# Collaborative genomics for human health and cooperation in the Mediterranean region

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**The US government has proposed the development of scientific centers of excellence to solve global challenges. We propose such a center of excellence devoted to the genomic analysis of Mediterranean populations of all creeds. This genomic focus is rooted in the region's demographic history, builds on the area's rapidly developing expertise in human genetics, and will yield scientific discoveries of both local and global significance. The genome sequence data of Mediterranean populations will offer unique insights into human evolution and early human migration. The potent combination of highly consanguineous populations in the Mediterranean's southern and eastern rims and regional medical and scientific expertise could lead to the identification and characterization of many genes responsible for human disease. Such discoveries will enable genetic knowledge to be translated into medical knowledge that will benefit local populations and contribute substantially to the understanding of the genetic bases of human diseases worldwide.**

In Cairo in June 2009, US President Obama spoke of the importance of international collaboration for scientific and technological development[1]. This speech was followed by fact-finding visits by American Science Envoys to the Middle East, North Africa, Europe, and South and Southeast Asia[2].

Shared genes and shared cultures are key factors that unite people. As a group of Mediterranean geneticists committed to addressing local genetic issues and to borderless global scientific collaboration[3], we welcome the US initiative. We propose that human genomics is an excellent common resource for addressing common challenges and for deepening existing scientific relationships in the Mediterranean basin across all countries and populations.

In this commentary, following discussions held during the Mediterranean Medical Genetics Meeting (MediMedGen) at Bilkent University in Ankara in June 2009, we propose a genomics initiative consisting of collaborative studies in human genomics that can provide a solid foundation to the American Science Envoys Program, with practical benefit to people in the region and worldwide.

## A vision for Mediterranean collaboration in human genomics

Sequencing the human genome generated a landmark scientific resource that provides a common platform for biomedical research. To realize the promise of genomic medicine will require further advances on several fronts, including reductions in sequencing and data analysis costs to enable many more individual sequences to be generated, more complete annotation of the human genome sequence, the creation of additional computational tools and databases, the translation of human genomic research into clinical practice, the delivery of services through national health systems, the development and training of a skilled workforce, and consideration of the ethical, social and legal issues that accompany these innovations[4].

Although local issues exist, these challenges are global. The human genomics initiative for the Mediterranean region that is proposed here makes a unique contribution to science and medicine because it takes advantage of the specific strengths and characteristics of the region's population and undertakes an integrated approach, using both whole-genome sequencing of Mediterranean individuals and family-based studies to identify genes for specific diseases.

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### Whole genome sequencing in Mediterranean individuals

Whole genome sequencing of individuals from the Mediterranean basin has not yet been performed, even though the region was one of the first stations of human migration out of Africa. Indeed, Mediterranean individuals have exerted both genetic and cultural influence well beyond their ancestral home. The complete genome sequences reported so far have been for individuals of ancestries from Northwest Europe, China, Korea and sub-Saharan Africa. Although the international 1,000 Genomes Project will create a more detailed picture of human genetic variation (http://www.1000genomes.org/page.php), whole-genome sequencing of individuals from Mediterranean populations will reveal new information on human evolution, migration and diversity.

Sequencing a sufficient number of representative Mediterranean individuals will provide a reference and scaffold for further genetic studies in the region. As rapid advances in DNA sequencing technology have led to marked reductions in cost as well as profound improvements in efficiency over the last decade, there are now many sequencing centers worldwide, including in the Mediterranean basin. This capacity could be further developed and exploited to contribute to the understanding of human genetic variation in a concerted fashion. It would be feasible to generate a comprehensive Mediterranean catalog of single nucleotide and small insertion-deletion polymorphisms and copy number variations, with corresponding allele and haplotype frequencies and linkage disequilibrium patterns. Performing such studies locally will lead the regional community into the next stage of genomic studies. To ensure free and open access to the data generated, a virtual database, *Genotheca Mediterranea*, could be established.

