments of Pediatrics under the administration of Institutes of Child Health. PhD programs in Medical Biology are offered under the doctoral program of Institutes of Health Sciences. The Society of Medical Genetics was founded in 1992. In addition, there are some other local societies and patient groups for specific disorders.

Clinical Cytogenetics

There are approximately 70 cytogenetics laboratories in Turkey in the private sector and at universities. Until 1996, no guidelines or standardization for clinical cytogenetic practices existed. A quality assurance system is now established which functions on a volunteer basis.

Since 1998, there has been a licensing procedure through the MOH both for cytogenetics and molecular genetic testing laboratories. About 35 laboratories are currently registered in this system.

Preimplantation Genetic Diagnosis (PGD) has been used for chromosomal and some molecularly diagnosed diseases such as thalassemia since 1999[8]. There are presently at least five laboratories performing this procedure.

Molecular Genetic Testing

Around the 1980's, the widespread technology transfer for diagnostic methods was very influential in the development of genetic tests for monogenic diseases. Research results from molecular pathology studies of these diseases eventually led to diagnostics both at university hospitals and in private laboratories. Genetic testing is used mostly for confirmation of diagnosis and also for carrier testing and prenatal diagnosis. In addition to hemoglobinopathies, a high volume of genetic tests are done for phenylketonuria (PKU), cystic fibrosis (CF), Becker/Duchenne muscular dystrophy (B/DMD), spinal muscular atrophy (SMA) and FMF.

A voluntary National Quality Assurance (QA) System (UMGEKA) for genetic testing was created in 2004 through an international grant from Istituto Superiore di Sante of Italy to the Department of Medical Biology at Hacettepe University. The Turkish Society for Medical Genetics has been a partner in the coordination of this scheme. Quality assurance is being done for the applications in polymerase chain reaction (PCR) technology and DNA variation analysis in CF, FMF and factor V Leiden. Genotyping results as well as reports that are issued from the labs have been included in the evaluation scheme. There are two private and 18 university-based laboratories that have subscribed to the QA network. Besides this national scheme, EMQN (European Molecular Quality Network) and CF European Network have also been used effectively by some genetic testing labs.

Since Hacettepe Medical Center is a referral center especially for pediatric cases with rare genetic diseases, a DNA/Cell Bank was established in 1994 to create an infrastructure

for genetic/genomics research in this area. The establishment of this Biobank was through a World Bank/TTGV (Technology Development Fund of Turkey) grant. Since 1995, the Bank (http://www.dna.tubitak.gov.tr) categorized as an infrastructure has been supported by TUBITAK. The main mission of the Bank is to create a clinical data base and a biorepository of families with rare genetic disorders.

As everywhere else in the world, gene technologies are accompanied by ethical and legal concerns. Even though there is a licensing procedure through the MOH for genetic testing labs, there is not yet a laboratory accreditation and certification system for genetic testing. There are no national laws or legal guidelines specific for biobanks. Generally, international guidelines are followed for genetic studies, for example informed consent is required from subjects for biobanking and for genetic testing. Ethical review is required for all projects. International documents such as Helsinki Declaration, UNESCO Declarations, and relevant European Community directives are all consulted and used in the application for review procedures.

SPECTRUM OF GENETIC DISEASES

Congenital Malformations and Down Syndrome

According to a study conducted in 22 university hospitals, 21,907 births were evaluated and birth prevalence of congenital malformations was found as 36.5 per thousand[9]. Despite some methodological setbacks, this hospital-based study is the best possible study that can be done in Turkey since an important fraction of all births take place out of a health facility and are not registered.

According to this survey, Turkey has a very high prevalence (30 per 10,000) of neural tube defects (NTD) when compared with the EUROCAT registries. One explanation for the high prevalence of NTD in Turkey would be the high frequency of 677 CT and 1298 AC polymorphisms in the MTHFR gene, but studies did not show an increased frequency of these polymorphisms when compared with the control group[10,11]. High frequency of NTD may indicate the role of folic acid and/or other environmental or genetic factors.

The incidence of Down syndrome was found as 1.2 per 1,000 live births in the same survey. The age of the mother was above 35 in 51.9% of the babies with Down syndrome. According to 1993 TDHS, which covers the same period, the percent of mothers above 35 years of age at birth was 9.2[12]. This figure was found as 11.7 10 years later in the 2003 TDHS[3].

