RESEARCH REVIEW

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# Genetic Diseases in the Tunisian Population

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**Tunisia is one of the North African countries, geographically situated in a central position at the crossroad between Africa and Europe. The demographic features of the Tunisian population include among others high rates of consanguinity. We report, here on the spectrum of genetic diseases in Tunisia. The review of the literature, including other available information (gray literature) showed that there are at least 346 genetic disorders for which cases have been identified in the Tunisian population. Among these, 62.9% are autosomal recessive, 23% autosomal dominant, 5.4% X-linked, and the remaining are of Y-linked, mitochondrial, and unknown mode of transmission. Fifty percent of the reported conditions in this study are caused by at least one mutation. For autosomal recessive diseases, most of the mutations were identified at homozygous state among the affected individuals. Part of the mutations was the result of a founder effect; these are the consequences of the high rate of consanguinity. The congenital malformations, diseases of the nervous system and metabolic disorders are the major groups of genetic diseases affecting the Tunisian population. The large spectrum of diseases and their relatively high frequency could be explained by the high degree of inbreeding and the presence of multiple mutations, either allelic or in different genes. This is due to the richness of the genetic background of the studied population. A multidisciplinary approach is essential to develop adequate preventive programmes adapted to the social, cultural, and economic context.** © 2010 Wiley-Liss, Inc.

**Key words:** genetic disorders; Tunisian population; consanguinity; mutations

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## INTRODUCTION

Genetic disorders in the Arab world are a major cause of mortality, disability, and chronic disease. Several of these disorders, being monogenic ones like hemoglobinopathies or due to chromosomal abnormalities (e.g., Down syndrome) or multifactorial conditions (breast cancer, diabetes, hypertension, etc.), have reached epidemic proportions in certain countries of the region [Al-Gazali et al., 2006]. The population is characterized by the large family size, high maternal and paternal age, and a high level of inbreeding with consanguinity rates in the range of 25–60% [Al-Gazali et al., 2005; Hamamy et al., 2007a]. These high consanguinity rates lead to the emergence of autosomal recessive diseases at high frequencies [Teebi, 1994].

Tunisia is one of the Muslim North African countries, geographically situated in a central position at the crossroad between Africa and Europe. The population numbers 10,486,339 inhabitants with a population growth rate of 0.98%. Nearly all Tunisians, 98% of the population, are Muslims, the rest being Christians, Jews, and belonging to other minorities. Modern Tunisians, who are descendents of indigeneous Berbers, are an admixture of heterogeneous ethnic groups who invaded and occupied the Tunisian territory through its history including Phoenicians, Vandals, Romans, Arabs, Ottomans, and finally Frenchs during the protectorate established from 1881 to 1956. According to the Human Development Report, Tunisia is classified as being in an intermediate situation: middle-income country, with obvious improvement of health indicators and control of infectious diseases [Human

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Development Reports Statistics, 2008]. Since the end of the French Protectorate, the social life in Tunisia has changed as illustrated by the nationwide education and economic progress. Demographic profiles showed a clear decrease in infant mortality from 175 (between 1950 and 1955) to 19.8 infant deaths per 1,000 live births (between 2005 and 2009). For the same periods, the Tunisian population also registered declines in birth and death rates [Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat, World Population Prospects: The 2008 Revision Population Database, 2009].

Tunisian women education, legalization of use of contraceptions and abortion, late women age at marriage (25.9 years) and at childbearing (30.7 years) impacted on the process of fertility in the country. The total fertility rate measured as the number of children born per women decreased from 6.1 in 1970 to 1.72 in 2009 [United Nations, Department of Economic and Social Affairs, Population Division, World Fertility Patterns, 2007]. Despite these social and behavioral changes intrafamilial marriages are still culturally favored as in other Arab and Muslim communities. Consanguineous unions range between 24.81% in Central Tunisia [Kerkeni et al., 2007], to 32% in the North [Riou et al., 1989; Ben Arab et al., 2004] and could reach up to 60% in rural areas.

In addition, as for developing or emerging countries, Tunisia is challenged by the epidemiological transition, with an increase in the prevalence of noncommunicable diseases and a high prevalence of birth defects evaluated to 73 per 1,000 live births [Christianson et al., 2006]. As a consequence of all these facts, there is an increase of the prevalence of genetic diseases; nevertheless, no precise epidemiological data are available and the spectrum of genetic diseases has not been assessed.

Genetic services still remain inadequate and do not cover all regions of the country. In Tunisia, there are three genetic centers controlled by the Ministry of Health and located in three governorates, respectively, the North, Center, and South of the country. Cytogenetic and molecular diagnoses are performed at both the postnatal and prenatal stages either in Tunisia, or in particular cases, in reference laboratories mainly in France or in other European countries [Chaabouni-Bouhamed, 2008].

The purpose of this study is to identify the spectrum of genetic diseases in Tunisia by summarizing the data available up to now on genetic conditions and to evaluate their frequency and specificities in Tunisia as an example of a North African and Middle Eastern population.

## MATERIALS AND METHODS

The data were collected from a review of the literature based on several PubMed and OMIM searches, through April 2010, using key-words "genetic disease Tunisia" and "Tunisian patients." Searches were also realized using physician and researcher names known to be working on genetic diseases in Tunisian population. Furthermore, references cited in the published articles were examined until no further study was identified. Publications in English and French languages provided essential informations. Two kinds of articles were analyzed: those that characterize the clinical manifestations of an inherited disease and those that depict the molecular basis of a genetic disease. MD and PhD theses and abstracts presented at meetings were also retrieved from universities and web sites or reports of knowledge societies.

In order to evaluate the genetic disorders distribution according to the affected tissue, process, system, or organ, the World Health Organization (WHO) International Classification of Disease (WHO ICD-10) version 2007 was utilized (http://apps.who.int/classifications/apps/icd/icd10online/). As some diseases are unclassified, we tried to adopt the most likely classification according to the phenotypes or clinical symptoms associated with the condition.

Statistical analysis and plots were handled with Microsoft Excel software.

## RESULTS

Most of the data on genetic diseases among Tunisian population that may be found in the literature are from patients living in Tunisia. Many reports were found about Tunisians living in France or in other European countries.

In the review of the literature, a nonexhaustive list of 346 genetic disorders has been identified. Fifty percent of the genetic diseases reported in this study have a defined molecular etiology and are caused by at least one mutation in one gene. For the remaining diseases, no molecular data were available, these correspond to conditions either not yet investigated in the Tunisian population or for which the causative gene is still unknown.

In multiple diseases, genetic heterogeneity is responsible for their relatively high frequency in the Tunisian population. Six different genes were responsible for the Bardet–Biedel syndrome. Allelic heterogeneity is also noticed with multiple mutations affecting one or different genes that trigger to a single morbid phenotype.

A founder effect was noticed in 50 genetic disorders. Among those, 25 are specific to the Tunisian population, the remaining correspond to founder alleles shared with other North African and Arab populations (unpublished data).

### Genetic Disorder Classification According to the Inheritance Mode

Nearly all the genetic disorders that we report have a known mode of inheritance. Some of them are described as having multiple modes of transmission: autosomal recessive (AR) and sporadic, autosomal recessive and autosomal dominant (AD) and finally, autosomal dominant and sporadic. Thus, 62.9% are autosomal recessive, 22.9% autosomal dominant, 5.4% X-linked, 0.3% Y-linked, 1.7% mitochondrial, 3.7% sporadic, and 0.9% of unknown mode of transmission. The conditions which could be transmitted with two different modes of transmission are encountered at low frequencies. Diseases inherited as both autosomal dominant and autosomal recessive are observed at 1.15%; those with sporadic inheritance in addition to autosomal dominant or autosomal recessive mode are less frequent (0.29% and 0.57%, respectively).

### Autosomal Recessive Diseases

In the 225 autosomal recessive diseases, 59% were caused by at least one mutation, while in the remaining other cases, the molecular basis of the condition were not available (unknown gene, mutation not yet identified). The results are summarized in Tables I and II, respectively.