It has become increasingly difficult to define mutations as causative as the extent of human variation has been revealed. There is a renewed realization that one means of addressing this complexity is by linking functional mutations with specific phenotypes, a link that is highlighted, often in stark relief, by recessive diseases. Although in most populations recessive deleterious mutations will never be fully expressed, such mutations and their effects become clearly evident in consanguineous populations, where individuals homozygous for a deleterious trait are significantly more common. In this respect, studies in Mediterranean populations can provide a new genotype-phenotype map of the human genome.

### Consanguinity and disease gene identification in Mediterranean populations

The southern and eastern rims of the Mediterranean basin have among the highest levels of consanguinity in the world, comprising part of a region of consanguinity that extends from the southern shores of the Mediterranean Sea through the Middle East, Mesopotamia, the Gulf and the Indian subcontinent to Southeast Asia. The roots of consanguinity in Mediterranean populations date to ancient times[5], reflecting both historical and contemporary social preferences for marriages between relatives. The social and cultural advantages of this practice include maintenance of family structure and property, and financial advantages relating to dowry. Better relations with in-laws, and the perception that consanguineous marriages might be more stable than marriages between non-relatives, are also important. At present, in many areas of the region ~25% of marriages are between first cousins. True rates of consanguinity are even higher because there is additional endogamy (that is, marriage within the extended clan; *hamuleh* in Arabic, *hısım* in Turkish)[6], leading to homozygosity rates greater than those predicted by the degree of kinship alone[7]. By contrast, consanguinity on the northern rim of the Mediterranean basin is generally low.

Consanguinity has a direct impact on the frequency of recessive diseases. With multiple layers of consanguinity, the number of individuals affected with any recessive disease is proportional to the disease allele frequency. By contrast, in a large, randomly mating population, the number of affected individuals is proportional to the square of the disease allele frequency[8]. Coupled with the large family size that is characteristic of the southern rim of the Mediterranean and the Middle East, this statistic results in increased frequency of recessive disease, creating human and medical challenges, but also the scientific opportunities to address them.

Recessive diseases in consanguineous communities vary in frequency, based on the ages of the mutations responsible for them and selective pressures on the phenotype[9]. The hemoglobinopathies, G6PD deficiency and familial Mediterranean fever are frequent throughout the region. Inherited hearing loss, Bardet-Biedl syndrome and Meckel Gruber syndrome are frequent in many communities in the region. Other conditions appear in a local community or clan, or specifically in one family. The number of diseases is very large, because any mutation that is not lethal early in pregnancy can be revealed through consanguinity. Many of these traits, particularly the most rare, have not yet been studied. For example, of the 577 recessive diseases that have been reported in Arab families (http://www.cags.org.ae/ctga_search.html), the responsible loci are not known for 168. Many other recessive diseases, especially those confined to single families, are not even reported.

The gap in identifying genes responsible for Mendelian diseases is not unique to Mediterranean populations: the molecular bases of at least 3,800 known or suspected Mendelian diseases are unknown (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim). Southern and eastern Mediterranean populations are unique in that for recessive traits in consanguineous communities, identification of the causative genes is eminently feasible using homozygosity mapping and sequencing. The success of this approach can be seen from the large number of disease genes that have been identified by studying Mediterranean families (**Table 1**).

### Current genomics research in the Mediterranean basin

Molecular studies of disease genes began in the 1980s with the identification of the mutation spectrum of X-linked diseases such as Duchenne/Becker muscular dystrophy and hemophilia, and recessive diseases such as the thalassemias, phenylketonuria and cystic fibrosis. These studies extended in the 1990s to linkage mapping of rare diseases, and have evolved today to homozygosity mapping using SNP arrays, which is powerful enough to identify disease loci even in families too small to obtain meaningful results using traditional linkage approaches[10]. In the early years genetic analysis of Mediterranean families was often performed outside the region, in collaborations with American and European centers. However, over time these collaborations have evolved and genetic analyses are increasingly performed in regional laboratories. Examples of genes that have been identified in the region include those responsible for deafness (*FGF3*, *MYO3A*, *OTOA*, *OTOF*, *POU4F3*, *SERPINB6*, *TECTA*, *TRIOBP*, *WHRN*), neurodevelopmental disorders (*ALS2*, *FA2H*, *FGD4*, *SNAP29*, *VLDLR*, *VRK1*) and other rare diseases (*ALX1*, *BBS10*, *CHST14*, *DDR2*, *SLC34A2*, *TAC3*, *TACR3*) (see **Table 1** for a comprehensive list). In parallel, biobanks and genomic databases funded through governmental research programs have been established in several countries in the region, with active participation in Orphanet (http://www.orpha.net/consor/cgi-bin/index.php), the EU-funded portal for rare diseases and orphan drugs. If properly supported, these developments in general and local capacity are likely to lead to an explosion in gene discovery