Inherited Metabolic Diseases and Newborn Screening

Prevalence of different recessive metabolic diseases in Turkey is high compared to figures from different countries. In a survey by using amino acid analysis, a total of 225 cases with 21 different hereditary metabolic diseases were detected in 6,050 high-risk infants for metabolic disorders. Prevalence was found as 3.8%, and PKU, maple syrup urine disease, methylmalonic acidemia, hereditary urea cycle defects and galactosemia were the most commonly seen metabolic diseases in this group. There was parental consanguinity in 72% of the 225 detected cases, which is three times higher than the prevalence of consanguineous marriages in Turkey[13].

In another survey in Hacettepe Ihsan Doğramacı Children's Hospital, selective screening of at risk children for inborn errors of metabolism by tandem mass spectrometry showed the prevalence of different metabolic disease as 5.1%[14].

A nationwide "Newborn Screening Program" was started in 1986 for PKU and is now a part of the national child health program and covers all the metropolises of the country. Birth prevalence of hyperphenylalaninemia was found as 1:4192 and PKU as 1:5049[15]. Turkey has the highest PKU prevalence at birth, next to Ireland. The screening for congenital hypothyroidism (CH) was added later to the program; its coverage is not as large as for PKU. The incidence of permanent CH was found as 1:2659[16]. Screening of biotinidase deficiency was started among newborns in İstanbul. The prevalence at birth of profound and partial deficiency (combined) of biotinidase was found as 1:11763[17]. Galactosemia deficiency was 1:23775[18].

Hematological Disorders

Like in most countries in the Mediterranean basin, hemoglobinopathies are an important health problem in Turkey. Since 1958, various

studies have been performed on this topic. In 1993, a law was issued entitled "Fight Against Hereditary Blood Diseases Especially for Thalassemia and Hemoglobinopathies".

In 2000, the Turkish National Hemoglobinopathy Council (TNHC) was created to combine all centers, foundations and associations into one organization coordinated by the MOH. The TNHC comprises seven subcommittees dealing with registration, education, screening, prenatal diagnosis, conventional treatment, bone marrow transplantation and social issues. In 2001, the MOH and the TNHC made an inventory of all recorded patients with thalassemia and abnormal hemoglobin in Turkey. In 2003, the hemoglobinopathy scientific committee was set up, a guidebook was published and a national hemoglobinopathies control program (HCP) was started in the high-risk provinces[19].

The MOH and the TNHC have started to register the results of screening from 16 different cities, and have recorded the average frequency of the β-thalassemia trait as 4.3%. The highest prevalence of the β-thalassemia trait (13.1%) was found in the Antalya region and of the HbS trait (10%) in Adana[19].

Beta-Thalassemia

The frequencies of mutations do not reveal a significant region-specific distribution pattern. DNA studies indicate that β-thalassemia mutations are very heterogeneous in Turkey. Seven of the most common mutations account for 67% of the total β-thalassemia alleles in the Turkish population. The most prevalent mutation is IVSI-110, with a frequency of 40%, which is close to the figure found in neighboring countries. Beta-thalassemia with increased HG A_2 and low HbF was first reported in Turkish patients. Later, these patients were found to have the IVSI-6 mutation, which is the second most frequent mutation, with a frequency of 15%[20]. Many β-thalassemia mutations are very rare and are confined to a single family. The rate of consanguinity in families with β-thalassemia was found as 65% in this study and 9% of 133 consanguineous couples were found to be genetic compounds[20]. In another survey, the consanguinity rate of patients with thalassemia in southern Turkey was found as 22.2%. The consanguinity rate in the same area was 10.2% and the difference was found statistically significant ($p<0.0001$)[21].

Since 1990, prenatal diagnosis of hemoglobinopathies in Turkey has been performed using DNA methods.

Neurodegenerative Disorders

During a period of five years, 300 patients with sphingolipidoses were diagnosed at Hacettepe Medical Faculty, Department of Pediatrics, Neurology Unit. Thirty-one percent (31%) were diagnosed as metachromatic leukodystrophy (MLD), 20.7% as Sandhoff disease (SHD), 5% as Tay-Sachs disease (TSD), 11.7% as GM1 gangliosidosis, 0.3% as Fabry disease, 21.7% as Krabbe disease and 9.6% as Gaucher's disease. In the study group, more than 80% of the parents were consanguineous. The combined incidence of sphingolipidoses was calculated as 4.6 per 100,000 live births in this study. The calculated incidences were 1.43, 0.95, 1, 0.23, 0.54, 0.45, and 0.015 per 100,000 live births for MLD, SHD, Krabbe, Gaucher, TSD, GM1 gangliosidosis and Fabry diseases, respectively[22].