TABLE I. Autosomal Recessive Diseases Due To At Least One Mutation

| Disease | OMIM | Gene | Mutations | Refs. |
|---|---|---|---|---|
| 3M syndrome | 273750 | *CUL7* | 2 | Huber et al. [2005] |
| Abetalipoproteinemia | 200100 | *MTP* | 4 | Najah et al. [2009], Benayoun et al. [2007] |
| Acral peeling skin syndrome | 609796 | *TGM5* | 1 | Kharfi et al. [2009] |
| Achromatopsia 2 | 216900 | *CNGA3* | 1 | Wissinger et al. [2001] |
| Acrodermatitis enteropathica | 201100 | *SLC39A4* | 4 | Meftah et al. [2006], Küry et al. [2002, 2003] |
| Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency | 201910 | *CYP21* | 15 | Kharrat et al. [2004, 2005] |
| | | *CYP21P* | 3 | |
| Afibrinogenemia | 202400 | *FGA* | 1 | Neerman-Arbez and de Moerloose [2007] |
| Albinism, oculocutaneous, type IA | 203100 | *TYR* | 3 | Gershoni-Baruch et al. [1994] |
| Allgrove syndrome | 231550 | *AAAS* | 1 | Tullio-Pelet et al. [2000] |
| Amaurosis congenital of Leber II | 204100 | *RPE65* | 1 | El Matri et al. [2006] |
| Amyotrophic lateral sclerosis 2, juvenile | 205100 | *ALSIN* | 2 | Hadano et al. [2001], Yang et al. [2001] |
| Aspartylglucosaminuria | 208400 | *AGA* | 1 | Ikonen et al. [1991] |
| Ataxia, Friedreich-like, with selectice vitamin E deficiency | 277460 | *TTPA* | 1 | Ouahchi et al. [1995] |
| Ataxia-Telangiectasia | 208900 | *ATM* | 1 | Gilad et al. [1996] |
| Bardet–Biedl syndrome | 209900 | *BBS1* | 1 | Smaoui et al. [2006], Hichri et al. [2005] |
| | | *BBS2* | 1 | |
| | | *BBS5* | 1 | |
| | | *BBS6* | 1 | |
| | | *BBS7* | 1 | |
| | | *BBS8* | 2 | |
| BCG infection, generalized familial | 209950 | *IFNGR1* | 1 | Jouanguy et al. [1996], Elloumi-Zghal et al. [2002] |
| | | *IL12RB1* | 2 | |
| | | *IL12p40* | 1 | |
| Bernard–Soulier syndrome | 231200 | *GP1BB* | 3 | Hadjkacem et al. [2009a,b] |
| Beta-thalassemias | 141900 | *HBB* | 29 | Chibani et al. [1988], Jacquette et al. [2004], Molchanova et al. [1992], Khelil et al. [2003], Fattoum et al. [2004], Chebil-Laradi et al. [1994], Fattoum [2006], Bibi et al. [2006], Laradi et al. [2000], Moumni et al. [2007] |
| Blood group-Kidd system | 111000 | *JK* | 1 | Lucien et al. [2002] |
| Cerebrotendinous xanthomatosis | 213700 | *CYP27A1* | 1 | Verrips et al. [2000] |
| Chanarin–Dorfman syndrome | 275630 | *ABHD5* | 1 | Lefevre et al. [2001] |
| Charcot–Marie–Tooth disease, type 4A | 214400 | *GDAP1* | 3 | Baxter et al. [2002] |
| Charcot–Marie–Tooth disease, type 4B2 | 604563 | *SBF2* | 1 | Azzedine et al. [2003] |
| Chronic granulomatous disease, cytochrome *b*-negative | 233690 | *CYBA* | 1 | El Kares et al. [2006] |
| Chronic granulomatous disease, cytochrome *b*-positive, type II | 233710 | *NCF2* | 2 | El Kares et al. [2006] |
| Chronic granulomatous disease, cytochrome *b*-positive, type I | 233700 | *NCF1* | 1 | El Kares et al. [2006] |
| Colorectal adenomatous polyposis | 608456 | *MUTYH* | 1 | Bougatef et al. [2008a] |
| Combined deficiency of Factor V and Factor VIII | 227300 | *LMAN1* | 2 | Segal et al. [2004], Abdallah et al. [2010] |
| Combined deficiency of vitamin K-dependent clotting factors | 277450 | *GGCX* | 3 | Darghouth et al. [2006] |
| Congenital analbuminemia | 103600 | *ALB* | 1 | Caridi et al. [2009] |
| Congenital myasthenic syndrome | 608931 | *CHRNE* | 1 | Richard et al. [2008] |
| Congenital nephrogenic diabetes insipidus | 125800 | *AQP2* | 1 | Bougacha-Elleuch et al. [2008] |

(*Continued*)

TABLE I. (*Continued*)

| Disease | OMIM | Gene | Mutations | Refs. |
|---|---|---|---|---|
| Corneal dystrophy, gelatinous drop-like | 204870 | *TACSTD2* | 2 | Ren et al. [2002] |
| Crigler–Najjar syndrome type I | 218800 | *UGT1A1* | 1 | Francoual et al. [2002a,b], Petit et al. [2008] |
| Cystic fibrosis | 219700 | *CFTR* | 17 | Messaoud et al. [1994, 1995, 1996, 2005] |
| Deafness, autosomal recessive 31; DFNB31 | 607084 | *DFNB31* | 1 | Tlili et al. [2005a] |
| Deafness, autosomal recessive 63; DFNB63 | 611451 | *LRTOMT* | 2 | Ahmed et al. [2008] |
| Deafness, congenital neurosensory, autosomal recessive 10; DFNB8/10 | 605316 | *TMPRSS3* | 2 | Masmoudi et al. [2001] |
| Deafness, neurosensory, autosomal recessive 2; DFNB2 | 600060 | *MYO7A* | 1 | Weil et al. [1997] |
| Deafness, neurosensory, autosomal recessive 3; DFNB3 | 600316 | *MYO15A* | 3 | Belguith et al. [2009], Masmoudi [2001] |
| Deafness, neurosensory, autosomal recessive 7; DFNB7 | 600974 | *TMC1* | 3 | Tlili et al. [2008] |
| Deafness, neurosensory, autosomal recessive 1; DFNB1 | 220290 | *GJB2* | 4 | Belguith et al. [2005], Denoyelle et al. [1997], Alemanno et al. [2009] |
| Distal renal tubular acidosis with progressive nerve deafness | 267300 | *ATP6V1B1* | 2 | Vargas-Poussou et al. [2006] |
| Dyggve–Melchior–Clausen disease | 223800 | *DYM* | 1 | El Ghouzzi et al. [2003] |
| Early onset ataxia with oculomotor apraxia and hypoalbuminemia | 208920 | *APTX* | 2 | Amouri et al. [2004] |
| Epidermolysis bullosa dystrophica, Hallipeau-siemens type, RDEB-sg, and RDEB-O | 226600 | *COL7A1* | 8 | Cherif et al. [2005], Ouragini et al. [2008, 2010], Hovnanian et al. [1997], Ben Brick [2008] |
| Faber lipogranulomatosis | 228000 | *ASAH1* | 1 | Bär et al. [2001] |
| Factor V deficiency | 227400 | *F5* | 1 | Schrijver et al. [2002] |
| Familial mediterranean fever | 249100 | *MEFV* | 8 | Chaabouni et al. [2007a] |
| Fanconi anemia | 227650 | *FANCA* | 5 | Bouchlaka et al. [2003] |
| Fragilitas oculi with hyperextensibility | 229200 | *ZNF469* | 1 | Abu et al. [2008] |
| Friedreich ataxia 1 | 229300 | *FXN* | 1 | Marzouki et al. [2001] |
| Gaucher disease, type I | 230800 | *GBA* | 3 | Dandana et al. [2007], Cherif et al. [2007] |
| Gaucher disease type II | 230900 | *GBA* | 1 | Dandana et al. [2007] Chaabouni et al. [2004], Ben Turkia et al. [2009] |
| Gaze palsy, familial horizontal, with progressive scoliosis | 607313 | *ROBO3* | 4 | El Bahri-Ben Mrad et al. [2004], Amouri et al. [2009] |
| Generalized atrophic benign epidermolysis bullosa | 226650 | *COL7A1* | 1 | Adala et al. [2009] |
| Ghosal hematodiaphyseal dysplasia | 231095 | *TBXAS1* | 2 | Genevieve et al. [2008] |
| Giant axonal neuropathy 1 | 256850 | *GAN* | 5 | Bomont et al. [2000] |
| Glycogen storage disease type Ia | 232200 | *G6PC* | 2 | Barkaoui et al. [2007] |
| Glycogen storage disease type III | 232400 | *AGL* | 1 | Lucchiari et al. [2002] |
| Glycogen storage disease V | 232600 | *PYGM* | 1 | Aquaron et al. [2004] |
| Hereditary hemochromatosis | 235200 | *HFE* | 2 | Mellouli et al. [2006], Sassi et al. [2004], Zorai et al. [2003] |
| Hurler syndrome | 607014 | *IDUA* | 6 | Laradi et al. [2001, 2005, 2006], Chkioua et al. [2007] |
| Hyperoxaluria, primary, type I | 259900 | *AGXT* | 1 | Chemli et al. [2007a] |
| Hypomagnesemia 3, renal | 248250 | *CLDN16* | 1 | Kuwertz-Bröking et al. [2001] |
| Hypophosphatasia, infantile | 241500 | *ALPL* | 1 | Haliouli-Louhaichi et al. [2007] |
| Ichthyosis, lamellar, 1 | 242300 | *TGM1* | 1 | Hennies et al. [1998] |
| Immunodeficiency with hyper-IgM, type 2 | 605258 | *AICDA* | 1 | Fiorini et al. [2004] |
| Inclusion body myopathy 2 | 600737 | *GNE* | 2 | Amouri et al. [2005] |
| Joubert syndrome 3 | 608629 | *AHI1* | 1 | Tory et al. [2007] |
| Kindler syndrome | 173650 | *FERMT1* | 2 | Jobard et al. [2003] |

(*Continued*)