which in the near future might be limited only by the phenotype discovery rate.

World Health Organization statistics indicate that the global burden of disease is shifting from infectious to noncommunicable diseases[11]. Many of these diseases are genetically influenced. The responsible genes can be identified using population resources and tools now at hand. A concentrated effort to solve the genetic bases of noncommunicable diseases will have an important public health impact far beyond the specific alleles identified in the first families to be studied. The genetic dissection of well characterized disease phenotypes in large kindreds will reveal genes that underlie complex, heterogeneous diseases. Indeed, pathways relevant to common diseases are often identified through genes responsible for related rare disorders[12].

## Translating human genomic research into clinical practice

As a consequence of consanguinity, the prevalence at birth of severe congenital genetic disorders in the eastern Mediterranean is among the highest in the world: >65 affected children per 1,000 live births[13]. From a regional perspective, programs that address recessive diseases have a high priority and need to go beyond gene identification to the characterization of the mutational spectrum relevant to each locale, and to the provision of community-based medical genetics services. This extremely sensitive issue, owing to its ethical, legal and social aspects, can best be addressed by professionals from the same cultures as the affected families, and this is most likely to lead to clinically effective outcomes. From a global perspective, this agenda is relevant to the challenges of the post-genome era[14], especially in the fields of personalized medicine and identification of new drug targets emerging from genomic analysis of common and rare diseases. According to currently available statistics, more than 1,500 laboratories perform genetic tests in the EU, and the annual growth in testing is close to 300%. With a population size comparable to the EU, the development, harmonization, validation and standardization of genetic testing services is a high-priority area in the Mediterranean basin.

The implementation and delivery of services through national health systems is not easy, but the large and diverse populations of the Mediterranean basin have access to excellent universities, institutes and clinics. In many parts of the region, medical genetics is a recognized clinical specialty or sub-specialty, strengthened by highly trained dysmorphologists, pediatricians and human geneticists. Close collaboration with the European Society of Human Genetics, the American Society of Human Genetics and the American College of Medical Genetics has led to many national and regional congresses, workshops, and symposia focused on training, education, and workforce planning in medical genetics. Future MediMedGen meetings are planned, including one in Cyprus in 2011. The Mediterranean basin is also the home of the European Genetics Foundation, which organizes regular courses in genetic medicine, attended by more than 6,000 students over the last two decades (http://www.eurogene.eu/). To address the standardization and harmonization of genetics services, Mediterranean geneticists have taken active roles in projects such as EuroGenTest (http://www.eurogentest.org/), MedGenMed and MedGeNet (http://www.eurogene.eu/), through which resources for assessing and addressing ethical, social and legal issues are also available (http://www.cags.org.ae/ctga_search.html). Finally, progress in the computational use of medical and genomic data is reflected in genetic and genomic databases of Mediterranean populations that have already been launched[15]. We predict that these assets will be crucial for the integration of genetics research into the delivery of health outcomes in the region and the world.

## A plan for the future

On the basis of these considerations, we propose an international collaborative Center of Excellence for Genomics Research in the Mediterranean region, supported by international and national funding agencies. We suggest that this Center of Excellence be geographically decentralized and function as a network of researchers and genomics research centers whose primary remit would be to support and facilitate joint research proposals. Members of the Center would include scientists from the region and those supporting the development of genomics in the region. They would engage in projects centered in Mediterranean laboratories whenever possible, and involving transfer of technology and training, to make the Mediterranean focus increasingly realistic with time.

