A study in pleiotropy – Jalili syndrome

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Abstract

Jalili syndrome, first described 25 years ago in a Palestinian family, is a rare autosomal recessive genetic disorder that is characterized by the comorbid appearance of cone–rod dystrophy (CRD) and amelogenesis imperfecta. To date, 71 patients with this condition belonging to 17 different families have been reported worldwide. Studies into the molecular aetiology of Jalili syndrome have identified mutations in the CNNM4 gene, located on chromosome 2q11. Other members of this protein family have been shown to be involved in mineral transport. We postulate a role for the CNNM4 protein in metal ion transport and homeostasis and especially in the transport of magnesium ions. Mutations in the gene could interfere with the depolarization process of retinal cells, as well as in the dental mineralization process. We also show that mutations localized to the transmembrane domain of this protein result in more severe phenotypes of the syndrome, indicating an important function for this domain, probably as a transmembrane channel for metal transport. Jalili syndrome offers an example of how a single mutation in a gene is capable of affecting two independent traits by causing a defect in a single protein that carries out essentially the same function in two different tissue types. Given that 274 inherited disorders, almost exclusively reported in Arab families, have no defined genetic aetiologies as yet, and with the increasing trend of genome-wide association studies in the region, it is highly plausible that more conditions will be assumed to be manifestations of pleiotropy.

Introduction

Cone–rod dystrophy (CRD) refers to a clinically and genetically heterogeneous group of retinal disorders in which the cone photoreceptors are initially, and primarily, affected by a progressive and degenerative process. This is followed by the degeneration of the rod photoreceptors; however, simultaneous degeneration of both types of photoreceptors can occur. Clinically, CRD is characterized by a progressive loss of vision, photoaversion (photophobia) and achromatopsia, but it can also present as nystagmus and visual impairment. Cone dysfunction is followed by the loss of photopic function during electrodagnostic tests and various degrees of abnormalities in the scotopic responses, which is commonly known as night blindness. The loss of central vision in those suffering from CRD is progressive, with an eventual loss of peripheral visual fields and total blindness. The severity and rapidity of the loss of vision with CRD is worse than in rod–cone dystrophy (RCD) and is commonly referred to as retinitis pigmentosa (RP).1

CRD occurs in both non-syndromic and syndromic forms. At least 15 subtypes of non-syndromic CRD are currently recognized, each with a distinct genetic locus. X-linked forms of CRD include CORD1 [Online Mendelian Inheritance in Man (OMIM): 304020], CORD2 (OMIM: 300085) and CORD3 (OMIM: 300476). Autosomal forms of CRD are more common and include dominant forms such as CORD2 (OMIM: 120970), CORD6 (OMIM: 601777), CORD7 (OMIM: 603649) and CORD14 (OMIM: 602093), and recessive forms such as CORD3 (OMIM: 604116), CORD5 (OMIM: 600977), CORD8 (OMIM: 605549) and CORD9 (OMIM: 612775). These loci contain genes that code for a diverse range of proteins that play an important role either in the visual cycle, including forming structural components of photoreceptors and acting as photoreceptor-specific transcription factors, or in ocular neuronal development. Many of these genes are also involved in RCD, macular
dystrophies and cone dystrophies. Syndromic CRD has been increasingly reported.

Amelogenesis imperfecta (AI) is another group of heterogeneous disorders; however, this relates to dental development. All AI cases are characterized by abnormal structure and/or clinical appearance of the tooth enamel, which is seen in both primary and secondary dentitions. Neglect results in various degrees of decay with the eventual loss of teeth. Based on the histological and morphological changes in enamel, two forms of AI exist, a hypoplastic form and a hypomineralized form; however, these types may overlap. Genetically, all except one form of non-syndromic AI are transmitted autosomally; the one exception, AI1E (OMIM: 301200), is an X-linked form. Autosomal dominant forms of AI are predominantly hypoplastic and include AI1B (OMIM: 104500), AI3 (OMIM: 130900) and AI4 (OMIM: 104510). The autosomal recessive forms of AI are seen predominantly in countries with high rates of consanguinity or with a high frequency of the mutated gene within the population. These include AI1C (OMIM: 204650), AI2A1 (OMIM: 204700) and AI2A2 (OMIM: 612529). The genes at the above-mentioned loci are all involved in the process of highly mineralized dental enamel formation. AI can also present alongside other syndromes, such as enamel renal syndrome, Kohlschutter–Tonz syndrome and trichodento-osseous syndrome.