TABLE I. (*Continued*)

| Disease | OMIM | Gene | Mutations | Refs. |
|---|---|---|---|---|
| L-2-@hydroxyglutaric acidemia | 236792 | *L2HGDH* | 2 | Rzem et al. [2004], Larnaout et al. [2008] |
| Lamellar cataract | 116800 | *HSF4* | 1 | Smaoui et al. [2004] |
| Leber congenital amaurosis, type I | 204000 | *GUCY2D* | 3 | Perrault et al. [1996] |
| Leucocyte adhesion deficiency | 116920 | *ITGB2* | 5 | Fathallah et al. [2001], Ben Mustapha et al. [2008] |
| Lipodystrophy, congenital generalized, type I | 608594 | *AGPAT2* | 2 | Magre et al. [2003] |
| Lysinuric protein intolerance | 222700 | *SLC7A7* | 1 | Sperandeo et al. [2000] |
| Mal de Meleda | 248300 | *SLURP1* | 3 | Charfeddine et al. [2003], Marrakchi et al. [2003] |
| Male infertility with large-headed multiflagellar, polyploid spermatozoa | 243060 | *AURKC* | 1 | Dieterich et al. [2007] |
| Meckel syndrome; type 4 | 611134 | *CEP290* | 3 | Baala et al. [2007] |
| Megalencephalic leukoencephalopathy with subcortical cysts | 604004 | *MLC1* | 2 | Omezzine et al. [2008], Tinsa et al. [2009] |
| Megaloblastic anemia 1 | 261100 | *AMN* | 1 | Bouchlaka et al. [2007] |
| Metachromatic leukodystrophy | 250100 | *ARSA* | 1 | Dorboz et al. [2009] |
| Mitochondrial DNA depletion syndrome, hepatocerebral form | 251880 | *DGUOK* | 1 | Brahimi et al. [2009] |
| Mucopolysaccharidosis type IVA | 253000 | *GALNS* | 2 | Laradi et al. [2006], Chaabouni et al. [2001] |
| Muscular dystrophy, congenital merosin-deficient, 1A | 607855 | *LAMA2* | 3 | Siala et al. [2008a,b, 2007] |
| Muscular dystrophy, congenital, 1C | 606612 | *FKRP* | 1 | Louhichi et al. [2004] |
| Muscular dystrophy, limb-girdle, type 2D | 608099 | *SGCA* | 1 | Fendri et al. [2006] |
| Muscular dystrophy, limb-girdle, type 2C | 253700 | *SGCG* | 2 | Noguchi et al. [1995], Kefi et al. [2003] |
| Muscular dystrophy, limb-girdle, type 2E | 604286 | *SGCB* | 1 | Bonnemann et al. [1998] |
| Muscular dystrophy, limb-girdle, type 2I | 607155 | *FKRP* | 3 | Kefi et al. [2008], Driss et al. [2000, 2003] |
| Myasthenia, limb-girdle, familial | 254300 | *DOK7* | 1 | Ben Ammar et al. [2010] |
| Myoclonic epilepsy of Unverricht and Lundborg | 254800 | *CSTB* | 1 | Manai-Lazizi [2003], Gouider et al. [1998], Moulard et al. [2002] |
| Nephronophthisis 1 | 256100 | *NPHP1* | 1 | Sellami et al. [2006] |
| Nephronophthisis 4 | 606966 | *NPHP4* | 1 | Sellami et al. [2006] |
| Nephrotic syndrome, steroid-resistant | 600995 | *NPHS2* | 1 | Kammoun et al. [2003] |
| Osteopetrosis with renal tubular acidosis | 259730 | *CA2* | 1 | Fathallah et al. [1994, 1997] |
| Parkinson disease 2 | 600116 | *PARK2* | 1 | Gouider-Khouja et al. [2003] |
| Parkinson disease 6 | 605909 | *PINK1* | 4 | Ishihara-Paul et al. [2008] |
| Pendred syndrome | 274600 | *SLC26A4* | 2 | Masmoudi et al. [2000], Ben Said et al. [2007] |
| Phenylketonuria | 261600 | *PAH* | 2 | Weinstein et al. [1993] |
| Pituitary hormone deficiency, combined | 262600 | *PROP1* | 2 | Reynaud et al. [2004, 2005] |
| Protein 4.2, erythrocytic; complete absence | 177070 | *EPB42* | 1 | Hayette et al. [1995], Ghanem et al. [1990] |
| Renal tubular dysgenesis | 267430 | *REN* | 1 | Gribouval et al. [2005] |
| Retinitis pigmentosa 40 | 180072 | *PDE6B* | 1 | Hmani-Aifa et al. [2009b] |
| Richner–Hanhart syndrome | 276600 | *TAT* | 2 | Charfeddine et al. [2006] |
| Schwartz–Jampel syndrome, type 1 | 255800 | *HSPG2* | 2 | Nicole et al. [2000] |
| Sickle cell anemia | 603903 | *HBB* | 1 | Abdennebi et al. [1994] |
| Spastic ataxia, Charlevois–Saguenay type | 270550 | *SACS* | 5 | El Euch-Fayache et al. [2003], Bouhlal et al. [2007] |
| Spastic paraplegia 11, autosomal recessive | 604360 | *SPG11* | 3 | Stevanin et al. [2007], Del Bo et al. [2007], Boukhris et al. [2009] |
| Spastic paraplegia 15, autosomal recessive | 270700 | *ZFYVE26* | 3 | Hanein et al. [2008] |
| Spastic paraplegia 5A, autosomal recessive | 270800 | *CYP7B1* | 5 | Tsaousidou et al. [2008], Boukhris et al. [2009], Goizet et al. [2009] |

(*Continued*)

TABLE I. (*Continued*)

| Disease | OMIM | Gene | Mutations | Refs. |
|---|---|---|---|---|
| Spinal muscular atrophy, type I | 253300 | *SMN1* | 2 | Mrad et al. [2006] |
| | | *BIRC1* | 1 | |
| Spinal muscular atrophy, type II | 253550 | *SMN1* | 2 | Mrad et al. [2006] |
| | | *BIRC1* | 1 | |
| Spinal muscular atrophy, type III | 253400 | *SMN1* | 2 | Mrad et al. [2006] |
| | | *BIRC1* | 1 | |
| Spinal muscular atrophy, type IV | 271150 | *SMN1* | 2 | Mrad et al. [2006] |
| Stargardt disease 1 | 248200 | *ABCA4* | 1 | Turki [2008] |
| Succinic semialdehyde dehydrogenase deficiency | 271980 | *ALDH5A1* | 1 | Bekri et al. [2004] |
| Tay–Sachs disease | 272800 | *HEXA* | 1 | Akli et al. [1990] |
| Thiamine-responsive megaloblastic anemia syndrome | 249270 | *SLC19A2* | 1 | Gritli et al. [2001] |
| Thrombotic thrombocytopenic purpura, congenital | 274150 | *ADAMTS13* | 1 | Meyer et al. [2008] |
| Usher syndrome, type I B | 276900 | *MYO7A* | 2 | Adato et al. [1997], Boulila-Elgaied et al. [1997] |
| Usher syndrome, type IG | 606943 | *USH1G* | 1 | Weil et al. [2003] |
| Usher syndrome, type II C | 605472 | *GPR98* | 1 | Hmani-Aifa et al. [2009b] |
| Usher syndrome, type IIA | 276901 | *USH2A* | 1 | Hmani-Aifa et al. [2002] |
| Waardenburg–Shah syndrome | 277580 | *EDNRB* | 1 | Attie et al. [1995] |
| Wilson disease | 277900 | *ATP7B* | 6 | Bziouech et al. [2008], Elleuch et al. [2010], Ben Hariz et al. [2004] |
| Wolcott–Rallison syndrome | 226980 | *EIF2AK3* | 1 | Delepine et al. [2000] |
| Xeroderma pigmentosum, complementation group A | 278700 | *XPA* | 1 | Nishigori et al. [1993], Messaoud et al. [2010a] |
| Xeroderma pigmentosum, complementation group C | 278720 | *XPC* | 1 | Ben Rekaya et al. [2009] |
| Xeroderma pigmentosum, variant type | 278750 | *POLH* | 1 | Broughton et al. [2002] |

## Autosomal Dominant Diseases

Eighty-three autosomal dominant disorders were reported. Among them 31.3% are caused by one or multiple mutations (Table III); the 68.7% others were of unknown etiology (Table IV).

## X-Linked Diseases

Nineteen X-linked disorders were reported among Tunisians (Table V). Nine of them were of known etiology (Table V) ( Table VI).

## Y-Linked, Mitochondrial, Sporadic, and With Unknown Mode of Transmission Diseases

Other genetic conditions were described in the Tunisian population. They include Y-linked, mitochondrial, and sporadic diseases and are summarized in Table VII. Some of them were of unknown mode of inheritance.

## Classification of Genetic Disorders Among Tunisians

Using the WHO International Classification of Disease, it was possible to classify the 346 genetic disorders identified among the Tunisian Population according to the affected organ, tissue, system, or biologic process (Fig. 1). Congenital malformations, deformations, and chromosomal abnormalities account for a major proportion with 30.5%. They encompass, essentially, congenital malformations and deformations of the musculoskeletal system, congenital malformations of nervous system, congenital malformations of eye, ear, face and neck, congenital malformations of the urinary system, and others. Endocrine, nutritional, and metabolic disorders are observed at 23%. Diseases of the nervous system are also frequent among Tunisians as they represent 17% of the total of genetic disorders reported.