There is much greater strength in using resources to support science in existing institutions rather than creating a new physical structure. A decentralized, international, collaborative, investigator-initiated model alleviates hurdles of bureaucracy and facilitates international decision-making. We believe that work to facilitate the generation of whole-genome sequence data from representative Mediterranean populations, and the discovery and characterization of genes based on well defined phenotypes in large kindreds and/or consanguineous families, should be scientifically and socially attractive to funding agencies within and beyond the Mediterranean region. A wide range of human traits, both rare and common, could be evaluated. The proposed scientific structure and objectives are excellent models and realistic goals for collaborative genomics for human health and cooperation in the Mediterranean basin, and could have an important impact on public health.

## Conclusion

During the past two decades, working with families from the Mediterranean region, scientists from Algeria, Cyprus, Egypt, France, Greece, Israel, Italy, Jordan, Lebanon, Morocco, Palestine, Tunisia and Turkey have collaborated with each other and with geneticists worldwide to identify the genes responsible for many inherited diseases, both common and rare. Active collaborations across the region are presently exploring human genomic variation to better understand susceptibility and resistance to disease. These projects demonstrate the shared culture and goals of human genetics, and serve as a testimony to the commitment to international collaboration. The present interest of the US government encourages us to take another important step in these efforts.

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This Commentary is dedicated to the memory of Ihsan Dogramaci, a pioneer and reformer in child health and higher education, one of the founders of WHO, the longest serving Executive Board member of UNICEF and a tireless campaigner for world peace.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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**Table 1 Examples of genes for Mendelian diseases identified in consanguineous families from the Mediterranean region**

