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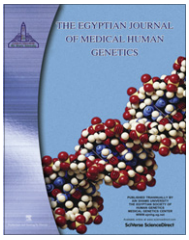

ORIGINAL ARTICLE

Profile of genetic disorders prevalent in northeast region of Cairo, Egypt

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Abstract As clinical geneticists, we recently reviewed our 43 years experience in an attempt to represent the frequency of genetic disorders in the Division of Genetics at Pediatric Hospital, Faculty of Medicine, Ain-Shams University, Cairo, Egypt, during the period from 1966 to 2009.

All patients (from birth up to 18 years) suspected of having a genetic disorder were referred to the Genetics Clinic in the same hospital. 28,689 Patients were proved to have genetic disorders after full investigations among 660,280 children attending the Pediatrics Hospital which constituted 4.35% or 43.5/1000. Neurologic disorders were the most common (31.38%) followed by hematologic disorders (18.48%), chromosomal abnormalities (11.51%), fetal, neonatal and infant deaths (6.56%), special senses (5.82%), inborn errors of metabolism (4.24%), endocrine disorders (3.87%), skeletal disorders (3.17%), genito-gonadal anomalies (3.10%), neuromuscular disorders (2.86%), syndromes (2.08%), genodermatoses (1.92%), cardiac disorders (1.47%), gastrointestinal tract anomalies (1.37%), renal anomalies (0.26%), connective tissue disorders (0.26%), respiratory defects (0.22%), vascular anomalies (0.21%), and immunologic disorders were the least common (0.19%).

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Our study showed a high prevalence of genetic diseases among Egyptians which are nearly the same in the other studies in Egypt and are rapidly becoming a major public health concern. Establishment of national or hospital based registers for genetic disorders is very important to know the magnitude of the problem so that the national program for the prevention of genetic disorders can be implemented.

1. Introduction

Hereditary diseases and congenital malformations have been reported to affect 2–5% of all livebirths [1]. The British Columbia Health Surveillance Registry shows that before the age of 25, at least 53 out of 1000 liveborn individuals can be expected to have a disease with an important genetic component. This comprises 3.6 single gene disorders per 1000, 1.8 chromosomal disorders per 1000, 46.4 multifactorial or part-genetic disorders per 1000 and 1.2 genetic type of uncertain disorders per 1000. In this analysis, congenital anomalies were included only if a multifactorial or part-genetic etiology had been established, but if all congenital abnormalities were included the cumulative figure rose to more than 79 per 1000 livebirths [2]. Available evidence suggests that congenital and genetic disorders are responsible for a major proportion of infant mortality, morbidity, and handicap in Arab countries [3].

Egypt was classified as one of the more developed Arab countries according to categorization of the Committee of Development Policy (CDP) [4]. Egypt, one of the main civilisations of the ancient world, has a history that goes back more than 5000 years. It enjoys a distinguished geographical location at the juncture of the ancient world continents of Africa, Asia and Europe. It has always been a place of inter-civilization and reactivation between the East and West as well as the North and South. It was also the crossing road of the heavenly religious of the World. It is about 1 million (m) km^2 and is located in the north-eastern corner of Africa and Southwestern Asia [5].

Egypt is divided into three main geographical regions: the Nile Vally, the Eastern desert and the Western desert. The Nile Vally represents 4% from the area of Egypt and is divided into Upper Egypt region, Lower Egypt region, Suez Canal region and Northern coast lakes region. It is also divided into 27 governorates.

Cairo, the most populous Arab country, is the glorious capital of Egypt. Cairo's population rose to more than 18 millions (the highest population density in Egypt). Egyptians are mainly descended from ancient Egyptian Society (94%). Ethnic minorities in Egypt include, Nubians, Berbers, Bedouin Arabs, Beja and Dome (4%) and others (2%) [5].

1.1. Demographic features of Egypt

Egyptian population according to census 2006 hit 76.5 million, around 3.9 million are living abroad. One Egyptian baby is born every 23 s, birth rate 22.94 births/1000.

In Egypt, birth rates among women over 35 years have been almost twice (65/1000) as often as those occurring among women of the same age in USA (33.7/1000) [6]. Old maternal age is associated with aberrant genetic recombination or similar genetic mechanisms together with one or more environmental factors [7]. Moreover, risks to the fetus could have been modulated by the effects of aging on the mother's general or reproductive health [8]. Other investigators have suggested that physiologic changes associated with aging and or environmental factors may increase birth defects [9,10]. In Egypt advanced maternal age has significant role in causation of repeated abortions [11].

1.2. Consanguinity among Egyptians

While ancient Egyptians of the reigning dynasty (1580–1350 BC) favored marriages of brother and sisters among the royal family, current laws of the Egyptian society emphasize the value of outbreeding and prohibit marriages between relatives closer than first cousins.

Consanguineous marriage is still high in Egypt (35.3%) especially among first cousins (86%). However, the frequency varies by region. It is higher in Sohag (42.2%) and Cairo (36.1%) than in Assuit (21.7%). Also it was higher in rural areas (59.9%) than in semiurban and urban areas (23.5%) and (17.7%), respectively [12]. This increase in consanguinity rate is due to the fact that many families prefer marriage among first cousins to preserve family structure, links and provide social, economics and cultural benefits. Many Egyptians believe that there may be more compatibility and less tendency to divorce between husband and wife from a family. This favored the appearance of complex phenotypes of genetic disorders which result in difficulties in phenotype classification.

1.3. Effect of inbreeding on the genetic morbidity

This high consanguinity rate is reflected on higher risk of infant and child mortality in Egypt. There was 30% and 19% higher risk of infant mortality among close and remote consanguineous couples, respectively. Similarly the risk of child mortality is found higher among close consanguineous couples by more than 50% and among remote consanguineous couples by 27% as compared to non-consanguineous marriage [12,13].

Consanguinity also increases birth prevalence of severe recessive disorders, appearance of new autosomal recessive syndromes, multiple genetic disorders in the same individual or same family and homozygosity for autosomal dominant disorders. Consanguinity also increases the risk of birth of a child with a malformation [14].

Several genetic disorders have been reported to be frequent among Egyptians [4,15]. This observation could be the result of an ascertainment bias resulting from a possible higher awareness of the hereditary disorders in Egypt.

2. Aim of the study

As clinical geneticists, we recently reviewed our 43 years experience in an attempt to represent the frequency of genetic

disorders in the Division of Genetics at Pediatric Hospital, Faculty of Medicine, Ain-Shams University.

This faculty was constructed in 1947, to be the third Medical school in Egypt. Ain-Shams University Hospitals contain 3200 beds. The educational hospitals and specialized clinics serve 1 million patient/year at the outpatient and inpatient departments [16].

The Pediatric Hospital is located in the northeast section of Cairo. It has a good reputation and high standard of health care so nearly all patients in this area attend this hospital. Also patients come nearly from all governorates to receive good health care in this hospital (Fig. 1) [17]. The Genetics Clinic present in this hospital is constructed in 1964, it is the first Genetics Clinic not only in Egypt but also in all Arabic countries. It offers counseling to patients with partial and total genetic diseases. Counseling is available for patients of both sexes and all ages, from public and private health centers and several medical specialties. So the frequency of genetic disorders in this hospital will represent to a great extent the frequency in the general population. This will greatly help in determining the size of the problem in Egypt and increase health authorities, physician and public awareness of genetic disorders.

3. Subjects and methods

The sample size studied was 660,280 patients attending the Pediatric clinic, Ain-Shams University hospital (from birth up to 18 years), during the period of the study from 1966 to 2009. All children suspected of having a genetic disorder were referred to the Genetics Clinic in the same hospital. Charts of children with proved genetic disorders were extracted (28,689). We studied the frequency of genetic disorders in the genetic clinic as well as in the Pediatric Hospital.

Patients selection was based on history (personal, medical, family and developmental), pedigree analysis clinical examination of all body systems and investigations related to various diseases, e.g. karyotype, FISH, molecular study, metabolic screening, enzyme assay, psychological evaluation, IQ scoring, X-rays, ultrasonography, echocardiography, ECG, EMG, nerve conduction velocity, histopathology, brain imaging, etc.

In addition to depending on retrospective surveys of medical records in Genetics Clinic to ascertain genetic cases, we depended also on various studies published on national and international journals on patients attending our hospital.