## Spectrum of Hereditary Diseases and Phenotypic Differences

Although the prevalence and incidence are not estimated for the majority of the conditions reported in this study, some hereditary diseases are relatively frequent in Tunisia according to patient series reports. Congenital malformations are obviously the most common as they are detected at birth. There are several reports on diseases of the nervous system. Most of the reports are from the National Institute of Neurology at La Rabta-Tunis which has been considered the reference center for neurological diseases in the country for 30 years. Thus, informative families affected with different neurogenetic diseases were identified and allowed new loci and genes identification. They include autosomal recessive limb girdle muscular dystrophy (LGMD) type 2C [Ben Othmane et al.,

TABLE II. Autosomal Recessive Disease in Which There Are No Molecular Data

| Disease | OMIM | Gene | Refs. |
|---|---|---|---|
| 3-@Methylcrotonyl-CoA carboxylase 1 deficiency | 210200 | *MCCC1* ? | Elpeleg et al. [1992] |
| Acro-fronto-facio-nasal dysostosis syndrome | 201180 | Unknown | Chaabouni et al. [2008] |
| Achondrogenesis type I | 600972 | *ACG1B* ? | Lahmar-Boufaroua et al. [2009] |
| Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency | 202010 | *CYP11B1* ? | White et al. [1991] |
| Aicardi–Goutieres syndrome 1 | 225750 | *TREX1* ? | Akopova-Larbi et al. [2006] |
| Alpha-ketoglutarate dehydrogenase deficiency | 203740 | *OGDH* ? | Kohlschütter et al. [1982] |
| Alpha-methylacetoacetic aciduria | 203750 | *ACAT1* ? | Monastiri et al. [1999] |
| Alstrom syndrome | 203800 | *ALMS1* ? | Daoud et al. [2004] |
| Amyotrophic lateral sclerosis 5 | 602099 | Unknown | Hentati et al. [1998] |
| Arthropathy, progressive psudorheumatois, of childhood | 208230 | *WISP3* ? | Al Kaissi et al. [2007a] |
| Asphyxiating thoracic dysplasia | 208500 | Unknown | Lahmar-Boufaroua et al. [2009] |
| Biettli crystalline corneoretinal dystrophy | 210370 | *CYP4V2* ? | Chaker et al. [2007] |
| Bloom syndrome | 210900 | *RECQL3* ? | Bouguerra et al. [1994] |
| Canavan disease | 271900 | *ASPA* ? | Kraoua et al. [2009] |
| Charcot–Marie–Tooth disease, axonal, type 2H | 607731 | Unknown | Barhoumi et al. [2001] |
| Constitutional factor VII deficiency | 227500 | *F7* ? | Sfaihi Ben Mansour et al. [2009] |
| Cystinosis, nephropathic | 219800 | *CTNS* ? | Kamoun [1997] |
| Cystinuria | 220100 | *SLC3A1* ?<br>*SLC7A9* ? | Belhadj et al. [2008] |
| Dandy–Walker syndrome | 220200 | Unknown | Ben Hamouda et al. [2001] |
| Deafness, autosomal recessive 13; DFNB13 | 603098 | Unknown | Masmoudi et al. [2004] |
| Deafness, autosomal recessive 32; DFNB32 | 608653 | Unknown | Masmoudi et al. [2003] |
| Deafness, autosomal recessive 66; DFNB66 | 610212 | Unknown | Tlili et al. [2005b] |
| Deafness, autosomal recessive 4; DFNB4 | 600791 | *SLC26A4* ? | Masmoudi [2001] |
| Desbuquois syndrome | 251450 | *CANT1* ? | Al Kaissi et al. [2005a] |
| Ectodermal dysplasia, hypohidrotic, autosomal recessive | 224900 | *EDAR* ?<br>*EDARADD* ? | Al Kaissi et al. [2005b] |
| Epidermodysplasia verruciformis | 226400 | *EVER1* ?<br>*EVER2* ? | Messaoud et al. [2007] |
| Epidermolysis bullosa, junctional, Herlitz type | 226700 | *LAMA3* ? | Cherif et al. [2005], Ouragini et al. [2008] |
| Fucosidosis | 230000 | *FUCA1* ? | Ben Turkia et al. [2008] |
| Gapo syndrome | 230740 | Unknown | Goucha et al. [2002] |
| Gaucher disease type III | 231000 | *GBA* ? | Dandana et al. [2007], Chaabouni et al. [2004] |
| Glanzmann thrombasthenia | 273800 | *ITGA2B* ?<br>*ITGB3* ? | Ben Aribia et al. [2005] |
| Glutaric acidemia I | 231670 | *GCDH* ? | Gouider-Khouja and Ben Youssef-Turki [2006] |
| Glycine encephalopathy | 605899 | *GLDC* ?<br>*AMT* ?<br>*GCSH* ? | Esseghir et al. [2007] |
| Guanidinoacetate methyltransferase deficiency | 601240 | *GAMT* ? | Kraoua et al. [2008] |
| Hallervorden–Spatz disease | 234200 | *PANK2* ? | Gouider-Khouja et al. [2000] |
| Holoprosencephaly | 236100 | Unknown | Lahmar-Boufaroua et al. [2008] |
| Homocystinuria | 236200 | *CBS* ? | Azzabi et al. [2009] |
| Hypermethioninemia with deficiency of *S*-adenosylhomocysteine | 180960 | *AHCY* ? | Labrune et al. [1990] |
| Junctional epidermolysis bullosa, non-Herlitz type | 226650 | *LAMA3* ? | Cherif et al. [2005], Ouragini et al. [2008] |
| Kartagener syndrome | 244400 | *DNAI1* ? | Abdelmoula et al. [2006] |
| Kenny syndrome | 241410 | *TBCE* ? | Fitouri et al. [2005] |
| Krabbe disease | 245200 | *GALC*? | Kraoua et al. [2009] |
| Lafora disease | 254780 | *EPM2A* ?<br>*NHLRC1* ? | Kraoua et al. [2009] |
| Lamellar ichthyosis 3 | 604777 | *CYP4F22* ? | Lefevre et al. [2006] |
| Larsen syndrome | 245600 | Unknown | Al Kaissi et al. [2003] |

(*Continued*)

TABLE II. (*Continued*)

| Disease | OMIM | Gene | | Refs. |
|---|---|---|---|---|
| Maple syrup urine disease | 248600 | *DBT* ? | Monastiri et al. [1997] |
| Microspherophakia | 251750 | Unknown | Ben Yahia et al. [2009] |
| Miyoshi myopathy | 254130 | *DYSF* ? | Bejaoui et al. [1995] |
| Mucopolysaccharidosis type III A | 252900 | *SGSH* ? | Ouesleti et al. [2008] |
| Mucopolysaccharidosis type IIIB | 252920 | *NAGLU* ? | Laradi et al. [2001], Chaabouni et al. [2001] |
| Mucopolysaccharidosis type IIIC | 252930 | *HGSNAT* ? | Laradi et al. [2001] |
| Mucopolysaccharidosis type IIID | 252940 | *GNS* ? | Laradi et al. [2001] |
| Mucopolysaccharidosis type VI | 253200 | *ARSB* ? | Laradi et al. [2001], Chaabouni et al. [2001] |
| Muscular dystrophy, congenital, 1B | 604801 | Unknown | Triki et al. [2003] |
| Netherton syndrome | 256500 | *SPINK5* ? | Boussofara et al. [2007] |
| Niemann–Pick disease, type A | 257200 | *SMPD1* ? | Kraoua et al. [2009] |
| Niemann–Pick disease, type B | 607616 | *SMPD1* ? | Vanier et al. [1993] |
| Non syndromic hearing loss linked to 1q13–31 | None | Unknown | Masmoudi [2001] |
| Non syndromic posterior microphthalmia | 610093 | *CHX10* ? | Hmani-Aifa et al. [2009a] |
| Nonbullous congenital ichthyosiform erythroderma 1 | 242100 | *ALOX12B* ?<br>*ALOXE3* ?<br>*TGM1* ? | Herman et al. [2009] |
| Nyssen–van Bogaert syndrome | None | Unknown | Larnaout et al. [1998] |
| Opsismodysplasia | 258480 | Unknown | Al Kaissi et al. [2009] |
| OSA syndrome | 265050 | Unknown | Al Kaissi et al. [2007b] |
| Phenylketonuria II | 261630 | *QDPR* ? | Miladi et al. [1998] |
| Pierre–Marie's hereditary ataxia | 109150 | *ATXN3* ? | Ben Hamida et al. [1986] |
| Polyscystic kidney disease, autosomal recessive | 263200 | *FCYT* ? | Kamoun [1997] |
| Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy | 221770 | *TYROBP* ?<br>*TREM2* ? | Chaabane et al. [2000] |
| Roberts syndrome | 268300 | *ESCO2* ? | Kacem et al. [2006] |
| Robinow syndrome | 268310 | Unknown | Samoud et al. [1993] |
| Rosai–Dorfman syndrome | Unknown | Unknown | Meyer et al. [2008], Kharrat et al. [2008] |
| Say–Barber–Miller syndrome | 251240 | Unknown | Kechaou et al. [2009] |
| Schneckenbecken dysplasia | 269250 | *SLC35D1* ? | Lahmar-Boufaroua et al. [2009] |
| Senior–Loken syndrome 1 | 266900 | *NPHP1* ? | Sellami et al. [2006] |
| Short rib polydactyly syndrome or majewski type | 263520 | Unknown | Lahmar-Boufaroua et al. [2009] |
| Short rib polydactyly syndrome IV or Beemer–Langer type | 269860 | Unknown | Abdelmoula et al. [2008] |
| Sjogren syndrome | 270150 | Unknown | Béji et al. [2007] |
| Sjogren–Larsson syndrome | 270200 | *ALDH3A2* ? | Kraoua et al. [2009] |
| Spastic paraplegia 5B, autosomal recessive | 600146 | Unknown | Hentati et al. [1994b] |
| Spondylocarpotarsal synostosis syndrome | 272460 | *FLNB* ? | Al Kaissi et al. [2006a] |
| Spondyloepimetaphyseal dysplasia with joint laxity | 271640 | Unknown | Al Kaissi et al. [2008a] |
| Sulfatidosis juvenile, Austin type | 272200 | *SUMF1* ? | Kraoua et al. [2009] |
| Syndactyly, type I, with micocephaly and mental retardation | 272440 | Unknown | Heron et al. [1995] |
| Teebi–Shaltout syndrome | 272950 | Unknown | Froster et al. [1993] |
| Teebi–Shaltout syndrome like | None | Unknown | Chaabouni et al. [2005a] |
| Testicular regression syndrome | 273250 | Unknown | de Grouchy et al. [1985] |
| Wolfram syndrome 1 | 222300 | *WFS1* ? | Bouslama et al. [2002] |
| Wolman disease | 278000 | *LIPA* ? | Mnif et al. [1994] |
| Xeroderma pigementosum, complementation group F | 278760 | *ERCC4* ? | Zghal et al. [2003] |

?: As the Tunisian patients are not necessarily mutated for the gene already reported in the literature, we have added a question mark following each "candidate" gene.
NB: Not all the reports have included the mode of inheritance of the disease in Tunisian patients, in this case, the mode of transmission is inferred from OMIM.