| Disease ID from Mendelian Inheritance in Man | OMIM# | Gene | Family origin | Reference |
|---|---|---|---|---|
| Adducted thumb-clubfoot syndrome | 601776 | *CHST14* | Turkey | *Am. J. Hum. Genet.* **85**, 873–882 (2009) |
| Alopecia, neurologic defects and endocrinopathy | 612079 | *RBM28* | Israel (Palestinian) | *Am. J. Hum. Genet.* **82**, 1114–1121 (2008) |
| Amyotrophic lateral sclerosis 2, juvenile | 205100 | *ALS2* | Tunisia | *Nat. Genet.* **29**, 160–165 (2001) |
| Ataxia-telangiectasia | 208900 | *ATM* | Israel (Moroccan Jewish) | *Science* **268**, 1749–1753 (1995) |
| Bardet-Biedl syndrome 10 | 209900 | *BBS10* | Lebanon, Turkey | *Nat. Genet.* **38**, 521–524 (2006) |
| Birk-Barel mental retardation dysmorphism syndrome | 612292 | *KCNK9* | Israel (Palestinian) | *Am. J. Hum. Genet.* **83**, 193–199 (2008) |
| Cenani syndactylism | 212780 | *LRP4* | Egypt, Turkey | *Am. J. Hum. Genet.* **86**, 1–11 (2010) |
| Cerebellar ataxia, mental retardation and disequilibrium syndrome 1 | 224050 | *VLDLR* | Turkey | *Proc. Natl. Acad. Sci. USA* **105**, 4232–4236 (2008) |
| Cerebral dysgenesis, neuropathy, ichthyosis and palmoplantar keratoderma syndrome | 609528 | *SNAP29* | Israel (Palestinian) | *Am. J. Hum. Genet.* **77**, 242–251 (2005) |
| Charcot-Marie-Tooth disease, type 4H | 609311 | *FGD4* | Algeria, Lebanon | *Am. J. Hum. Genet.* **81**, 1–16 (2007) |
| Charcot-Marie-Tooth disease, type 4A | 214400 | *GDAP1* | Tunisia | *Nat. Genet.* **30**, 21–22 (2002) |
| Cutis Laxa, autosomal recessive, type IIB | 612940 | *PYCR1* | Italy, Jordan, Palestine, Turkey | *Nat. Genet.* **41**, 1016–1021 (2009) |
| Dyggve-Melchior-Clausen disease | 223800 | *DYM* | Lebanon, Portugal, Morocco, Tunisia | *J. Med. Genet.* **39**, 714–717 (2002) |
| Deafness, congenital with inner ear agenesis, microtia and microdontia | 610706 | *FGF3* | Turkey | *Am. J. Hum. Genet.* **80**, 338–344 (2007) |
| Deafness, autosomal recessive 9, DFNB9 | 601071 | *OTOF* | Lebanon | *Nat. Genet.* **21**, 363–369 (1999) |
| Deafness, autosomal dominant 15, DFNA15 | 602459 | *POU4F3* | Israel (Italian Jewish) | *Science* **279**, 1950–1954 (1998) |
| Deafness, autosomal recessive 21, DFNB21 | 603629 | *TECTA* | Lebanon | *Hum. Mol. Genet.* **8**, 409–412 (1999) |
| Deafness, autosomal recessive 22, DFNB22 | 607039 | *OTOA* | Palestine | *Proc. Natl. Acad. Sci. USA* **99**, 6240–6245 (2002) |
| Deafness, autosomal recessive 28, DFNB28 | 609823 | *TRIOBP* | Palestine | *Am. J. Hum. Genet.* **78**, 144–152 (2006) |
| Deafness, autosomal recessive 30, DFNB30 | 607101 | *MYO3A* | Israel (Iraqi Jewish) | *Proc. Natl. Acad. Sci. USA* **99**, 7518–7523 (2002) |