We used the outpatients index files to identify diagnosed cases of albinism referred from the dermatologic and

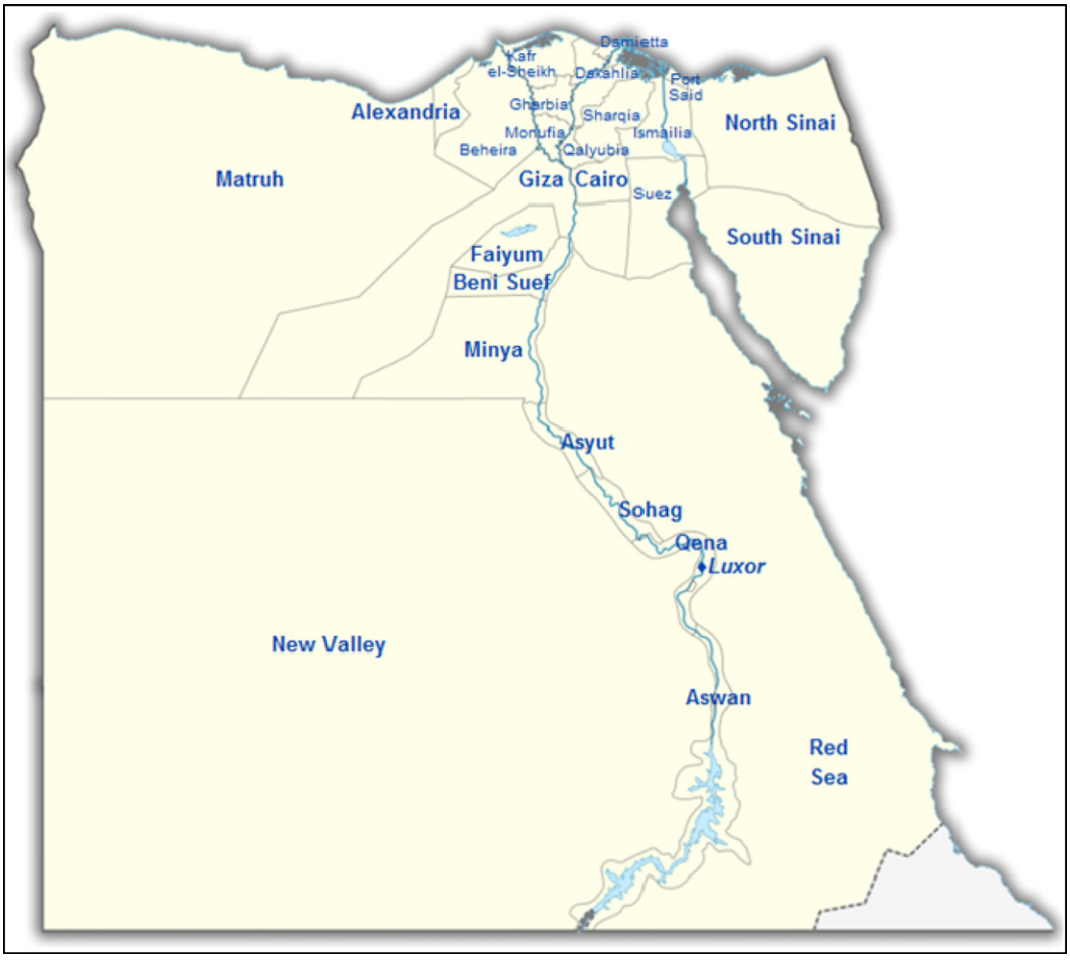

Figure 1 Map of Egypt [17].

ophthalmologic departments with different genodermatoses over 43 year period. We used specifically designed data collection protocol forms to extract epidemiological and clinical data from the patients medical records. These were entered into a computer database and analyzed using standard statistical software (Standard Package for Social Sciences version VII).

4. Results and discussion

28,689 Patients were proved to have genetic disorders after full investigations among 660,280 children attending the Pediatrics Hospital which constituted 4.35% or 43.5/1000. Neurologic disorders were the most common (31.38%) followed by hematologic disorders (18.48%), chromosomal abnormalities (11.51%), fetal, neonatal and infant deaths (6.56%), special senses (5.82%), inborn errors of metabolism (4.24%), endocrine disorders (3.87%), skeletal disorders (3.17%), genito-gonadal anomalies (3.10%), neuromuscular disorders (2.86%), syndromes (2.08%), genodermatoses (1.92%), cardiac disorders (1.47%), gastrointestinal tract anomalies (1.37%), renal anomalies (0.26%), connective tissue disorders (0.26%), respiratory defects (0.22%), vascular anomalies (0.21%), and immunologic disorders were the least common (0.19%). (Table 1 and Fig. 2).

Table 1 Demonstrate frequency of genetic disorders among 28,689 patients attending the Genetics Clinic and 660,280 patients attending the Pediatrics Hospital. It is a representative of prevalence of genetic diseases in Egypt to a great extent.

Categories	No.	% In Genetics Clinic	% In hospital
Neurologic disorders	9005	31.38	1.36
Hematologic disorders	5304	18.48	0.80
Chromosomal abnormalities	3376	11.51	0.51
Fetal, neonatal and infant deaths	1924	6.56	0.29
Special senses	1708	5.82	0.26
Inborn errors of metabolism (IEM)	1244	4.24	0.19
Endocrine disorders	1136	3.87	0.17
Skeletal disorders (osseous and chondral)	930	3.17	0.14
Genito-gonadal anomalies	908	3.10	0.14
Neuromuscular disorders	823	2.86	0.12
Syndromes	610	2.08	0.09
Genodermatosis	553	1.92	0.08
Cardiac disorders	432	1.47	0.07
Gastrointestinal tract anomalies	403	1.37	0.06
Renal anomalies	75	0.26	0.01
Connective tissue disorders	75	0.26	0.01
Respiratory defects	64	0.22	0.01
Vascular anomalies	62	0.21	0.01
Immunologic disorders	57	0.19	0.01
Total	28,689	100.00	4.44

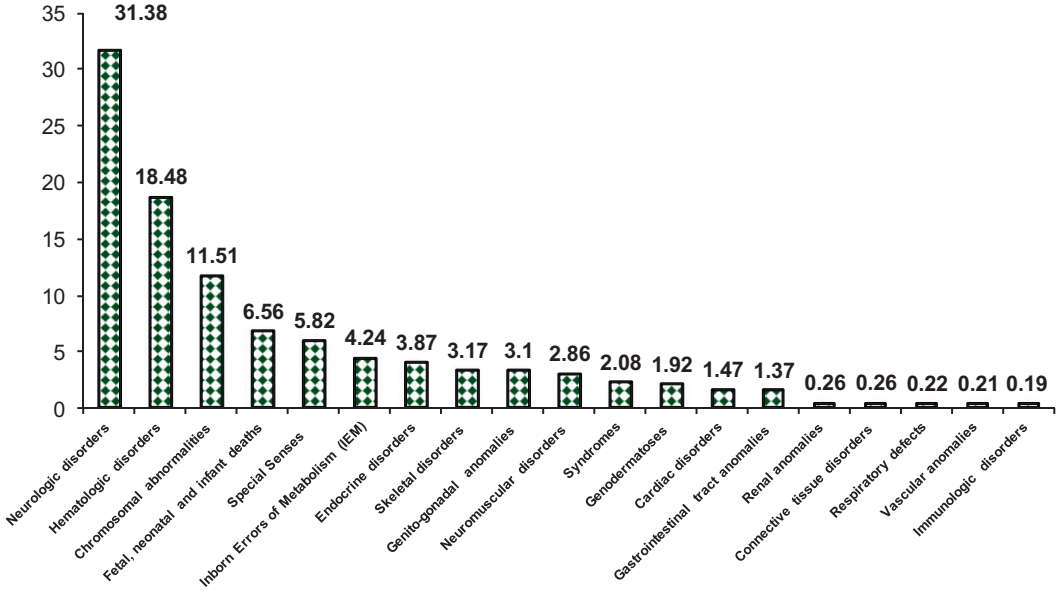

Figure 2 Frequency of genetic disorders among 28,689 patients attending the Genetics Clinic and 660,280 patients attending the Pediatrics Hospital.

In another study done in Egypt, but in another locality, (Giza, upper Egypt), the genetic counseling group represented the highest percentage (17%), followed by neurologic disorders (9.5%), chromosomal disorders (9.3%), mental retardation and behavioral disorders (8.1%), neuromuscular disorders (5.7%), metabolic disorders (5.3%), endocrine disorders and skeletal disorders (4.9%) each. Dermatological and renal disorders represented the least common referral disorders (1.1% and 0.5%), respectively. In 27.9% of this study the etiology was unknown [15].

A considerable variation in the frequency of various genetic/malformation disorders had been previously reported in different Arab countries [3,18,19]. This variability could be due to different classifications used in different studies.

4.1. Neurologic disorders

They constituted 31.38% of patients attending the Genetics Clinics and 1.36% in the Pediatric Hospital. Mental deficiency was the commonest disorder and neuroectodermal disorders were the least common (Table 2).

Mental retardation: Mental retardation constituted 46.48% of neurologic disorders among our patients. As regards the etiology of mental retardation, prenatal causes was detected in 32.6% of cases, perinatal in 18.2%, postnatal in 3.7%, metabolic causes in 22.7% and 22.8% were unclassified. Genetic causes of mental retardation were more common (80.4%) than non-genetic causes (19.6%). Among the genetic causes, chromosomal aberrations (33%), followed by inborn errors of metabolism (22.6%) were among the most common causes [20]. A prevalence of Fragile X syndrome among Egyptian males was reported as 0.9/1000 or 6.4% among mentally subnormal males [21].

Convulsive disorders: In our study, inherited epilepsy was detected in 22.22% of our patients with neurologic disorders. A study to evaluate the state of zinc (Zn), copper (Cu), magnesium (Mg) and manganese (Mn) in different convulsive disorders affecting children and to evaluate the effect of anticonvulsant therapy on these trace elements was conducted by Shawky et al. [22]. Results revealed that serum Cu was higher in epileptics whether treated or not than controls ($p < 0.05$).

Table 2 Genetic varieties of neurologic disorders prevalent among Egyptians.