1992], LGMD 2I [Driss et al., 2000], Friedreich ataxia with vitamin E deficiency [Ben Hamida et al., 1993], recessive familial amyotrophic lateral sclerosis [Hentati et al., 1994a], giant axonal neuropathy [Ben Hamida et al., 1997], autosomal recessive cerebellar ataxia [Mrissa et al., 2000], and Charcot–Marie–Tooth disease [Ben Othmane et al., 1999; Barhoumi et al., 2001].

Nonsyndromic hearing loss is prevalent in Tunisia, as its frequency ranges from 2% to 8% especially in isolates. Classical studies

TABLE III. Autosomal Dominant Diseases Due To At Least One Mutation

| Disease | OMIM | Gene | Mutations | Refs. |
|---|---|---|---|---|
| Adenomatous polyposis of the colon | 175100 | *APC* | 3 | Bougatef et al. [2008a,b] |
| | | *BRAF* | 1 | |
| | | *MUTYH* | 2 | |
| Alpha thalessemia | 141750 | *HBA1* | 4 | Siala et al. [2005], Darbellay et al. [1995] |
| Blepharophimosis, ptosis, and epicanthus inversus | 110100 | *FOXL2* | 1 | Houiji [2008], Chouchene et al. [2010] |
| Bare lymphocyte syndrome, type II | 209920 | *RFXANK* | 2 | Lennon-Dumenil et al. [2001], Wiszniewski et al. [2000] |
| Breast cancer | 114480 | *BRCA1* | 7 | Troudi et al. [2007, 2008], Mestiri et al. [2000], Monastiri et al. [2002] |
| | | *BRCA2* | 3 | |
| Congenital antithrombin deficiency type HBS | 107300 | *SERPINC1* | 1 | Guermazi et al. [2007] |
| Creutzleldt–Jakob disease | 123400 | *PRNP* | 1 | Goldfarb et al. [1991], Byers [2000], Suk Lee et al. [1999] |
| Darier–White disease | 124200 | *ATP2A2* | 9 | Zeglaoui et al. [2005], Bchetnia et al. [2009a,c] |
| Elliptocytosis, Rhesus-unlinked type | 130600 | *SPTA1* | 3 | Baklouti et al. [1991], Morle et al. [1989], Alloisio et al. [1992] |
| Factor XIII deficiency | 134570 | *F13A* | 2 | Elmahmoudi et al. [2007], Louhichi et al. [2010] |
| Familial hypercholesterolemia | 143890 | *LDLR* | 8 | Jelassi [2009], Jelassi et al. [2008, 2009], Slimane et al. [2001, 2002] |
| Generalized epilepsy with febrile seizures plus | 604233 | *SCN1A* | 1 | Fendri-Kriaa et al. [2009b], Bel Hedi et al. [2007] |
| | | *SCN1B* | 1 | |
| Hereditary multiple exostoses | 133700 | *EXT1* | 2 | Sfar et al. [2009] |
| Hypobetalipoproteinemia, familial | 107730 | *APOB* | 1 | Najah et al. [2009] |
| Hypophosphatemic rickets | 193100 | *FGF23* | 1 | Bouyacoub [2008], Gribaa et al. [2010] |
| Lynch syndrome | 120435 | *MLH1* | 1 | Aissi-Ben Moussa et al. [2009] |
| Melanoma, cuteneous malignant, susceptibility to, 2 | 155601 | *CDKN2A* | 1 | Yakobson et al. [2003] |
| Multiple endocrine neoplasia, type IIA | 171400 | *RET* | 1 | Harzallah et al. [2008] |
| Noonan syndrome | 163950 | *PTPN11* | 2 | Louati et al. [2009] |
| Parkinson disease 8 | 607060 | *LRRK2* | 1 | Ishihara et al. [2006, 2007] |
| Porphyria cutanea tarda | 176100 | *UROD* | 1 | De Verneuil et al. [1986] |
| Pretibial epidermolysis bullosa dystrophica | 131850 | *COL7A1* | 1 | Cherif et al. [2005], Ouragini et al. [2008, 2009] |
| Severe hypertriglyceridemia | 145750 | *APOA5* | 1 | Priore Oliva et al. [2005] |
| Spastic paraplegia 4 | 182601 | *SPG4* | 5 | Hentati et al. [2000], Boukhris et al. [2009] |
| Spinocerebellar ataxia 2 | 183090 | *ATXN2* | 1 | Belal et al. [1994], Cancel et al. [1997] |
| Thrombophilia due to activated protein C resistance | 188055 | *F5* | 1 | Frere et al. [2003] |
| | | *F2* | 1 | |

have demonstrated genetic heterogeneity for nonsyndromic autosomal recessive congenital neurosensory deafness. Many loci responsible for sensorial impairment were also identified by investigating Tunisian families. The autosomal recessive forms, named DFNB, are the most frequent forms of the prelingual genetic forms of deafness as they represent 80% among the studied cases [Ben Arab et al., 2004]. The first two DFNB1 and DFNB2 loci were identified by homozygosity mapping in two consanguineous Tunisian families, respectively, from the North and the South of the country [Guilford et al., 1994; Boulila-Elgaied et al., 1997]. The list of new loci and causative mutations identification in Tunisian pedigrees is continuously increasing [Roume et al., 1998; Masmoudi et al., 2001, Masmoudi et al., 2003, Masmoudi et al., 2004; Thauvin-Robinet et al., 2002; Tlili et al., 2005a, Tlili et al., 2005b; Abu et al., 2006; Belguith et al., 2009; Hmani-Aifa et al., 2009a, 2009b].

Genetic epidemiology investigations allowed identification of families with Mendelian inheritance of multifactorial diseases. As an example, in Tunisian families with Parkinson disease, a genetic study revealed that the disease is genetically heterogeneous with at