| Deafness, autosomal recessive 31, DFNB31 | 607084 | *WHRN* | Palestine | *Eur. J. Hum. Genet.* **10**, 210–212 (2002) |
| Deafness, autosomal recesive 91, DFNB91 | NA | *SERPINB6* | Turkey | *Am. J. Hum. Genet.* **86**, 797–804 (2010) |
| Hypertrophic neuropathy of Dejerine-Sottas | 145900 | *PRX* | Lebanon | *Hum. Mol. Genet.* **10**, 415–421 (2001) |
| Ectopia lentis, isolated, autosomal recessive | 225100 | *ADAMTSL4* | Iraq, Jordan | *Am. J. Hum. Genet.* **84**, 274–278 (2009) |
| Epilepsy, progressive myoclonic, 1B | 612437 | *PRICKLE1* | Israel (Palestinian), Jordan | *Am. J. Hum. Genet.* **83**, 572–581 (2008) |
| Exocrine pancreatic insufficiency, dyserythropoeitic anemia and calvarial hyperostosis | 612714 | *COX4I2* | Israel (Palestinian) | *Am. J. Hum. Genet.* **84**, 412–417 (2009) |
| Frank-Ter Haar syndrome | 249420 | *SH3PXD2B* | Israel, Lebanon, Turkey | *Am. J. Hum. Genet.* **86**, 254–261 (2010) |
| Fraser syndrome | 219000 | *FRAS1* | France, Greece, Lebanon, Spain | *Nat. Genet.* **34**, 203–208 (2003) |
| Frontonasal dysplasia | NA | *ALX1* | Turkey | *Am. J. Hum. Genet.* **86**, 789–796 (2010) |
| H syndrome | 612391 | *SLC29A3* | Israel (Palestinian), Bulgaria | *Am. J. Hum. Genet.* **83**, 529–534 (2008) |
| Hyperostosis-hyperphosphatemia syndrome | 610233 | *GALNT3* | Israel (Druze), Palestine | *J. Mol. Med.* **83**, 33–38 (2005) |
| Hypogonadotropic hypogonadism | 146110 | *TAC3, TACR3* | Turkey | *Nat. Genet.* **41**, 354–358 (2009) |
| Hypotrichosis, congenital, with juvenile macular dystrophy | 601553 | *CDH3* | Israel (Druze) | *Nat. Genet.* **29**, 134–136 (2001) |
| Ichthyosis, lamellar 3 | 604777 | *CYP4F22* | Algeria, France, Italy, Lebanon | *Hum. Mol. Genet.* **15**, 767–776 (2006) |
| Ichthyosis with hypotrichosis, autosomal recessive | 610765 | *ST14* | Israel (Palestinian) | *Am. J. Hum. Genet.* **80**, 467–477 (2007) |
| Jalili syndrome | 217080 | *CNNM4* | Kosovo, Lebanon | *Am. J. Hum. Genet.* **84**, 259–265 (2009) |
| Joubert syndrome 2 | 608091 | *TMEM216* | Israel (Ashkenazi Jewish) | *Am. J. Hum. Genet.* **86**, 93–97 (2010) |
| Kindler syndrome | 173650 | *FERMT1* | Algeria, Tunisia | *Hum. Mol. Genet.* **12**, 925–935 (2003) |
| Krabbe disease | 245200 | *GALC* | Israel (Palestinian) | *Am. J. Hum Genet.* **53**, 1250–1255 (1993) |
| Kufor-Rakeb syndrome | 606693 | *ATP13A2* | Jordan | *Nat. Genet.* **38**, 1184–1191 (2006) |
| Lethal congenital contracture syndrome 2 | 607598 | *ERBB3* | Israel (Bedouin) | *Am. J. Hum. Genet.* **81**, 589–595 (2007) |
| Lethal congenital contractural syndrome 3 | 611369 | *PIP5K1C* | Israel (Bedouin) | *Am. J. Hum. Genet.* **81**, 530–539 (2007) |