This article reviews the rare Jalili syndrome (OMIM: 217080), which is characterized by the co-occurrence of CRD with AI, and highlights the contribution of Arab scientists in the identification of rare and novel genetic disorders.

**Historical background**

The appearance of CRD and AI as comorbidities in the same individual was named Jalili syndrome in honour of Ismail Jalili, an ophthalmologist of Iraqi origin who first reported the condition in 29 members of an extended Arab family from the Gaza Strip (the Jalili A subjects). These patients, identified during blind school surveys, presented with photophobia, nystagmus and achromatopsia, and all dentate members showed abnormal teeth, with either a complete absence of enamel or gross hypoplasticity. The affected family had a very high rate of consanguinity, with 91% of marriages being between cousins. This high level of consanguinity pointed towards an autosomal recessive mode of inheritance.

In the 20 years since the identification of Jalili syndrome, families affected with this rare syndrome have been found in several ethnically diverse populations. Jalili reported on another affected family from Gaza City (the Jalili B subjects) as well as a singleton from another family in the Gaza Strip (the Jalili C subject). Interestingly, several other cases from the Jalili A family are known to reside in some oil-producing countries. In addition to the published cases, a further six patients with Jalili syndrome have been identified from four families. One is a Caucasian child, while all of the others are of Middle Eastern or North African origin (Professor Chris Inglehearn, St. James’s University Hospital, 2012, personal communication). Over 71 patients, including the unreported cases, have been recognized to be suffering from Jalili syndrome to date and these patients belong to approximately 38 sibships (Figure 1 and Table 1). In most cases of Jalili syndrome, it is the ocular phenotype that is most prominent and is the first anomaly observed. In a recent study of a family with achromatopsia, the presence of Jalili syndrome was initially suggested by the results of molecular analysis testing, prompting the researchers to look for a corresponding dental phenotype, which they then found.

**FIGURE 1** Graphical representation of the cyclin M4 (CNNM4) protein domains (coloured boxes), polymorphisms (labelled in blue) and disease-causing mutations (labelled in red) that were discovered in those members of a family suffering from Jalili syndrome. The mutation data are adapted from Table 1. Polymorphism and protein domain data are from Swiss-Prot (www.uniprot.org), PhosphoSitePlus (www.phosphosite.org), and InterPro (www.ebi.ac.uk/interpro/) databases. CBS, cystathionine beta-synthase domain; cNMP, cyclic nucleotide monophosphate domain; DUF21, domain of unknown function; TM, transmembrane helix.
Clinical heterogeneity

Wide intrafamilial and interfamilial phenotypic variability is noted in the families affected by Jalili syndrome. On the basis of retinal morphology, Jalili distinguished two phenotypes: one with early-onset macular dystrophy (type A) and a second with no morphological evidence of macular involvement (type B). Macular lesions ranged from an early bull’s eye and/or chorioretinal excavation to large-scale excavation of the macula and posterior staphyloma (coloboma). As the disease advances, the peripheral retina becomes more involved with eventual contraction of the peripheral fields and ultimately total blindness. This creates a very similar presentation to classical RP, including the development of cataracts in some patients. The tendency for wide heterogeneity in the retinal phenotype has been explained by the embryological origin of the retina, which develops from the part of the brain that exhibits variable expression, as well as variable levels of disease susceptibility, second site modifiers and epigenetics. This may also explain the absence of such phenotypical variability of dental forms of the disease.

Molecular genetics

Cone–rod dystrophy and AI seem to be distinct entities that affect two entirely different tissues, and their co-occurrence could be due either to chance alone or to a tight linkage between the individual genes concerned. However, the fact that this comorbidity has been observed in a large number of individuals in the present study, and within several different families, shifts the balance from a random association, or strong linkage, to a single underlying factor.