Category	Genetics Clinics	
	No.	%
Neurological disorders	9005	100.00
Mental deficiency	4186	46.48
Inherited epilepsy	1977	22.22
Craniocerebral anomalies	1366	15.35
Microcephaly	581	6.53
Hydrocephalus	210	2.36
Craniosynostosis and other cranial anomalies	116	1.30
Unidentifiable	459	5.16
Neural tube defects	910	10.23
Neurodegenerative disorders	468	5.26
Neurocutaneous disorders	98	1.10
Neurofibromatosis	55	0.62
Sturge weber syndrome	24	0.27
Tuberous sclerosis	19	0.21

As regards serum Zn, Mg and Mn, there was no significant difference between epileptics compiled as one group and controls ($p > 0.05$).

Type, etiology and frequency of seizures had no effect on serum level of the studied trace elements. Interval from last seizure to sampling had effect only on serum Mn which was lower when sampling was done on the same day and one or two days after the last seizure ($p < 0.05$). There was no correlation between duration of therapy or plasma level of phenobarbital and phenytoin on one hand and serum level of Zn, Cu, Mg or Mn on the other hand ($p > 0.05$).

Shawky et al. [23] estimated the serum haptoglobin level (using radial immune diffusion) in 32 epileptic children (10 with familial and 22 with non-familial epilepsy) and compared to its level in 14 healthy age and sex matched children and 10 relatives of familial epilepsy. Serum haptoglobin was found to be significantly lower in familial epileptics and the group of relatives. There was also an insignificant decrease of haptoglobin in relatives than in healthy children, while non-familial epileptics had higher values than healthy children, familial epileptics and their relatives. Lower values of haptoglobin in familial epileptics which might be inherited would suggest possible relation to the etiology of epilepsy; while higher values in non-familial epileptics could reflect an acute phase reactant which might act in the pathogenesis of epilepsy.

Craniocerebral anomalies: Craniocerebral anomalies constituted 15.35% of neurologic disorders and included:

Microcephaly, constituted 6.53% of neurologic disorders among our patients. Isolated microcephaly was detected in 3.4%. Forty-eight percent of cases were part of a syndrome. Environmental causes were detected in 17.2% and 6.8% were manifested in cases of inborn errors of metabolism (IEM) [24].

Hydrocephalus, constituted 2.36% of the neurologic disorder group. Forty-four Egyptian hydrocephalic infants and children were included in a study to detect the genetic aspects and possible modes of inheritance in different types of hydrocephalus. The study revealed that 37 cases had congenital hydrocephalus, (13 with congenital aqueductal stenosis (CAS), eight with Arnold Chiari malformation, five with congenital toxoplasmosis, one with Dandy walker malformation, one with Aneurysm of Galen, one with arachnoid cyst and eight with undefined causes). Seven had acquired hydrocephalus (four postmeningitic and three posttraumatic). Male predominance (1.6:1) was noticed in congenital hydrocephalus. In CAS, increased male incidence (8/13) and positive family history (4/8) with affected males on the maternal side might suggest X-linked recessive trait. On the other hand, consanguineous mating was detected in 46% of cases with congenital hydrocephalus that may give some impression of the role of autosomal recessive mode of inheritance. First born infants were more frequently affected (38%) than in subsequent pregnancies (19%). History of mental retardation in sibs of three cases with congenital hydrocephalus was suggestive of limited expression of the gene. Maternal toxoplasmosis was the only environmental antenatal factor involved in the development of hydrocephalus while the influences of maternal age, nutrition, and medications were not impressive [25].

Craniosynostosis, constituted 1.30% of neurologic disorders group. Craniosynostosis is a heterogeneous condition characterized by premature closure of sutures. A study was conducted on 50 patients in our clinic with craniosynostosis to detect the etiology. Patients were classified into primary and

secondary craniosynostosis according to history, clinical examination and investigations. Primary craniosynostosis included 30 patients and was further subdivided into three subgroups according to the shape of the skull and sutures involved; subgroup I "Oxycephaly" included 56.7% of patients: 76.44% of them with primary isolated oxycephaly, 5.9% of cases were associated with Arnold Chiari malformation, 11.76% with Crouzon syndrome and 5.9% with Apert syndrome; subgroup II "scaphocephaly" included 33.3% with primary isolated scaphocephaly; subgroup III "heterogeneous" included 10% of cases out of whom 33.3% had plagiocephaly, 33.3% had brachycephaly and 33% had oxy-scaphocephaly. Forty percent of the primary craniosynostosis cases had mental retardation and 86.7% were sporadic. Secondary craniosynostosis included 20 patients (40%), 50% had cerebral palsy, 20% had mucopolysaccharidosis, 15% with postshunt craniosynostosis, 5% with osteopetrosis, (5%) with neglected vitamin D deficiency rickets and 5% had encephalocele with multiple congenital anomalies [26].

Neural tube defects: Neural tube defects constituted 10.23% of neurologic disorders among our patients. Hafez and Hashem [27] reported an incidence of NTD among Egyptian children of 3.7–6.96% which is considered high. Thirty-seven percent had severe defects and 16% had other associated abnormalities as a part of a syndrome. Abdelaleem et al. [28] reported that C677T polymorphism of the 5,10-methylene tetrahydrofolate reductase (MTHFR) gene is a risk factor for neural tube defects among Egyptians.

Neurodegenerative disorders: Neurodegenerative disorders constituted 5.26% of neurologic disorders among our patients. A study was conducted in order to detect the etiology among a sample of our children suffering from neurodegenerative diseases. Among them 3.33% had Gaucher disease, 3.33% had aryl sulfatase A pseudodeficiency, 3.33% had most probably Pelizaeus–Merzbacher disease, 6.66% had infantile metachromatic leukodystrophy while another 6.66% had congenital muscular dystrophy. No cases with Krabb's disease were detected in this study [29].

Neurocutaneous disorders: Neurocutaneous disorders constituted 1.10% of our patients with neurologic disorders. Neurofibromatosis was the commonest, followed by Sturge–Weber syndrome and tuberous sclerosis while in another study the most common type was tuberous sclerosis (34.8%), followed by neurofibromatosis type 1 (26.1%), Sturge–Weber syndrome (21.7%), Klippel–Trenauny–Weber syndrome (8.7%), incontinentia pigmenti (4.3%) and multiple lentiginous syndrome (4.3%). The presenting manifestations of neurocutaneous syndromes were diverse and included developmental delay and/or learning disabilities in 43.5%, recurrent fits in 39.1%, skin lesions in 30.4%, growth retardation in 26.1%, skeletal abnormalities in 13% and hearing, visual and speech defects in 4.3% [30].

4.2. Hematologic disorders

During the period of the study, 5304 new patients with various hematologic disorders attended the Pediatric Hematology/Oncology Clinic, Ain-Shams University.

Hematologic disorders constituted 18.48% of genetic disorders and 0.8% of patients attending the Pediatric Hospital. Table 3 represents the distribution of different hematologic disorders. G6PD deficiency was the most common hematologic disorder detected in our clinic (24.89%) followed by β-Thalassemia (21.19%), idiopathic thrombocytopenic purpura (ITP) (17.97%), and hemophilia A (6.26%).

Table 3 Genetic varieties of hematologic disorders prevalent among Egyptians (Khalifa AS. Personal communication) [36].

Category	Hematologic clinic	
	No.	%
Hematologic disorders	5304	100.00
β-thalassemia (Major, intermediate)	1124	21.19
β-thalassemia Trait	127	2.39
α-thalassemia	13	0.25
Sickle cell anemia	195	3.68
G6PD	1320	24.89
ITP	953	17.97
Hemophilia A	332	6.26
Hemophila B	29	0.55
Aplastic anemia	201	3.79
AIA	120	2.26
FA	10	0.19
Other HA	216	4.07
AFI	97	1.83
Thrombasthenia	95	1.79
Cong. Spherocytosis	91	1.72
vonWillibrand disease	68	1.28
Pure red cell aplasia	38	0.72
Megalobalstic anemia	38	0.72
Gaucher	35	0.66
Marble bone disease	13	0.25
Others	189	3.56

Thalassemias

β-Thalassemia

β-Thalassemia is a congenital hemolytic anemia characterized by partial or complete deficiency in the production of beta globin chains [31]. In Egypt, β-thalassemia is the commonest cause of chronic hemolytic anemia and it represents a major genetic disease and a public health problem [32]. In Egypt more than one thousand affected cases are expected to be born every year in Egypt [33]. The estimated carrier rate is 9–10% [34], with a gene frequency of 0.03 [35]. Although the available treatment has increased the life expectancy of patients, it is still unsatisfactory and represents a significant drain on the country's resources. In a study on 5304 patients attending the hematology clinic (Table 3). β-Thalassemia major patients represented (21.19%) and β-thalassemia minor (2.39%) [36].

The relative frequency of different β-thalassemia mutations and their association with beta-globin haplotypes was studied by Novelletto et al. [35], in the first Egyptian study in patients from the Nile delta region, Egypt. They found eight mutations accounting for 77% of β-thalassemia mutations, the commonest three being IVS-1 nt 110, IVS-1 nt 6 and IVS-1 nt 1. This is consistent with all next studies on Egyptian patients where these first three mutations were the most frequent alleles in Egyptian patients with a different frequencies; 55.88% [37,38], 62.5% [39], 78% [40], and 73% [32].

Less frequent mutations were 15 CD 22 A–C and 1 FS CD 28 −C mutations in exon 1 [41], codon 24 (−G; +CAC) [34]

and promoter region −87 (C → G), codon 27 (G → T), IVS-II-848 (C → A) mutation, Codon 37 (G →), frameshift codon 5 (−CT) mutation, and codon 15 (TGG → TGA) mutation [42].