(continued)

**Table 1 Examples of genes for Mendelian diseases identified in consanguineous families from the Mediterranean region (continued)**

| Disease ID from Mendelian Inheritance in Man | OMIM# | Gene | Family origin | Reference |
|---|---|---|---|---|
| Leukodystrophy, dysmyelinating and spastic paraparesis with or without dystonia | 612443 | *FA2H* | Israel (Palestinian) | *Am. J. Hum. Genet.* **83**, 643–648 (2008) |
| Lipodystrophy, congenital generalized, type 2 | 269700 | *BSCL2* | Lebanon, Turkey | *Nat. Genet.* **28**, 365–370 (2001) |
| Liver failure, acute infantile | 613070 | *TRMU* | Israel (Yemenite Jewish) | *Am. J. Hum. Genet.* **85**, 401–407 (2009) |
| Macrocephaly, alopecia, cutis laxa and scoliosis | 613075 | *RIN2* | Israel (Palestinian) | *Am. J. Hum. Genet.* **85**, 254–263 (2009) |
| Majeed syndrome | 609628 | *LPIN2* | Jordan | *J. Med. Genet.* **42**, 551–557 (2005) |
| Mal de Meleda | 248300 | *SLURP1* | Algeria, Croatia | *Hum. Mol. Genet.* **10**, 875–880 (2001) |
| Microcephalic osteodysplastic primordial dwarfism, type II | 210720 | *PCNT2* | Lebanon | *Science* **319**, 816–819 (2008) |
| Microcephaly, seizures and developmental delay | 613402 | *PNKP* | Italy, Palestine, Jordan, Turkey | *Nat. Genet.* **42**, 245–249 (2010) |
| Mitochondrial complex IV deficiency | 220110 | *FASTKD2* | Israel (Bedouin) | *Am. J. Hum. Genet.* **83**, 415–423 (2008) |
| Mitochondrial DNA depletion syndrome, enephalomyopathic form with methylmalonic aciduris, autosomal recessive | 612073 | *SUCLA2* | Israel (Palestinian) | *Am. J. Hum. Genet.* **76**, 1081–1086 (2005) |
| Mitochondrial DNA depletion syndrome, hepatocerebral form, autosomal recessive | 251880 | *DGUOK* | Israel (Druze) | *Nat. Genet.* **29**, 337–341 (2001) |
| Mucolipidosis IV | 252650 | *MCOLN1* | Israel (Ashkenazi Jewish) | *Nat. Genet.* **26**, 118–121 (2000) |
| Multiple pterygium syndrome, Escobar variant | 265000 | *CHRNG* | Lebanon, Turkey | *Am. J. Hum. Genet.* **79**, 303–312 (2006) |
| Myoglobinuria, acute recurrent, autosomal recessive | 268200 | *LPIN1* | Israel (Palestinian) | *Am. J. Hum. Genet.* **83**, 489–494 (2008) |
| Neurodegeneration with brain iron accumulation 2A | 256600 | *PLA2G6* | Israel (Bedouin) | *Am. J. Hum. Genet.* **79,** 942–948 (2006) |
| Odontoonychodermal dysplasia | 257980 | *WNT10A* | Lebanon | *Am. J. Hum. Genet.* **81**, 821–828 (2007) |
| Osteogenesis imperfecta | NA | *FKBP65* | Turkey | *Am. J. Hum. Genet.* **86**, 551–559 (2010) |
| Papillon-Lefevre syndrome | 245000 | *CTSC* | Egypt, Lebanon | *Nat. Genet.* **23**, 421–424 (1999) |
| Parietal foramina 2 | 609597 | *ALX4* | Turkey | *Hum. Mol. Genet.* **18**, 4357–4366 (2009) |
| Periodontitis, aggressive, 1 | 170650 | *CTSC* | Jordan, Turkey | *J. Med. Genet.* **37**, 95–101 (2000) |
| Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy | 221770 | *TREM2* | Lebanon | *Hum. Mutat.* **29**, E194–E204 (2008) |
| Polymicrogyria, bilateral frontoparietal | 606854 | *GPR56* | Israel (Palestinian) | *Science* **303**, 2033–2036 (2004) |
| Pontocerebellar hypoplasia type 1 | 607596 | *VRK1* | Israel (Ashkenazi Jewish) | *Am. J. Hum. Genet.* **85**, 281–289 (2009) |
| Pontocerebellar hypoplasia type 6 | 611523 | *RARS2* | Israel (Sephardic Jewish) | *Am. J. Hum. Genet.* **81**, 857–862 (2007) |
| Pulmonary alveolar microlithiasis | 265100 | *SLC34A2* | Turkey | *Am. J. Hum. Genet.* **79**, 650–656 (2006) |
| Seborrhea-like dermatitis with psoriasiform elements | 610227 | *ZNF750* | Israel (Moroccan Jewish) | *Nat. Genet.* **38**, 749–751 (2006) |
| Sex reversal, female, with dysgenesis of kidneys, adrenals and lungs | 611812 | *WNT4* | Israel (Palestinian) | *Am. J. Hum. Genet.* **82**, 39–47 (2008) |
| Split-hand/foot malformation 6 | 225300 | *WNT10B* | Turkey | *Hum. Mol. Genet.* **17**, 2644–2653 (2008) |
| Spondylo-meta-epiphyseal dysplasia, short limb-hand type | 271665 | *DDR2* | Israel (Sephardic Jewish), Palestine | *Am. J. Hum. Genet.* **84**, 80–84 (2009) |
| Three M syndrome 1 | 273750 | *CUL7* | France, Italy, Lebanon, Portugal | *Nat. Genet.* **37**, 1119–1124 (2005) |
| Tumoral calcinosis, hyperphosphatemic familial | 211900 | *GALNT3* | Israel (Druze), Palestine | *Nat. Genet.* **36**, 579–581 (2004) |
| Tumoral calcinosis, normophosphatemic familial | 610455 | *SAMD9* | Israel (Yemenite Jewish) | *Am. J. Hum. Genet.* **79**, 759–764 (2006) |
| Usher syndrome, type IG | 606943 | *USH1G* | Jordan (Palestinian) | *Hum. Genet.* **110**, 348–350 (2002) |
| Vitamin E, familial isolated deficiency of | 277460 | *TTPA* | France, Italy, Morocco, Tunisia | *Nat. Genet.* **9**, 141–145 (1995) |
| Warburg micro syndrome | 600118 | *RAB3GAP* | Lebanon, Morocco | *Nat. Genet.* **37**, 221–223 (2005) |
| Weill-Marchesani syndrome, autosomal recessive | 277600 | *ADAMTS10* | Lebanon | *Am. J. Hum. Genet.* **75**, 801–806 (2004) |
| Wolfram syndrome 2 | 604928 | *CISD2* | Jordan | *Am. J. Hum. Genet.* **81**, 673–683 (2007) |