TABLE IV. Autosomal Dominant Diseases in Which There Are No Molecular Data

| Disease | OMIM | Gene | Refs. |
|---|---|---|---|
| Achondrogenesis type II | 200610 | *COL2A1* ? | Lahmar-Boufaroua et al. [2009] |
| Acrofacial dysostosis, 1, Nager type | 154400 | Unknown | Benjemaa et al. [2002] |
| Acute intermittent porphyria | 176000 | *HMBS* ? | Kraoua et al. [2009] |
| Alport syndrome | 104200 | Unknown | Kharrat et al. [2006] |
| Alzheimer disease | 104300 | *APP* ? | Smach et al. [2009] |
| Antiphospholipid syndrome | 107320 | Unknown | Chabchoub et al. [2009] |
| Atrial septal defect | 108900 | Unknown | Nouira et al. [2008] |
| Apert syndrome | 101200 | *FGFR2* ? | El Afrit et al. [2007] |
| Beckwith–Wiedemann syndrome | 130650 | *CDKN1C* ? | H'mida et al. [2008] |
| | | *H19* ? | |
| | | *KCNQ1OT1* ? | |
| Brooke–Spiegler syndrome | 605041 | *CYLD* ? | Zaraa et al. [2006] |
| Bullous erythroderma ichthyosiformis congenita of Brocq | 113800 | *KRT1* ? | Kharfi et al. [2008] |
| | | *KRT10* ? | |
| Central areolar choroidal dystrophy | 215500 | Unknown | Ouechtati et al. [2009] |
| Charge syndrome | 214800 | *CHD7* ? | Ben Becher et al. [1994] |
| | | *SEMA3E* ? | |
| Chondrocalcinosis 2 | 118600 | *ANKH* ? | Béjia et al. [2004] |
| Clouston syndrome (Hidrotic ectodermal dysplasia) | 129500 | *GJB6* ? | Mrad et al. [2007] |
| Dermatitis herpetiformis, familial | 601230 | Unknown | Khaled et al. [2008] |
| Dermatitis, atopic | 603165 | *ATOD2* ? | Kharfi et al. [2001] |
| | | *ATOD3* ? | |
| | | *ATOD6* ? | |
| Distal renal tubular acidosis, RTA-1 | 179800 | Unknown | Chaabani et al. [1994] |
| Dyschromatosis symmetrica hereditaria 1 | 127400 | *ADAR* ? | Kenani et al. [2008] |
| Dyschromatosis universalis hereditaria | 127500 | Unknown | Dhaoui and Doss [2001] |
| Dystrophia myotonica 1 | 160900 | *DMPK* ? | Miladi et al. [2009] |
| Emery–Dreifuss muscular dystrophy | 181350 | *LMNA* ? | Chabrak et al. [2006] |
| Epidermolysis bullosa simplex | 131800 | *KRT5* ? | Cherif et al. [2005], Ouragini et al. [2008] |
| Exfoliation syndrome | 177650 | *LOXL1* ? | Ayed et al. [1990] |
| Familial spastic paraplegia (Strumpell–Lorrain) | 182600 | *SPG3A* ? | Ben Hamida et al. [1986] |
| Familial vertebral segmentation defects, sprengel anomaly, and omovertebral bone | None | Unknown | Al Kaissi et al. [2005c] |
| Ferguson–Smith disease | 132800 | Unknown | Mamaï et al. [2009] |
| Fibrodyspalsia ossificans progressiva | 135100 | *NOG* ? | Lucotte et al. [2000] |
| Hailey–Hailey disease | 169600 | *ATP2C1* ? | Benmously-Mlika et al. [2008] |
| Ichthyosis vulgaris | 146700 | *FLG* ? | Kharfi et al. [2008] |
| Kabuki makeup syndrome | 147920 | Unknown | Abdelmoula et al. [2009] |
| Keratosis palmoplantaris papulosa | 148600 | Unknown | Bchetnia et al. [2009b] |
| Legg–Calve–Perthes disease | 150600 | *COL2A1* ? | Ben Miled et al. [1996] |
| Marfan syndrome | 154700 | *FBN1* ? | Chaouch et al. [1990], Slama et al. [2002] |
| Mayer–Rokitansky–Kuster–Hauser syndrome | 277000 | Unknown | Bouayed Abdelmoula et al. [2007] |
| Melkersson–Rosenthal syndrome | 155900 | Unknown | Rouissi et al. [2007] |
| Miller–Dieker lissencephaly syndrome | 247200 | *PAFAH1B1* ? | Ouertani et al. [2007] |
| Myoclonic dystonia | 159900 | *SGCE* ? | Miladi et al. [2003a] |
| | | *DRD2* ? | |
| | | *DYT1* ? | |
| Neurofibrimatosis, type I | 162200 | *NF1* ? | Mammou et al. [2008] |
| Novel form of ischio-vertebral syndrome | None | Unknown | Al Kaissi et al. [2007d] |
| Otosclerosis 3 | 608244 | Unknown | Ben Arab et al. [1993], Ali et al. [2007] |
| Paroxysmal kinesigenic dyskinesia | 128200 | Unknown | Mrabet Khiari et al. [2009] |
| Parry–Romberg syndrome | 141300 | Unknown | Mrabet Khiari et al. [2009] |
| Polycystic kidneys | 173900 | *PKD1* ? | Abderrahim et al. [2004], Kheder et al. [1992] |
| | | *PKD2* ? | |
| Pulmonary hemosiderosis | 178550 | Unknown | Maalej et al. [2005] |
| Thanatophoric dysplasia | 187600 | *FGFR3* ? | Lahmar-Boufaroua et al. [2009] |

(*Continued*)

TABLE IV. (*Continued*)

| Disease | OMIM | Gene | Refs. |
|---|---|---|---|
| Thrombocytopenic purpura, autoimmune | 188030 | Unknown | Zribi et al. [2008] |
| Tracheopathia osteoplastica | 189961 | Unknown | Hantous-Zannad et al. [2003] |
| Treacher–Collins–Franceschetti syndrome | 154500 | *TCOF1* ? | Chaabouni et al. [2007b] |
| Von Willebrand disease | 193400 | *VWF* ? | Guermazi et al. [2006], Znazen et al. [2007] |
| Weismann–Netter syndrome | 112350 | Unknown | Al Kaissi et al. [2006b] |
| Wolf–Parkinson–White syndrome | 194200 | *PRKAG2* ? | Nouira et al. [2007] |

?: As the Tunisian patients are not necessarily mutated for the gene already reported in the literature, we have added a question mark following each "candidate" gene.
NB: Not all the reports have included the mode of inheritance of the disease in Tunisian patients, in this case, the mode of transmission is inferred from OMIM.

least two inheritance patterns, autosomal dominant and autosomal recessive [Gouider-Khouja et al., 2003]. For Mendelian disorders, curious patterns of inheritance have been reported. For Mal de Meleda, an autosomal recessive palmo-plantar keratoderma, females heterozygous for different *ARS* gene mutations expressed attenuated signs of the skin disease [Mokni et al., 2004]. Genetic investigation of a large Tunisian family, with a wide range of clinical manifestations of dystrophic epidermolysis bullosa, showed autosomal semidominant model of inheritance with incomplete penetrance and variable expression for the causative mutation [Ouragini et al., 2009].

In 1980, Ben Hamida and Fardeau described, for the first time in Tunisian families, a new form of an autosomal recessive Duchenne-like muscular dystrophy, reported as "Maghrebian muscular dystrophy" [Ben Hamida and Fardeau, 1980, 1983]. This observation qualified by some neurologist as a misdiagnosis of DMD (Ben Hamida, personal communication) This observation is actually known as Limb-girdle muscular dystrophy type 2C [Teebi and Farag, 1997]. In the last decades, new syndromes or variants of very rare syndromes were reported among Tunisians [Chaabouni et al., 2005a; Al Kaissi et al., 2007b]. Persistent torticollis, facial asymmetry, grooved tongue, and dolicho-odontoid process in connection with atlas malformation

TABLE V. X-Linked Diseases Due To At Least One Mutation

| Disease | OMIM | Gene | Mutations | Refs. |
|---|---|---|---|---|
| Androgen insensitivity syndrome | 300068 | *AR* | 1 | Bel Hadj Youssef et al. [2008] |
| Cleft palate with ankyloglossia | 303400 | *TBX22* | 1 | Chaabouni et al. [2005b] |
| Fragile X mental retardation syndrome | 300624 | *FMR1* | 2 | Ben Jemaa et al. [2008], Frikha et al. [2007], Falik-Zaccai et al. [1997] |
| G6PD deficiency | 305900 | *G6PD* | 4 | Daoud et al. [2008] |
| Hypogonadotropic hypogonadism without adrenal insufficiency | 300200 | *DAX1* | 2 | Trimeche Ajmi et al. [2005], Turki et al. [2005] |
| Mental retardation, X-linked 30 | 300558 | *PAK3* | 1 | Rejeb et al. [2008] |
| Mental retardation, X-linked 54 | 300419 | *ARX* | 2 | Bienvenu et al. [2002], Jemaa et al. [1999] |
| Premature ovarian failure | 300510 | *BMP15* | 1 | Lakhal et al. [2009] |
| Rett syndrome | 312750 | *MECP2* | 2 | Triki and Mhiri [1999], Fendri-Kriaa et al. [2009a] |

TABLE VI. X-Linked Diseases in Which No Molecular Data Are Available

| Disease | OMIM | Gene | Refs. |
|---|---|---|---|
| Adrenoleukodystrophy | 300100 | *ABCD1* ? | Kraoua et al. [2009] |
| Coffin–Lowry syndrome | 303600 | *RPS6KA3* ? | Maazoul et al. [2002] |
| Duchenne muscular atrophy | 310200 | *DMD* ? | Fakhfakh et al. [1996], Mhiri et al. [1996] |
| Epileptic encephalopathy, early infantile, 1 | 308350 | *ARX* ? | Ben Hamida et al. [1992], Triki et al. [2001], Mahfoudh et al. [2007] |
| Fabry disease | 301500 | *GLA* ? | Kaaroud et al. [2007] |
| Ichthyosis, X-linked | 308100 | *STS* ? | Kharfi et al. [2008] |
| Lissencephaly, X-linked 1 | 300067 | *DCX* ? | Ben Rhouma et al. [2007] |
| Mucopolysaccharidosis type II | 309900 | *IDS* ? | Laradi et al. [2001] |
| Ornithine carbamoyltransferase deficiency | 311250 | *OTC* ? | Meddeb et al. [2009] |
| Properdin deficiency, X-linked | 312060 | *CFP* ? | Schlesinger et al. [1993] |

?: As the Tunisian patients are not necessarily mutated for the gene already reported in the literature, we have added a question mark following each "candidate" gene.