In 1993, Craig et al. [43] described an Egyptian family with δβ-thalassemia caused by 13.4-kb deletion that removes the 3′ region of the δ gene, the entire β gene, and its 3′ flanking sequences extending into the 6.4-kbL1 repeat element. They proved that this deletion is identical to those of the Sicilian (δβ) thalassemia.

Since 1990 the spectrum of β-thalassemia mutations were identified and prenatal diagnosis started in Egypt by applying amniocentesis and ARMS-PCR [44]. In 2003, prenatal diagnosis was done on fetal DNA in maternal circulation using denaturing high performance liquid chromatography (DHPLC) after ARMS-PCR amplification of all the DNA samples [45].

α-Thalassemia

In this study it represented 0.25% of patients in hematology clinic. Novelletto et al. [46] demonstrated a frequency of deletion of α-thalassemia among Egyptians as 0.08.

Sickle cell anemia: It is the commonest single gene disorder worldwide [47]. About 1.92% of the world's population carry sickle hemoglobin [48]. Hemoglobin S is found in the Mediterranean area and its presence there can be attributed to gene flow from Africa [49,50]. In parts of Africa, up to a third of the people carry a gene for hemoglobin S. About 120,000 babies with sickle cell disease are born yearly, but less than 2% survive to the age of five [51].

In our study it represented 3.68 of patients attending the hematology clinic. El Beshlawy et al. [52] found 1.6% prevalence of sickle cell disease, while Khalifa et al. [36] reported incidences 6.7% and 4.94%.

In 1999, Marin et al. [53] conducted a molecular investigation for the presence of sicklemia in six predynastic Egyptian mummies (about 3200 BC) from the Anthropological and Ethnographic Museum of Turin. DNA was extracted from dental samples with a silica-gel method specific for ancient DNA. Amplification refractory mutation system (ARMS) was then applied. In samples of three individuals, there was a band at the level of the HbS mutated fragment, indicating that they were affected by sicklemia.

In 1994, El Beshlawy et al. [39] found that the Benin haplotype is the predominant haplotype in the sickle cell disease in Egypt. The same results were also reported by Shawky et al. [54] with incidence of Benin haplotype (52%), followed by atypical haplotype (36%), and no correlation was observed between clinical severity and haplotype.

G6PD deficiency: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect, being present in more than 400 million people worldwide [55]. The first report on the incidence of G6PD deficiency among Egyptians appeared in early 1966, following an earlier WHO report which listed as "non-existent" [56]. In first report, Rageb et al. [57] reported incidence of 26.4%. Different incidences were reported later; 4.9% [58], 7.5–14.5% in Lower Egypt compared to 3% in Upper Egypt [59], and 5.9% [60]. Lippi [61] considered the hypothesis that the ancient Egyptians had noticed the potential deadly effect of broad beans' use. In this study, it represented an incidence of 24.89%.

A total of 3,501 male subjects from six Arab countries living in Kuwait were investigated for quantitative and phenotypic distribution of red cell glucose-6-phosphate dehydrogenase (G6PD). The ethnic origins of those investigated were Kuwait, Egypt, Iran, Syria, Lebanon and Jordan. The distribution of G6PD deficiency among the different ethnic groups varied widely, ranging from 1.00% for Egyptians to 11.55% for Iranians [62].

Settin et al. [63] reported that the minimum frequency of G6PD deficiency among jaundiced Egyptian neonates is 11.4% which is higher than population prevalence in Egypt (7–9.9%), and relatively higher than some countries like Iran (7.5%) but lower than Greece, Turkey and Jamaica.

Hemophilia: Hemophilia is an X-linked hereditary bleeding disorder caused by a deficient or defective coagulation factor VIII (hemophilia A) or factor IX (hemophilia B) [64]. Khalifa et al. [65] reported an incidence of 7.01% of hemophilia A and 0.47% of hemophilia B, and 0.63% of von Willebrand's disease of patients with bleeding disorder and in this study it represented 6.26% (hemophilia A) and 0.55% (hemophilia B) of patients attending the hematology clinic. In 2000, Khalifa et al. [65] also reported the possibility to offer diagnosis in 68.4% of the studied families with the combined use of both intron 13 and intron 22 repeats. Intron 13 and 22 of factor VIII gene are multi allelic- dinucleotide tandem repeats used for indirect gene tracking [66,67].

4.3. Chromosomal disorders and congential malformations

Chromosomal disorders represented a significant class of genetic disorders in Egypt and constituted 11.77% and 0.51% in genetics and general pediatrics clinics, respectively (Table 4).

It is the cause of congenital abnormalities in 5/1000 in infants and children, over 6% of early spontaneous abortions and 6–7% of still births and neonatal deaths. One percent of chromosomal disorders is transmitted from a carrier of a balanced chromosomal rearrangements and the rest are due to de-novo abnormality [68].

Autosomal chromosomal abnormalities: Down syndrome (DS) DS was the most common chromosomal abnormality in our study (74.7%) as well as in the other studies in Egypt [69], followed by chromosomal deletions (4.23%) and other trisomies (2.30), (Table 4). In our Down syndrome patients there was significant increase in maternal age (above 35 years in 32.31%) compared to mean maternal age (25.8 years) [5]. In

Table 4 Varieties of chromosomal abnormalities prevalent among Egyptians.

Category	Genetics Clinics	
	No.	%
Chromosomal abnormalities	3376	100.00
Autosomal abnormalities	2744	81.25
Down syndrome	2523	74.71
With maternal age > 30 years	1432	42.40
With maternal age < 30 years	1091	32.30
Other trisomies	78	2.30
Chromosome deletions	143	4.23
Sex chromosome abnormalities	632	18.72
Turner syndrome	254	7.52
Klinefelter syndrome	130	3.85
Fragile X syndrome	248	7.34

42.40% of cases the age of the mother was less than 35 years which was considered high at that age. The frequency of MTHFR 677 C/T and 1298 A/C polymorphism was significantly higher among Egyptian Down syndrome mothers, 32.1% and 57.1%, respectively compared to controls [70]. The same was also reported in another Egyptian study in young aged Down syndrome mothers by Shawky et al. [71]. This indicates that Egyptian mothers are in need of folic acid supplementations especially before and during the early months of pregnancy.

Cytogenetic analysis revealed that the most common chromosomal abnormality detected in Egyptian DS patients was non-disjunction which constituted 95.4% and 93.98% in different studies. This is followed by Robertsonian translocation (2.7% and 3.5%) and then mosaic DS which comprised 0.7 and 1.84% of studied patients with DS [69,72]. Most cases of translocation were t(21;21) which was present in 51.35% of cases, followed by t(14;21), in 40.5%, t(13;21) in 5.4%, and t(15;21) in 2.7% of cases [72]. Translocation was paternally inherited in 33.3% of cases and maternal transmission was twice as common as paternal [69]. Non-classical karyotypes reported in Egyptian patients with DS included: (46,X + 21/46,XX), (46,XX,der(21;21)(q10;q10),(47,XX + 21/45,X), (47,XXY,der (21;21)(q10;q10) + 21),(48,XY, + 21, + mar),(47,XY, + 21,t (4;21) (q31.1;q22),(46,XY,der(21;21)(q10;q10), + 21/46,XY) (45,X/ 47,XY, + 21) and (48,XXY, + 21) [72]; Zaki et al.) [73].

Eighty three percent of DS children had one or more congenital anomalies mainly affecting heart, kidney and vertebrae [74]. Also DS patients were five times more liable to develop acute leukemia than the general population [75]. Shawky et al. [76] reported a remarkable variability in COL6A1 coding region which can distinguish between individuals with DS with or without congenital heart disease. They recommended the study of other genes (COL6A2 and COL6A3) and their polymorphisms in these patients.

Different aspects of immune system were extensively studied in our DS children. A significant decrease of total T-cells, T helper cells and helper/suppressor ratio was found in these patients, while T suppressor cell and natural killer cell percentages were significantly increased when compared to controls [77]. The immune defect could be attributed to decrease in plasma zinc level. Therefore zinc supplementation is recommended in order to improve DS general health and development.

Autoimmune diseases such as celiac disease were also common in our DS patients. The frequency of antigliadin and antiendomyseal antibodies seropositivity was 26.2% which was higher among DS children with or without symptoms suggestive of celiac disease. The *seropositive* children had significantly lower symptoms suggestive of celiac disease. The seropositive children had significantly lower weight and height, lower mean hemoglobin level, lower serum albumin in comparison to seronegative counterparts. Therefore glutein free diet is recommended for the treatment of celiac disease in these patients [78].

The prevalence of thyroid autoantibodies and its association with thyroid dysfunction in DS patients was studied by Shawky et al. [79]. Sixty-five percent had positive antiperoxidase antibodies and 32.5% had subclinical hypothyroidism. Regular screening of thyroid dysfunction in DS and early administration of L-thyroxin in antithyroid antibodies positive patients is recommended.

The pattern of regional cerebral blood flow in our DS patients using brain single photon emission computed tomography (SPECT) was also studied by Shawky et al. [80]. The authors reported cerebral or cerebellar hypoperfusion in 82.35% using SPECT. Cerebellar hypoperfusion was encountered in cases with significant hypotonia while frontal hypoperfusion was significant in patients with behavioral disorders and language delay. However, the role of vasodilators needs further studies.

Early intervention program is the main worldwide supportive treatment for DS children. Shawky et al. [81] investigated the effect of program of Portage on the progress of mental development especially cognitive functions of DS children. The earlier the start of early intervention program the better the cognitive performance and the higher the IQ. They also demonstrated the great impact of maternal education and family size on the level of care the child receives.