Fragile X Syndrome

Fragile X syndrome is a common cause of inherited mental retardation in males. The frequency of fragile X syndrome among male patients with mental retardation of unknown etiology was found as 3% in Turkey by using PCR and Southern blot analysis[23]. A new noninvasive method for screening purpose was investigated. By using FMRP antibody test on hair root sample, which was developed by Willemsen et al.[24], high-risk children were screened and it was shown that this noninvasive test is a useful tool to identify fragile X patients in schools for children with learning disabilities, in institutes for the mentally handicapped and in sheltered houses. Between 1995-2005, in Hacettepe University Department of Pediatrics Genetic Unit, 1,600 molecular tests were performed with the clinical diagnosis of fragile X syndrome. Among them, 107 new families were diagnosed. In the beginning, the mean age of diagnosis was eight years. However, this figure decreased to 6.9 years at the end of this period. There were 118 male and 8 female patients in these 107 families. Prenatal diagnosis was performed in 15 (14%) cases. Three cases with fragile X premutation were diagnosed among one fragile X syndrome

family member with the history of premature ovarian failure (POF) and two cases with POF with no history of fragile X syndrome[26].

Deafness

The etiology of congenital or prelingual deafness is heterogeneous in Turkey. At least half of all affected are believed to have genetic alterations. The most common form of inheritance in genetic deafness in Turkey is autosomal recessive, for which a high level of heterogeneity should also be expected. Mutations in GJB2, encoding connexin 26, are the most commonly identified pathology in probands with congenital or prelingual nonsyndromic autosomal recessive deafness. Biallelic mutations have been identified in 20% of probands. The most common allele is 35 del G followed by del E 120[27].

The 35 del G mutation frequency is not homogeneously distributed in Anatolia, where a single origin has been demonstrated for this mutation. It is a hypothesis that a part of Anatolia could be the land where this mutation originated due to the ancient nature of this mutation and geographic significance of Anatolia in ancient times[27]. Results of another study demonstrated that 35 del G might have been introduced to the gene pool of the Eastern Black Sea region with a specific ancestral haplotype[28]. Its carrier frequency in individuals with healthy hearing was found to be 1.0%, 1.17% and 2.6% in different studies in Turkey[29-31].

The consanguinity rate among the parents of deaf probands was found to be high when the screening of the GJB2 gene was negative[29]. The role of consanguinity appears to be more important for the uncommon recessive deafness alleles in Turkey[32].

Issues in Medical Genetic Applications

There are some difficulties in the development of genetic tests arising from the genetic make- up of the population. In some diseases such as CF, the mutant alleles carry private mutations. For example, in CF, the most common mutation in Europe and the western world, deltaF508, is seen in only 23% of the mutant alleles[33]. Testing for six mutations, one can only type 36% of the mutant alleles. On the other hand, for example in FMF, by testing for four mutations, 75% of the alleles can be typed[34]. Hence, genetic testing for FMF is applied widely. However in CF, haplotyping is done in many families requesting prenatal diagnosis. In our population, consanguinity was found in about 50% of CF and PKU families. This sometimes leads to non-informative meiosis and haplotyping results cannot be used for determination of allele segregation. Increase in the number of genetic markers used may solve the problem in some families at the expense of increasing the cost of testing. International commercial kits that are being developed for genetic tests cannot find wide application in our population for some genetic diseases since multiple founding effects lead to heterogeneous mutation spectra with different allele frequencies than the European populations. Sequencing is still an expensive technology in Turkey due to importation of all reagents and kits. Thus, even though it is used for research purpose, it has not yet become a widespread routine method for genetic testing.

Although social security and government pension funds cover the cost of genetic testing, many families are devoid of social security. Furthermore, in some families where haplotyping is necessary, not only the proband but the entire family may need to be tested, complicating the pricing policy and also reimbursement.

As a general rule, genetic counselling is given to patients before and after the testing phase. However, there is no established gold standard for this practice. Different centers employ different practices. At some centers, medical staff from the Department of Medical Genetics see all the patients for genetic counselling, while at other centers the referring doctor also provides genetic counselling.

Although some local support groups for patients are present, such as for Down syndrome or PKU, there is a general lack of organizations to support patients, families and communities. Despite such issues, medical genetics and applications of genomics are being increasingly used in the public health arena for diagnosis of genetic disorders.

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