TABLE VII. Y-Linked, Mitochondrial, Sporadic, and With Other Modes of Transmission Disorders

| Disease | OMIM | Inheritance | Gene | Mutations | Refs. |
|---|---|---|---|---|---|
| Spermatogenic failure, nonobstructive | 415000 | Y-Linked | *USP9Y* | 4 | Hadj-Kacem et al. [2006] |
| Idiopathic dilated cardiomyopathy | None | Mitochondrial | *tRNAIle* gene | 1 | Mahjoub et al. [2007] |
| Leigh syndrome | 256000 | Mitochondrial | *MTATP6* | 3 | Adouani et al. [2009], Mkaouar-Rebai et al. [2009a] |
| | | | *MTTW* | 2 | Mkaouar-Rebai et al. [2009b] |
| Leukodystrophy | None | Mitochondrial | *ATPase 8* | 1 | Mkaouar et al. [2009] |
| MELAS syndrome | 540000 | Mitochondrial | *MTTL1* ?<br>*MTTQ* ?<br>*MTTH* ?<br>*MTTK* ?<br>*MTTS1* ?<br>*MTND1* ?<br>*MTND5* ?<br>*MTND6* ?<br>*MTTS2* ? | 0 | Kraoua et al. [2009] |
| MERRF syndrome | 545000 | Mitochondrial | *MTTK* ?<br>*MTTL1* ?<br>*MTTH* ?<br>*MTTS1* ?<br>*MTTS2* ?<br>*MTTF* ?<br>*MTND5* ? | 0 | Kraoua et al. [2009] |
| Non syndromic hearing loss | 561000 | Mitochondrial | *MTRNR1* | 1 | Mkaouar-Rebai et al. [2006] |
| Angelman syndrome | 105830 | Sporadic | *UBE3A* | 1 | Abaied et al. [2010] |
| Cushing's syndrome | 219080 | Sporadic | *GNAS* ? | 0 | Halioui-Louhaichi et al. [2005] |
| Flail arm syndrome | None | Sporadic | Unknown | 0 | Ben Youssef et al. [2004] |
| Jacobsen syndrome | 147791 | Sporadic | Unknown | 1 | Bedoui et al. [2005] |
| McCune–Albright syndrome | 174800 | Sporadic | *GNAS* ? | 0 | Halioui-Louhaichi et al. [2005] |
| MURCS association | 601076 | Sporadic | Unknown | 0 | Al Kaissi et al. [2008b] |
| Myasthenia gravis | 254200 | Sporadic | Unknown | 0 | Miladi et al. [2008], Trabelsi et al. [2006] |
| Proteus syndrome | 176920 | Sporadic | *PTEN* ? | 0 | Chelly et al. [2008] |
| Silver–Russell syndrome | 180860 | Sporadic | Unknown | 0 | Feki et al. [2007] |
| Sternal cleft | None | Sporadic | Unknown | 0 | Sayed et al. [2008] |
| Stiff–Person syndrome | 184850 | Sporadic | Unknown | 0 | Gouider-Khouja et al. [2002] |
| Rhombencephalo-synapsis | None | Sporadic | Unknown | 0 | Chemli et al. [2007b] |
| New form of spondyloepi-metaphysealdysplasia, with severe metaphyseal, changes similar to Jansen metaphyseal chondrodysplasia | None | Unknown | Unknown | 0 | Al Kaissi et al. [2005d] |
| Rasmussen syndrome | None | Unknown | Unknown | 0 | Miladi et al. [2003a] |
| Susac syndrome | None | Unknown | Unknown | 0 | Mili-Boussen et al. [2001], Lammouchi et al. [2004] |
| Moebius syndrome | 157900 | AD or Sporadic | Unknown | 0 | Al Kaissi et al. [2007c] |
| Moyamoya syndrome | 252350 | AR or Sporadic | Unknown | 0 | Sfaihi Ben Mansour et al. [2008] |
| Addison–Biermer anemia | None | AR or Sporadic | *GIF* ? | 0 | Maktouf et al. [2007] |
| Aplasia cutis congenita, nonsyndromic | 107600 | AR or AD | Unknown | 0 | Aloulou et al. [2008] |
| Congenital factor XI deficiency | 612416 | AR or AD | *F11* ? | 0 | Souabnia et al. [2008] |
| Myasthenic syndrome, congenital, slow-channel | 601462 | AR or AD | *CHRNA1* ?<br>*CHRNB1* ?<br>*CHRND* ?<br>*CHRNE* ? | 0 | Ben Youssef Turki et al. [2008] |

?: As the Tunisian patients are not necessarily mutated for the gene already reported in the literature, we have added a question mark following each "candidate" gene.
NB: Not all the reports have included the mode of inheritance of the disease in Tunisian patients, in this case, the mode of transmission is inferred from OMIM.

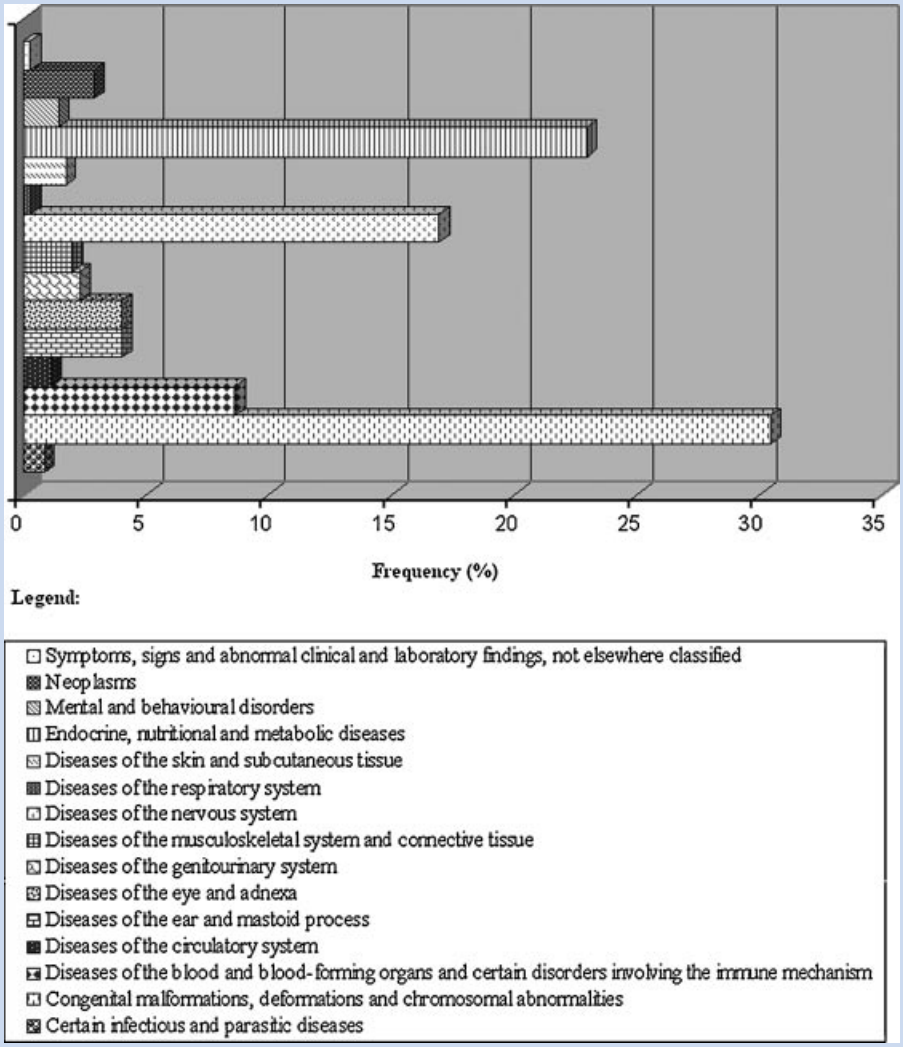


**FIG. 1. WHO ICD-10 classification of genetic disorders among Tunisians.**

complex was reported in three members of a Tunisian family by Al Kaissi et al. [2007e]. This author reported also rare variants of SEMDJL and Desbuquois syndromes [Al Kaissi et al., 2005a, 2008a], in addition to new clinical features associated to already known syndromes [Al Kaissi et al., 2007c, 2009]. Extremely rare syndromes were also reported in the Tunisian population. A third case of acro-fronto-facio-nasal dysostosis associated with genitourinary anomalies was recently described [Chaabouni et al., 2008]. With the development of local capacities for molecular diagnosis the list of new and rare phenotypes is continuously increasing [Messaoud et al., 2010b].

## DISCUSSION

In order to asses the spectrum and burden of hereditary conditions affecting the Tunisian population, a systematic review of the literature was performed and allowed identification of at least 346 disorders. Although population specific databases, including a general one on Arab population [Tadmouri et al., 2006] and one on mutations in the Tunisian population [The Tunisian National Genetic Database; http://www.goldenhelix.org/tunisian/] do exist, these databases are noncomprehensive and not always updated. Indeed, only 88 mutated genetic diseases are reported in the Tunisian National Genetic Database, this does not reflect the spectrum of inherited disorders in the Tunisian population. The available data suggest that genetic and congenital disorders are common in Tunisia, recessively inherited ones account for a substantial proportion of physical and mental disability. This is not a reporting bias and has been already reported by other authors on genetic diseases in consanguineous populations [Teebi, 1994; Hamamy et al., 2007b]. Several factors may contribute to the high prevalence of genetically determined disorders the most important being the high rate of inbreeding in the Tunisian population. The unions between Tunisian relatives represent more than 32%, which may reach 60% in rural areas [Riou et al., 1989; Ben Arab et al., 2004; Kerkeni et al., 2007]. As in the other Arab countries [Khlat, 1988; Teebi, 1994], first cousin marriages are the most represented in Tunisia [Ben Arab et al., 2004; Ben M'rad and Chalbi, 2004]. Traditions and motivations of social, cultural, and economical

order most often direct the candidates for the marriage to a marital choice inside the family, or the clan, thus installing endogamy and consanguinity [Ben M'rad and Chalbi, 2006]. Indeed, a man marries his first cousin in priority, or a distant relative or a neighbor. This choice could be considered as an obligation since any deviation in relation to these rules could lead to social reprobation or even a familial sanction [Ben M'rad and Chalbi, 2006]. The spouse or husband selections could also occur in a geographic proximity and most often in rural surroundings where people keep their traditional, farm, and social profiles [Ben M'rad and Chalbi, 2006]. This can be assessed as a geographic endogamy that leads to increment the consanguinity rate. This tendency to endogamy creates groups in the population where chances that two gametes carrying the same genetic information meet each other are more elevated than in the general population, and thus, increasing consanguinity as a consequence [Jakobi and Jacquard, 1971].