Sex chromosome abnormalities: They constituted 18.72% of all chromosomal abnormalities detected in our study (Table 4). We conducted a study on 103 of our index cases, 69 females and 34 males with suspected sex chromosome abnormalities. The diagnosis was based on phenotype, hormonal profile, pelvic-abdominal sonographic findings, and genotype (conventional cytogenetics and molecular cytogenetics). The female cases included 29 females with sex chromosome abnormalities and 40 females with normal karyotypes. G- and C-banding and subsequent FISH analysis of chromosomes revealed numerical abnormalities in 52% of female index cases [10 non-mosaic and five mosaic cases], and structural sex chromosome abnormalities in 48% of female index cases [seven mosaic and seven non-mosaic cases]. As regards male cases, sex chromosome abnormalities were detected in 14 male index cases and normal karyotype among 20 male index cases. Numerical abnormalities were present in 86% of cases, and structural abnormalities were found in 14% of cases. Klinefelter syndrome and its mosaic variants were present in 91.7% of numerical cases, yet most of the cases were non-mosaic (nine cases). One case with 47, XYY was found. Two types of structural abnormalities were present. One case with karyotype, 46, inv(X)(p11.4q11.2), and in the second case sequential Q-banding verified that the apparently normal Y chromosome was missing its heterochromatic region which was translocated to the terminal end of chromosome 7 sorting out the case as 46,XY,t(Y,7)(q;q).

Congenital malformations: Screening of newborns for congenital malformations Birth incidence of malformations in Egyptian newborns ranges between 1.16% and 3.17% [82]. CNS malformations were the most common (9.33/1000) [83].

In a cross sectional study on a 1000 newborn infants delivered consecutively at the Department of Obstetrics and Gynecology, Ain-Shams University, the incidence of congenital anomalies (CA) was 2.7%. The highest frequency of congenital anomalies involved the central nervous system (CNS) (33%), followed in descending order by multiple congenital anomalies (19%), skeletal system (15%), gastrointestinal tract (GIT) (11%), urinary system (7%), and cardiovascular system anomalies (4%). Minor malformations accounted for 11% of congenital anomalies. Multiparity and diabetes mellitus were associated with a higher incidence of congenital anomalies. As regards infants of diabetic mothers 11% had major congenital anomalies (two with VSD and one with spina bifida), 18% had minor congenital anomalies (accessory ear tags, umbilical

hernia, undescended testicles, squint, tongue tie and double whorl of hair) [84].

Congenital malformations in infants and children: 13,543 infants and children with congenital malformations attending the Genetics Clinic were detected during the period of the study (1995–2009), constituting 20/1000. The commonest system involved was the nervous system (26.92%), followed by chromosomal abnormalities (25%), genital organs (9.84), musculo-skeletal (8.82), urinary system (8.67%), circulatory system (6.55), eye, ear, face and neck anomalies (5.39%), other congenital anomalies (4.57%), digestive system (2.10%), cleft lip and palate (1.5%) and respiratory anomalies (0.6%). Among the maternal risk factors detected were multiparity, age of the mother at conception, maternal illness, exposure to pollutants and intake of drugs in first 3 months of pregnancy. Consanguineous marriages were detected among 45.8% of parents [85].

Vertebral anomalies: The most prevalent types of developmental vertebral anomalies in Egypt were congenital spinal anomalies (42.5%) followed by osteochondrodystrophies (35%). Meanwhile, miscellaneous disorders represented 22.5% of studied Egyptian children. Associated skull anomalies were significantly more encountered among patients belonging to the group of osteochondrodystrophies (85.7%) when compared with those having congenital spinal anomalies (23.5%) while none of the patients with the miscellaneous disorders had such anomalies. Craniofacial dysmorphism was evident in 42.9% of patients with osteochondrodystrophies. Idiopathic scoliosis was associated with cleft palate in one case. Congenital cardiac anomalies were reported in two patients only; one of them had hemivertebrae and PDA while the other had idiopathic scoliosis and VSD. Sacral agenesis was associated with micropenis and undescended testicles in one patient. Mental retardation was recorded in two patients with congenital hypothyroidism and one patient with spina bifida who developed it as postmeningitic sequelae [86].

Craniofacial dysmorphism: A study carried out to evaluate clinically as well as cytogenetically a non-selected group of Egyptian children with craniofacial dysmorphism whether isolated or part of a syndrome. 6.7% of patients had chromosomal abnormalities and 3.3% had microdeletion syndrome (Rubenstein Taybi syndrome). Craniofacial dysmorphism due to monogenic disorders was present in 34.3%, multifactorial etiology in 20%, environmental factors in 6.7%, and unknown etiology in 20% of cases. So the etiology of craniofacial dysmorphism is very heterogeneous in Egypt. Good observation and systematic examination can narrow the differential diagnosis and the laboratory investigations needed. High resolution karyotype is essential in all of these cases [87].

Multiple congenital anomalies associated with mental retardation: Another study was carried out to determine the prevalent forms of multiple congenital anomalies associated with mental retardation among Egyptians trying to find out if these abnormalities were related to certain teratogens, genetic syndromes or chromosomal aberrations. Twenty-six percent was due to chromosomal abnormalities, 28% was syndromes due to single gene affection, 13.3% was disorders caused by teratogens and 33.4% was unclassified. The frequency of associated anomalies was markedly increased in the mentally retarded patients compared to their controls, none of the controls had three or more congenital anomalies compared to 89.2% in the mentally retarded. The finding of three or more congenital anomalies in a patient appears to indicate a significant abnormality in prenatal development. The discovery of multiple associated anomalies in a mentally retarded child suggests that the defect in brain function is also a congenital abnormality. Minor anomalies may be useful diagnostic aids in the assessment of patients with mental retardation [88].

4.4. Special senses

Hearing defect: The most common sensory defect in humans is hearing impairment (HI). About 1/650 suffer from HI before speech acquisition [89]. The prelingual deafness has a genetic cause in 60% of cases [90].

In our Genetics Clinic hearing and verbal disorders constituted 1254 (4.37%) of our patients either isolated or part of a syndrome.

Five hundred subjects of childhood deafness were studied [91]. The patients were classified into three groups: the genetic group comprised 218 (43.6%) children, 26.6% of children with hearing loss alone, and 17% of children with hearing loss associated with genetic syndromes. The acquired group comprised 250 (50%) children with hearing loss due to different acquired causes: middle ear effusion in 23.6%, meningitis in 7.8%, perinatal anoxia in 6.4%, fever in 4%, viral infection in 2.2%, kernicterus in 2%, garamycin injection in 1.6%, trauma in 1%, maternal infection in 0.6%, tumors in 0.4%, burns in 0.2% and maternal drug therapy during pregnancy in 0.2%. The cryptogenic group (unknown cause) constituted 6.4% of patients.

Sequencing analysis of 159 Egyptians revealed C.35 del G mutation in 10.8% of cases making it the most frequent mutation in the GJB2 gene in Egypt. Five other mutations described previously and three other novel mutations were also detected. In contrast with most populations, the deletion (GJB6-D13S1830) mutation upstream to the GJB2 gene was not present in Egyptian population [92].

Ophthalmologic disorders prevalent among Egyptians: A vast array of hereditary eye disorders has been identified. These include conditions limited to the eye as well as ocular manifestations of other heritable disorders and complex syndromes. Congenital cataract and retinal degenerations rank high among the genetic causes of blindness [93]. Genetic ophthalmic diseases are prevalent in Egypt and they are assumed to cause at least half of all cases of childhood blindness [94]. In our study they constituted (1.58%). Optic nerve defects were the commonest, (31.14%), followed by retinal defects (19.95%), lens anomalies (cataract 18.81%), iris anomalies (3.69%), corneal anomalies (7.72%), eyelid anomalies (2.46%), anophthalmia (7.25%), microphthalmia (3.46%), and eye anomalies as part of a syndrome (5.52%).

Congenital cataract (CC): Mostafa et al. [95] reported that sporadic cases 23/30, i.e. (76.66%) of CC in Egypt are more common than familial cases 7/30, i.e. (23.33%). Temtamy and Shalash [96] suggested autosomal recessive inheritance for CC and microphthalmia.

Congenital glucoma (CG): El-Defrawy et al. [97] also reported that sporadic cases of CG were more common 28/42 (66.66%) than familial cases 14/42 (33.33%). Three CYP1B1 mutations were identified in 45.4% of Egyptian and Saudi patients of which two were novel (homozygous E 173K and heterozygous N 498D) and the 3rd (G6IE) had been previously reported. Also 10 single nucleotide polymorphisms were iden-

tified in CYP1B1 and MYOC genes of which two were novel [98].

Retinoblastoma: Molecular analysis of the RB 1 gene mutations in peripheral blood lymphocytes of Egyptian families were studied [99]. Specific molecular point mutations were identified in seven exons of the RB 1 gene in 11 of the 15 examined Egyptian patients. These exons included exons 2, 11, 12, 13, 14, 17 and 26. In order of frequency, mutations of exon 14 were detected in (27%), mutations of exons 17 and 26 were detected each in 18% and mutations of exons 2, 11, 12 and 13 were detected in 9% each. As regards genotype-phenotype correlation, patients with mutations within exon 26 had an earlier age of diagnosis and rapid progression of the tumor. Patients harboring mutations within exon 17 had a later age of diagnosis and slow progression of the tumor while mutation within exon 2 was detected in one child with multiple tumor foci. Sporadic occurrence of the tumor was identified in 60%, autosomal recessive inheritance in 27% and autosomal dominant inheritance in 13% of cases.

4.5. Inborn errors of metabolism (IEM)

IEM are individually rare, but collectively they constitute 4.24% of patients attending our Genetics Clinic, IEs of aminoacid (AA) metabolism were the commonest followed by lysosomal storage disorders (mainly mucopolysaccharidosis (Table 5). Hashem [100] reported that in Egypt one in every 32 individuals carries a gene for IEM.

In a study of the etiology of mental retardation in Egypt [101], genetic causes represented 54.4%, of which the metabolic causes represented 19.9%. These include IEs of AA (11.5%) and MPS (8.4%). In another study in our clinic, aminoacidopathies were represented in 1.5% of total patients attending the Genetics Clinic among them phenylketonuria (PKU) was found to be the commonest, 1.11%, while the remaining diagnosed cases represented 0.07% for each of alkaptonuria, citrulenemia, and trimethyl-aminuria [102].

Screening programs in Egypt: A general screening program including 2000 infants was done in 2001 from plasma samples [103]. Transient neonatal tyrosinemia was detected in 0.05% and generalized aminoacidemia in 0.05%. As regards the selective screening program, among the 450 cases of mental retardation (MR) examined, 280 cases were suspected of having inborn errors of amino acid metabolism by specific criteria taken as markers, e.g. convulsions and/or progressive neuromental deterioration, speech defect and/or deafness, mental retardation (MR) with no acquired or chromosomal etiology and organic brain damage of obscure etiology. Among the 51 cases (11.32%) with confirmed positive inborn errors of amino acid metabolism, 40 cases (78%) had (PKU), four cases (7.84%) had generalized aminoaciduria, two cases (3.92%) had non-ketotic hyperglycinemia, two cases (3.92%) had hyperprolinemia, two cases (3.92%) had histidinemia and one case (1.96%) had homocystinuria. PKU cases can be classified into, classic type (90%), atypical type (7.5%) and malignant type (2.5%). The main clinical findings included hypopigmentation (100%), MR (100%), physical retardation (90%), microcephaly (37.5%), hyperactivity (90%), seizures (25%), and abnormal EEG (42.5%). The associated abnormalities include three cases (7.5%) with albinism, and three cases (7.5%) with eye abnormalities; namely enophthalmos, glaucoma, and optic atrophy.

Table 5 Genetic varieties of hematologic disorders prevalent among Egyptians.

Category	Genetic Clinics	
	No.	%
Inborn Errors Of Metabolism	1104	100.00
Inborn Errors of amino acids metabolism	645	58.42
PKU	278	25.18
Tyrosinemia	15	1.36
Alkaptonuria	12	1.09
Histidinemia	200	18.12
Homocystinuria	69	6.25
Hypermethionemia	4	0.36
Citrulinemia	3	0.27
Hydroxyprolinemia	4	0.36
Leucine, isoleucin, valine (MSUD)	23	2.08
Urea cycle defects	10	0.91
Organic aciduria	9	0.82
Valinemia	5	0.45
Hartnup disease	7	0.63
Cystinuria	1	0.09
Arginino-succinic aciduria	3	0.27
Lysinuria	1	0.09
Trimethyaminuria	1	0.09
Inborn Errors of CHO metabolism (Glycogen storage diseases)	81	7.34
Lysosomal storage diseases	378	34.24
Mucopolysaccharidosis	307	27.81
Hurler	57	5.16
Hurler Schei	1	0.09
Schei	14	1.27
Hunter	93	8.42
Sanfilippo	17	1.54
Morquio	55	4.98
Maroteaux Lamy	70	6.34
Gaucher's disease	48	4.35
Mucolipidosis	23	2.08

In another extended metabolic screen done in 2004 on 232 cases (44 neonates and 187 children) with symptoms suggestive of IEM [104]. Abnormal results were detected in 22.73% of neonates. Organic acidemias were detected in 13.63%, aminoacidopathies in 4.55%, fatty acid oxidation defects in 4.55%. In children abnormal results were also detected in 8.56% of children, including aminoacidopathies in 5.88%, organic acidemias in 1.07%, cystic fibrosis, congenital adrenal hyperplasia and congenital hypothyroidism in 1.61%, PKU was detected in 6.48% of children with MR, and MSUD in 10% of children with convulsions.

Phenylketonuria (PKU): Phenylketonuria is the most common inborn error of metabolism in Egypt – 1:7500 [100,105]. It was found that classic PKU is the most prevalent type of hyperphenylalaninemia (92.08%), followed by atypical hyperphenylalaninemia (6.67%) and benign hyperphenylalaninemia (1.25%) [106].

Screening carriers and prenatal diagnosis: A study was done on our patients to screen the PAH locus for potentially useful short tandem repeats (STRs) as markers for carrier detection in PKU families and to determine the level of PAH heterozygosity within the Egyptian population. The system contains at least eight independent alleles in Egyptian population, transmitted in Mendelian fashion. The most frequent allelic fragment size was 246 bp (35.7%) which together with a

fragment of 254 bp accounted for 60.7% of the mutant chromosomes. Variations in the number of STR in the families studied gave rise to polymorphisms that proved to be suitable markers for PKU carrier detection and prenatal diagnosis [107].

Mutation analysis of PKU: A study for mutations and polymorphism in PAH gene among our patients was done. Four mutations were detected, IVS 10 nt-11 gla and Y 198fs, IVS 2 nt5 glc, E7 G247V. Interestingly the last mutation has only been described in Chinese, thus allowing future comparison with Chinese alleles. Also five polymorphism was identified, IVS2 nt 19t/c, E6 Q232Q, E11 L385L, E7V245V, IVS 12 nt16 t/g (not previously reported among Egyptian, although it was reported in Sicily). This suggests gene flow between Sicily and Arab countries [108]. In another study on our patients mutation analysis on unrelated 51 families was done. A novel missense CpG site R243P mutation was identified. Moreover, three new known mutations L48S, delEX3 and Y277D unreeled in the Egyptian population. The ten detected mutations covered 58%, representing 47 positive chromosomes. The most common mutation was represented by IVS10nt546 (10.8%), while the total missense mutations in our sample group accounted for the majority of mutations 40%. The high heterozygosity of the mutant PAH locus in Egypt suggests that multiple founder events would explain the presence of hyperphenylalaninemia in Egypt. Further studies will however be necessary to fully exploit the potential of PAH gene analysis to reconstruct the genetic history of PKU in Egypt in context with migrations among European and Mediterranean populations [109].

Glycogen storage: Endo et al. [110] detected three different individual AGL mutations in Egyptian glycogen storage disease patients, two were novel deletions (750–753del AGAC) and 1 bp deletion 2673del T. One, the non-sense mutation (W1327X) was previously reported. Haplotype analysis of mutant AGL alleles showed that each mutation was located on a different haplotype. Thus allelic heterogeneity of the AGL mutation in Egypt was confirmed.

Lysosomal storage: Hashem [100] reported 38 cases of neurolipidosis, Leigh disease in 13 cases, GM1 Gangliosidosis in 11 cases, GM2 gangliosidosis in six cases, mucolipidosis in six cases and a single case of Refsum disease. Metachromatic leucodystrophy was diagnosed in seven cases. In a study of 30 patients with developmental delay or loss of previously acquired milestones of development one case with Gaucher disease, one case with arylsulphatase A pseudodeficiency, one case with Pelizaeus–Merzbacher disease and 2 cases with infantile metachromatie leucodystrophy were diagnosed [29]. Deghady et al. [111] demonstrated that Egyptian patients with type 1 Gaucher disease, whether newly diagnosed or receiving enzyme replacement therapy, experience coagulation factor abnormalities regardless the clinical expression of bleeding diathesis. This should be taken into consideration before these patients are subjected to surgery for, e.g., splenectomy, which is common in these patients.

Mucopolysaccharidosis: Hashem [100] reported 77 index cases with mucopolysaccharidosis and 28 of their relatives. 23 cases had Hurler syndrome, 16 cases had Morquio disease, 12 cases had Hunter disease, 10 cases had Hurler/Schaie, 9 cases had Sanphillipo disease, four cases with Maroteau–Lamy and three cases had Schie. However, in another study MPS VI was the commonest type detected (33.3%), followed by MPS III and IV (22.2% for each), MPS I (11.1%), MPS II (5.6%), MPS VII (5.06) [112]. Cardiac abnormalities were detected in 61.1% of patients. The mitral valve was the most commonly affected valve (40%) in the form of thickening of the valve or mitral regurge, followed by interventricular septal hypertrophy (15%), ventricular wall hypertrophy (15%) and thickening of coronaries (10%). Ocular abnormalities were detected in 30% of our patients mainly as corneal opacities (16.7%), optic atrophy (5.6%), papilloedema 11.1%, pigmentary retinopathy (5%) and increased intra-ocular pressure (5.6%) [112].

Gaucher disease (GD): Most of Egyptian children with GD have type III disease and L444P/L444P genotype, and so a minimum dose of cerezyme 60 mg/kg/2 weeks should be maintained until adulthood. Higher doses started at an early age may delay the progression of neurological symptoms. Pulmonary involvement is not rare in Egyptian patients and may respond to dose increase or dose fractionation. Cardiovascular and renal symptoms should be further studied in our population [113]. Shawky and Elsayed [114] reported the unusual finding of concentric ventricular hypertrophy and multiple stones in the right kidney in a patient with Gaucher disease.