Endogamy and consanguinity have direct consequences on distribution, structure, and heterogeneity of the genetic flow of the population [Ben M'rad and Chalbi, 2006]. It was reported that the combined effects of founder effect, inbreeding added to genetic drift may increase the frequency of detrimental rare variants in human, leading to an overall worsening of population health, whereas admixture and outbreeding appear to have the opposite effect [Rudan et al., 2006]. When first cousin marriage is considered, the risk of recessively inherited disorders is multiplied by 15–30 times; hence, doubling the total frequency of congenital and genetic disorders [Alwan and Modell, 1997 *in* Tadmouri, 2004]. Consequently, a clear association may exist between the incidence of autosomal recessive disorders and inbreeding [Hoodfar and Teebi, 1996]. Because of their high frequencies, a part of the inherited conditions are considered as a public health problem in the country such as hemoglobinopathies which are a common group of inherited erythrocyte pathologies with thalassemia and sickle cell anemia. Regional screening programs assessed heterozygous frequency to be 4.5% of thalassemia and sickle cell anemia with a high prevalence in North Western (10.9%) and South-Western (5.3%) regions [Haj Khelil et al., 2004; Direction des Soins de Santé de Base (DSSB) du Ministère de la Santé Publique, DSSB, 2000]. The district of Nefza constitutes an important focus of sickle cell anemia with a prevalence of 13.3% [Haj Khelil et al., 2004; Direction des Soins de Santé de Base (DSSB) du Ministère de la Santé Publique, DSSB, 2000]. The high rate of consanguinity is also supposed to be the cause of the high-incidence of Fanconi anemia [Bouchlaka et al., 2003]. Cystic fibrosis is known to be the most frequent autosomal recessive genetic disease in North European population. This disease is not rare in Tunisia as 390 affected children belonging to 383 families were reported with an inbreeding rate of 86.44% [Messaoud et al., 2005]. The study carried out by Ben Arab et al. [2004] on deafness in the North of Tunisia, revealed that the relative risk due to the 35delG mutation, which is the most frequent allele for nonsyndromic recessive deafness in Tunisia, is 10 times more important for first cousin patients than for those who descend from nonconsanguineous parents. The village of Borj Salhi is reputed to show the highest frequency of this condition which exposes this community to medical, social, and economic problems [Direction des Soins de Santé de Base (DSSB) du Ministère de la Santé Publique, DSSB, 2000].

Another consequence of the high rate of inbreeding is the occurrence of two or more phenotypes within the same family with autosomal recessive mode of inheritance for both phenotypes like Mal de Meleda and congenital cataract [Bchetnia et al., 2010] or autosomal recessive and autosomal dominant phenotypes within the same families: Darier disease and ichthyosis [Bchetnia et al., 2009c], right ventricular hypertrophy and lamellar ichthyosis (unpublished data). In certain cases, this may conduct to erroneous genetic mapping [Hmani-Aifa et al., 2009b] and renders genetic counseling particularly challenging in particular for genetic heterogeneous phenotypes. In the report of Fendri et al. [2006], three Tunisian patients belonging to the same consanguineous family shared similar LGMD 2 phenotype but heterogeneous sarcoglycans immunohistochemical patterns. Thus, the existence of two recessive conditions in the same sibship, which seems to be exceptional, may be taken into consideration in high inbred communities.

In a previous study from an Arab country, the authors showed once again the strong association between high consanguinity rates and the prevalence of recessively inherited disorders [Hamamy et al., 2007b]. However, this correlation was not established with conditions of other etiological categories and modes of transmission among consanguineous families compared with the general population [Hamamy et al., 2007b]. In inbred populations, homozygosity is shown for dominant genes. In diseases in which the mutation leads to an abnormal structural protein, the homozygote may be more severely affected than the heterozygote such as in the case of dystrophic epidermolysis bullosa [Ouragini et al., 2009]. It is also likely that homozygosity for genes involved in the pathogenesis of multifactorial disorders is one of the major causes of the increased rate of familial cancers like breast and colorectal cancers which is the first cause of digestive cancer mortality in Tunisia [Bougatef et al., 2008b]. Recessive X-linked diseases are rare in females. Daoud et al. [2008] reported three homozygous females with G6PD deficiency. While they did not relate this phenomenon to consanguinity, it was the cause for the expression of X-linked juvenile retinoschisis in four females [Saleheen et al., 2008]. The homozygosity of the mutation in the affected females led to a severe phenotype [Saleheen et al., 2008].

The high inbreeding rate may explain the elevated number of deleterious mutations found at homozygous state in the affected patients [Ben Rekaya et al., 2009; Messaoud et al., 2010b; Ouragini et al., 2010]. Allelic homogeneity is not systematically shown in high inbred populations. Indeed, compound heterozygosity (30delG/E47X) for the *GJB2* gene in highly consanguineous kindred from an isolate in Northern Tunisia has been reported [Ben Arab et al., 2000]. This phenomenon has already been reported in an inbred Israeli-Arab community [Carrasquillo et al., 1997]. Eight mutations were found to cause FMF [Chaabouni et al., 2007a] and 29 mutations can lead to beta-thalassemia in the Tunisian population. These multiple mutations could be allelic or affecting many genes leading to the expression of a single phenotype. Many possibilities have been proposed to explain this observation in an isolated population [Zlotogora, 2007]. This phenomenon was argued as being random [Zlotogora, 2007], and as the result of a selective advantage for the carriers of each respective disease [Zlotogora et al., 1996; Zlotogora, 1998] or due to the high mutation rates [Crow, 1997]. This could also be due to the richness of the genetic

background as a consequence of the migratory flows in the Mediterranean region.

Consanguineous individuals are frequently observed to have long segments of uninterrupted homozygous genome sequences [Lander and Botstein, 1987]. Theoretical calculations predict that 6% (1/16) of the genome of a child of first cousins will be homozygous and that the average homozygous segment will be 20 cM in size [Woods et al., 2006]. This observation raised interest of genetic researchers for disease gene identification by investigating Tunisian families. The first use of homozygosity mapping by studying only three Tunisian consanguineous families has led to the localization of Friedreich ataxia phenotype with selective vitamin E deficiency to chromosome 8q [Ben Hamida et al., 1993]. The first locus of a hereditary nonsyndromic hearing loss was identified on chromosome 13 by a study of two large Tunisian consanguineous families [Guilford et al., 1994].

Among the diseases studied so far in Tunisia, for approximately half of them no molecular data are available. Further investigations are needed in order to depict the molecular pathogenesis of these conditions. For 69 conditions, the causative gene was still unknown; this shows the great potential for novel genes and loci identifications. Epidemiological data are unfortunately unavailable; consequently the burden of diseases could not be appreciated precisely and not all genetic diseases are reported in the literature. From the experience of our referral center and from collaborators, we have estimated that there are at least 30 genetic diseases for which no publications have been reported including genodermatosis, neurological, metabolic, and ophthalmologic diseases. This corresponds to approximately 8% of the whole disease spectrum. Most of the diseases correspond to very rare phenotypes and confirmation of diagnosis is essential before reporting on new phenotypes. There is also a bias in management and reporting on the most severely and heavily disabilitating diseases. From our field studies on severe genodermatosis, we have noticed that patients with limited resources and with less severe phenotypes do not refer to clinical services; this is the case for hereditary epidermolysis bullosa simplex form (unpublished data).

As in the other Arab countries, genetic services do exist in Tunisia but are still limited in number. Premarital genetic counseling is mandatory for all couples before marriage, especially with a genetic disease history in the family and in case of consanguinity. Unfortunately, most of the couples do not give enough importance to the premarital counseling. The spouses are usually embarrassed to talk about a positive familial history, especially, in case of congenital malformations and mental retardation. National newborn screening programs for common genetic defects are still deficient in Tunisia [Saadallah and Rashed, 2007]. Thus, North Africa and Middle East region need to take big steps towards developing national strategies for prevention and should learn from experiences of regional and international screening programmes [Saadallah and Rashed, 2007].

## CONCLUSION

As a consequence of the high inbreeding rate in Tunisia, many genetic disorders emerged with autosomal recessive inheritance being the most prevalent. Improvement of health indicators together with strengthening of competencies in different fields of biomedical sciences contributed to a major increase in the identification and reporting on genetic diseases in Tunisia. Combination of founder effect and selection forces, in addition to the consanguinity have a negative impact on health of endogamous populations while outbreeding and admixture are shown to have the opposite effect. Currently in Tunisia, there are several studies on prevention of disabilities through multi-institutional pluri-disciplinary networks. Primary prevention must be conducted by genetic counseling prior to marriage or prior to the first pregnancy and secondary prevention focuses on early genetic screening during the pregnancy, especially for the families having an affected child. Because of geographical, historical, and socio-cultural reasons, our study has an impact at the regional level, as the population structure is very similar to the neighboring countries. Availability of data as reported in this article are of high impact for decision making and orientation of future studies for a more precise evaluation of the burden of genetic diseases on public health and establishment of preventive programs.

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