4.6. Neuromuscular disorders

The genetic varieties of the neuromuscular disorders depicted in the present survey were drained from different areas of Egypt. The diagnosis was mainly ascertained on clinicogenealogic basis. They constitute 2.86% in Genetics Clinics and 0.12% in the Pediatric Hospital with Duchenne/Becker muscular dystrophy being (D/BMD) the commonest error (Tables 1 and 6).

In 1998, Hashem and Elsayed [115] conducted a study in our clinic to determine the phenotypic expression and gene frequency of the different groups of primary myopathies. The genealogic pedigree analysis of the studied index families revealed that Duchenne muscular dystrophy (DMD) also had the highest incidence followed by the congenital myopathies and limb girdle muscular dystrophy (LGMD). As regards the phenotypic expression of muscle dysfunction: weakness, hypotonia and hyporeflexia was detected in 100% of cases. No sensory or cerebellar affection has been detected. Pseudohypertrophy was noted in 40.41% of cases, of whom 36% had DMD 3% had LGMD and 1% myotonia congenita. Atrophy occurred in about 72.83% of cases and contractures occurred in 10%. The gene frequency of the different groups of primary myopathies was 0.000136 for X-linked, 0.0059 for autosomal recessive and 0.0000097 for autosomal dominant. The carrier % of the different groups of primary myopathies was 0.0272 for X-linked, 1,180 for autosomal recessive. The total anticipated patient load of the different groups of primary myopathies was 4132 for X-linked, 351,872 for autosomal recessive and 573 for autosomal dominant. The anticipated carrier load of the different groups of primary myopathies was 7883 for X-linked and 699,565 for autosomal recessive.

Duchenne muscular dystrophy: As Partial gene deletion is the major type of mutation leading to Duchenne muscular dystrophy (DMD), the commonest type of primary myopathy in this study, and its mild allelic form, Becker muscular dystrophy (BMD). A study was conducted on the dystrophin patients using multiple primers and detected 51.3% of probands with

deletion mutations [116]. In order to offer carrier detection, genetic counseling and prenatal diagnosis to families with D/BMD in our country, pedigree analysis, estimation of the CPK level and the segregation analysis of highly polymorphic short tandem repeats were evaluated by Elhawary et al. [117]. Analysis of the D/BMD index families allowed the categorization of the females at risk into three categories: 25.7% definite carriers, 5.71% probable carriers and 68.57% possible carriers.

Spinal muscular atrophy (SMA): It constituted 21.87% and the second most common neuromuscular disorder in our study is characterized by progressive hypotonia and muscular weakness because of progressive degeneration of alpha motor neuron from anterior horn cells in the spinal cord. It is inherited by an autosomal recessive pattern. The precise frequency of SMA in Egypt has not been determined previously. We tried to estimate the frequency, clinical and molecular characteristics of SMA in Egypt. The study included all patients with SMA attended the Pediatric Hospital, Ain-Shams University during the period (year 1966–2009). The study included 117 patients with SMA out of 660,280 patients attending the Pediatric Hospital. Frequency of SMA was 17.7/100,000, which is considered high. Type I was the commonest type (60.6%), followed by type II (26.79%), and type III (8.8%). Consanguinity was reported in 45.5% and family history in 47.8% of patients.

The most common complain were recurrent chest infection, hypotonia and weakness in all type I patients (67.5%) secondary inability to walk in all type II patients (27.3%), and weakness and difficulty in walking in all type III patients (5.2%). All type I patients presented with profound weakness and hypotonia, but wasting was not marked because of early death. Deep reflexes were absent, sensations were intact and mentality was normal. Tongue fasciculations were prominent and hand tremors were present in the second and third groups of patients.

Molecular study was done to identify mutations involving the SMA gene in Egyptian patients with proximal SMA, so that prenatal diagnosis in informed families can be performed. DNA molecular studies of the SMA gene on the long arm of chromosome 5 (5q11.2q13.3) revealed homozygous deletion of exon 7 in 55% of cases, 36.3% of whom also had homozygous deletion of exon 8. The adult patients were heterozygous for an abnormal size exon 8. The remaining patients had either compound heterozygote deletion of exons 7 and 8 or was normal for both. There may therefore be 5q unlinked SMA or SMA due to other mutations. Detection of deletions of SMA exons 7 and 8 is a powerful diagnostic test in patients with SMA, but other mutations among Egyptians must also be sought of [118,119].

Table 6 Genetic varieties of neuromuscular disorders prevalent among Egyptians.

Category	Genetic Clinics	
	No.	%
Neuromuscular disorders	823	100.00
Primary myopathies	627	76.18
Muscular dystrophies	523	63.54
X-linked muscular dystrophy	384	46.65
Autosomal muscular dystrophies	139	16.89
Myotonic disorders	20	2.43
Congenital myopathies	84	10.21
Neuromuscular junction disorders (myasthenia gravis)	8	0.97
Peripheral neuropathies (Charcot–Marie tooth disease)	8	0.97
Anterior horn cell diseases (hereditary spinal muscle atrophy)	180	21.87

4.7. Rare syndromes reported in our clinics

Melnick needles syndrome: We reported the first Egyptian patients with this syndrome with amenorrhea, short stature and characteristic facial dysmorphism [120].

Martsolf syndrome: An Egyptian girl was also reported with this syndrome [121].

Femoral hypoplasia unusual facies syndrome: It was reported in a four-year old male who had complete absence of both femora, and bilateral undescended testes [122].

Hypomelanosis of Ito (HI): HI and rapidly progressing neuroblastoma was described. To our knowledge, neuroblastoma was reported only once in the literature [123].

MURCS association: A two year old girl with typical features of this association was described with right deviation of anorectal canal, subglottic stenosis and unilateral oblique inguinal hernia [124].

Frontofacionasal dysplasia: A patient with this dysplasia was described who had severe craniofacial anomalies and was associated with facial heamangioma [125].

Peter's plus syndrome: A case of Peter's plus syndrome with some unusual features, such as progressive osseous hypoplasia was described [126].

Other syndromes reported in our locality include: Corpus callosum defect with dilated lateral ventricles and one occipital cyst in an Egyptian child with Diamond–Blackfan syndrome [127], acrocallosal syndrome [128], triple A syndrome presenting with myopathy [129], abnormal presentation of Peter's anomaly in a family with microcornea, and cataract [130], Ellis Van Creveled syndrome with facial dysmorphic features [131], Goldenhar syndrome with skin tags on the chest wall [132], multiple pterygium syndrome with marked pterigia of the fingers and MRI changes in the spine [133], juvenile hyaline fibromatosis (JHF): in an Egyptian 3 years old male child was also reported [134], progressive osseous heteroplasia was also described [135], C syndrome [136], holoprosencephaly, a report of two cases with different presentations [137] and the first report of an Egyptian patient with fibrodysplasia ossificans progressive (FOP) was also presented [138].

4.8. Genodermatoses prevalent among Egyptians

It is not an overestimate to state that at least 90% of chronic dermatoses are genetically mediated either totally or consequent to genomic interaction with specific environmental agents which are only noxious to genetically predisposed individuals.

The present survey depicts the genetic varieties of primary chronic dermatoses which were encountered amidst 553 index Egyptian families who consulted Ain-Shams University mainly for genetic counseling. They constitute 1.92 of patients attending the Genetics Clinics and 0.083 in the Pediatric Hospital. The genetic varieties of dermatoses in this study were drained from different areas in Egypt (Table 7).

Ichthyosis had the highest incidence (36.88%) followed by albinism (20.43%), epidermolysis bullosa (16.99%), xeroderma pigmentosa (15.91%) and ectodermal dysplasia (9.76%) (Table 7). This is in accordance with previous studies in the same locality [100,139]. The parental birth origin indicates that Lower Egypt had the highest parental birth origin (42.58%), followed by Cairo (26.89%), and then Upper Egypt (27.73%). It is important to know the parental birth origin, because there may be certain population groups in whom a mutant allele is carried more frequently because of the founder effect or heterozygote advantages. Such epidemiological information allows appropriate screening and counselling. Consanguinity was present in 75.63% of our patients, and constitutes 40% and 51.54% of patients had positive family history.

Age incidence was high in the neonatal period as in ichthyosis, early in the first year of life (1 month to < 1 year) in ectodermal dysplasia while in albinism it was higher in early childhood (2 years to < 6 years). As regards sex distribution, male to female ratio was 1.1:1. The same was also reported previously [139,140]. Strikingly there was high incidence of diabetes mellitus in 17.68%, mental retardation in 13.11% and seizures in 10.37% followed by hypertension in relatives of patients in this study.

Ichthyosis: Lamellar ichthyosis (LI) constituted the commonest type in our study 12.83%, followed by congenital ichthyosiform erythroderma 10.12% (Table 7). There was a high incidence in newborns (62.5%). The distribution of scales varies according to the type of ichthyosis. It was distributed all over the body in 60.58% of cases, over the extremities in 91.35% and over the trunk in 84.62% of cases. Erythema was present in 18.27%. Ectropion is present in 10.58%, spastic dysplasis in 11.54% and mental retardation in 22.12% of cases. Associated genome errors reported in our patients included seizures in 4.81%, Down syndrome in 0.96%, Duchenne muscular dystrophy in 0.96%, undescended testes in 2.88%, speech defect in 16.35% and growth retardation in 13.46%.

Analysis in both inbred and outbred families in United States and in Egypt showed that LI was linked to several markers within a 9.3-cM region on 14q11. Affected individuals in inbred families were found to have striking homozygosity for markers in this region. Linkage-based genetic counseling and prenatal diagnosis are now available for informative at-risk families. The transglutaminase-1 gene maps to the same region and encodes one of the enzymes responsible for cross-linking epidermal proteins during the formation of the stratum corneum [141]. Russell et al. [141,142] showed that TGM1 and LI were linked with no recombinants; maximum lod = 9.11.

We extended our previous dataset to update the detection of R142H mutation in 4 CIE and one LI phenotype Egyptian families. This mutation was detected in 28.8%; whereas we still had no R141H among our Egyptian population. There was no correlation between phenotype and genotype in our study. Surprisingly, the mutant alleles detected in intron-5 acceptor splice-site were associated with the other extreme of CIE phenotypes rather than the severe LI form. We clearly demonstrated that the ARCI Egyptian families in Upper Egypt was ethnically pure and had a tendency not to be a hybrid with other populations in Lower Egypt, Delta zone and Cairo city [143]. Sixteen percent of the index ichthyotic patients of the autosomal recessive category in the present survey manifested a wide spectrum of neurologic manifestations. All patients of this category were designated as having "Sjogren–Larsson syndrome" (SLS).

In seven pedigrees of diverse ethnic origins (three families from Egypt, three families from the United States and one Arab family from Israel), Rogers et al. [144] confirmed the linkage of SLS to the pericentric region of chromosome 17.

Albinism: The occurrence rate of Albinism in our clinic was 20.43% of all genodermatoses patients. The commonest type was complete OCA followed by partial albinism, syndromic albinism (Table 7). Associated genomic errors detected in our albino patients included microphthalmia in 27.27%, mental retardation in 19.32%, seizures in 15.91%, deafmutism in 4.55% and Down syndrome in 3.04% [145].

Xeroderma pigmentosa: There was high incidence of XP in the childhood period (53.18%). As regards sensitivity to sun, it was present in 100% of cases, photophobia in 71%, mental retardation in 73%, microcephaly in 59%, hyporeflexia in 36%, seizures in 34%, and corneal opacities in 26.79% of cases studied. Genomic errors detected in our patients included dwarfism in 16.07% and hypogonadism in 8.93%.

Epidermolysis bullosa: Epidermolysis bullosa constituted 16.99% of our patients with genodermatoses. There was also a high incidence in newborns (47.50%). As regards the phenotype blisters were present in 100% of cases, non-scaring lesions in 9% granulomas in 12.05%, secondary infection in 77.50%, dystrophic nails in 32.50% loss of teeth in 5%, growth retardation in 5% and hand and foot deformity in 7.5% of our patients.

Ectodermal dysplasia (ED): A high incidence of ED was detected in early infancy. As regards the phenotypic expression of ED, decreased sweating was present in 92%, dry skin in 69%, hypodontia in 65%, sparse eyebrows and eye lashes in 73%, sparse body hair in 65%, hypoplastic nails in 30% and hypotrichosis of the scalp in 88% of cases. Genomic errors detected in these patients included atrophic rhinitis in 3.85% of cases and hypopigmented periorbital skin in 50% of cases.

Table 7 Genetic varieties of genodermatoses prevalent among Egyptians.

Category	Genetic Clinics	
	No.	%
Genodermatosis	553	100.00
Ichthyosis	204	36.88
Lamellar	71	12.83
X-linked	23	4.15
Vulgaris	27	4.88
Congenital ichthyosiform erythroderma	56	10.12
Sjogren–Larsson syndrome	27	4.88
Albinism	113	20.43
Partial	52	9.40
Complete	49	8.86
Ocular albinism	2	0.36
Hemansky Pudlac Syndrome	2	0.36
Cross syndrome	2	0.36
Chediac Higashi Syndrome	6	1.08
Epidermolysis bullosa	94	16.99
Xeroderma pigmentosa	88	15.91
Isolated	67	12.11
De-Scantis Cacchione Syndrome	21	3.79
Ectodermal dysplasia	54	9.76

4.9. Cystic fibrosis

For a long time we believed that cystic fibrosis is not present in Egypt. Abdel Salam et al. [146] diagnosed cystic fibrosis in 4.6% of studied cases with clinical picture suggestive of disease. Median age of diagnosis of cystic fibrosis in Egypt is 4 years which was higher than the age reported in other studies in Arab and Western countries. This is due to the delay in diagnosis. Newborn screening was done using a three-tier neonatal screening method on 924 newborns taking a heel prick on Guthrie cards during first three days of life. The test included: quantitative immunoreactive trypsinogen, double sweat chloride test and DNA analysis for the detection of ΔF508 for positive cases. Cystic fibrosis was confirmed in 3 infants (0.32%). ΔF508 mutation was confirmed in two infants in heterozygous state (33%) [147]. Also this mutation comprised 25% of mutations in a high risk group of children with chronic lung disease [148]. This indicates the relatively low frequency of ΔF508 homozygotes among our normal populations. Accordingly we cannot depend on this mutation alone in our country which comprises over 80% of mutations in other countries [149] and further studies must be done to know the mutational pattern of the disease among our population to plan a strategy for screening.

4.10. Endocrine disorders and abnormalities of sexual differentiation

They constitute 3.87% of patients attending the Genetics Clinics and 0.17% in the Pediatric Hospital.

Congenital hypothyroidism: Hypothyroidism was found in 1/5495 newborns in our locality [100]. She found that 75% of all hypothyroidism was due to a primary defect in the thyroid gland or in the enzymatic synthesis of the thyroid hormone, while 25% was due to pituitary or hypothalamic disorders.

The Egyptian Ministry of Health and Population started to implement the national screening program for congenital hypothyroidism in the year 2000, in five governorates and by the end of 2003 all 27 governorates were covered.

The total No. of screened neonates is about 4.8 millions by the end of December 2005 coverage ranged from >95% in some rural areas to 75% in urban areas.

The overall incidence of hypothyroid patients was 1/2020 in the year 2005 [150].

The prevalence of goiter by clinical indicator was 11.8%. The prevalence of iodine deficiency disorders (IDD) by urinary iodine estimation was 31%, 90% of the cases were considered to have mild deficiency. Higher mean TSH levels were found among goitrous subjects. The prevalence of hypothyroidism among IDD children was 6.1% with 3.9% being compensated. A negative correlation ($p < 0.01$) was detected between the severity of iodine deficiency and the degree of salt iodization. On the other hand iodine deficiency was detected in 9.7% of children who consumed iodized salt, and normal urinary iodine levels were detected in 50.6% of children inspite of the use of non-iodized salt. This means that iodine deficiency continues to be a major health problem in Egypt [151].

Abnormal sexual differentiation: Prevalence and phenotypic expression of various genitogonadal differentiation errors were studied in 322 index cases registered in our Genetics Clinic. It was found that gonadal dysgenesis with abnormal chromosomal complement was the most common disorder, 34.67% (Klinefelter syndrome 14.24% and Turner syndrome 20.43%), followed by gonadal dysgeneses with normal chromosomal complement, 19.50% (XXY type 12.38% and XY type 7.12%). True hermaphroditism constituted 10.53% (complete androgen insensitively syndrome, 8.05%, and partial androgen insensitivity syndrome 2.48%). On the other hand female pseudohermaphroditism constituted 4.02% of studied subjects (congenital adrenal hyperplasia, 3.72% and androgen secreting tumors 0.31%). Mullerian dysgenesis constituted 29.10% of our patients. In this study adulthood was the most common presenting age group, 63.78%, Lower Egypt was the most common birth origin, 49.23% [152]. On the other hand Mazen et al. [153] reported that 46XY disorders of sexual differentiation (DSD) were more common in Egypt (65.9%) than 46,XX DSD. Also familial cases of male pseudohermaphroditism were reported by Hashem [154].

Shawky et al. [155] tested the presence or absence of SRY gene in patients with intersex using FISH technique and (LSI) SRY/CEP X dual color probes.

G banding revealed normal male karyotype in 48% of patients, normal female karyotype in 43% of patients and abnormal karyotype in (45,X, + mar) in 9% of patients. Gad [156] studied CYP21 mutations in two patients with CAH, both were homozygous for the II72N mutation. Their mothers were both heterozygous for the mutation.

5. Conclusion

Over the years, Egypt has made substantial progress in control of communicable diseases. This leads to emergence of non-communicable diseases including genetic disorders. Our study showed a high prevalence of genetic diseases among Egyptians which is nearly the same in the other studies in Egypt and are rapidly becoming a major public health concern.

Establishment of national or hospital based registers for genetic disorders are very important to know the magnitude of the problem so that the national program for prevention of genetic disorders can be implemented. This program should be carefully selected to match the unique, demographic, cultural and religious characteristics of the Egyptian populations and should take into considerations the priorities of the more common disorders. We have to expand genetic education of health professionals, officials in charge of patients, their families and general public. Carrier detection, genetic counseling, premarital diagnosis, neonatal screening, preconception, prenatal diagnosis and selective screening programs are of great importance in the prevention of genetic disorders. Promotion of scientific research efforts in the field of human genetics to implement country specific data-base mutations and development of Arab human variome project are also important.

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Conflict of interest

The authors declare that there is no conflict of interest.

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