The first clue in identifying the molecular pathology of Jalili syndrome was reported by Downey et al., who studied the two main families previously mentioned (Jalili A subjects and Jalili B subjects). This study utilized linkage analysis to pinpoint the locus to a 5-Mb region on chromosome 2q11. However, the strongest contender for a putative gene at this location, the CNGA3 gene, which codes for a part of the ion channels in photoreceptor cells, was found to not contain any pathogenic mutations in these families;11 similar results were obtained from an affected Kosovan family. The gene responsible for Jalili syndrome was discovered simultaneously by two groups working independently on families with both CRD and AI. In one of these studies, six patients belonging to three different families were screened for putative genes in the identified locus at 2q11. Sequencing of these genes led to the identification of mutations in the cyclin M4 (CNNM4) gene, which appeared to be the cause of the disorder. The other study utilized a much larger patient population, including the previously described families from Palestine (Jalili A subjects and Jalili B subjects) and Kosovo as well as other newly identified families from Guatemala, Turkey, Iran and Scotland, and arrived at the same conclusion.

The CNNM4 gene codes for a protein that belongs to the ancient conserved domain protein (ACDP) family. This family of proteins is characterized by the presence of a highly conserved region found in evolutionarily divergent species from bacteria to mammals. Additionally, all four proteins in this family contain a 31-residue cyclin box motif, a cyclic nucleotide monophosphate (cNMP)-binding domain and two cystathionine beta-synthase domains.

In addition, the CNNM4 protein contains four transmembrane helices, which suggests plasma membrane localization, and a domain of unknown function. At least two other members of this family have been shown to be involved in mineral transport: cyclin M1, which functions as a cytosolic copper chaperone, and cyclin M2, which has a role in the transport of magnesium. It is, therefore, possible to visualize a role for CNNM4 in metal ion transport and homeostasis, especially in the transport of magnesium ions. Further support for this hypothesis comes from the known interaction of CNNM4 with COX11, an intracellular metal ion chaperone.

So far, 12 different mutations have been identified in the CNNM4 gene in 13 families worldwide (Table 1). As expected, in all affected individuals with a history of parental consanguinity, the mutations were homozygous, whereas patients belonging to the non-consanguineous families (the Guatemalan and Scottish cases) carried heterozygous mutations (Table 1). More recently, Zobor et al. identified the same mutation in all patients with Jalili syndrome from Kosovo, indicating the possibility of a founder mutation in this population.

The families from the Gaza Strip carried two different mutations, each in homozygous form. Interestingly, these two mutations were found to exhibit considerably variant phenotypic effects. The c.599C>A (p.Ser200Tyr) mutation, in the homozygous
<table>
<thead>
<tr>
<th>Origin (family code)</th>
<th>Number of patients</th>
<th>Sibships</th>
<th>Age/age range</th>
<th>Male–female ratio</th>
<th>Consanguinity</th>
<th>Mutation 1/mutation 2</th>
<th>Protein change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaza (Jalili A)</td>
<td>36</td>
<td>20</td>
<td>3 months–50 years</td>
<td>20:16</td>
<td>Yes</td>
<td>c.599C &gt; A/c.599C &gt; A</td>
<td>p.Ser200Fyr</td>
</tr>
<tr>
<td>Gaza (Jalili B)</td>
<td>3</td>
<td>1</td>
<td>5, 6 and 10 years</td>
<td>1:2</td>
<td>Yes</td>
<td>c.1813C &gt; T/c.1813C &gt; T</td>
<td>p.Arg605X</td>
</tr>
<tr>
<td>Gaza (Jalili C)</td>
<td>1</td>
<td>1</td>
<td>17 years</td>
<td>1:0</td>
<td>Yes</td>
<td>Was not tested</td>
<td>–</td>
</tr>
<tr>
<td>Lebanon (Polok B)</td>
<td>3</td>
<td>2</td>
<td>2 years</td>
<td>1:0</td>
<td>Yes</td>
<td>c.707G &gt; A/c.707G &gt; A</td>
<td>p.R236Q</td>
</tr>
<tr>
<td>Kosovo (Michaleides UK)</td>
<td>2</td>
<td>1</td>
<td>7 and 14 years</td>
<td>2:0</td>
<td>No</td>
<td>c.1312dupC/c.1312dupC</td>
<td>p.Leu438ProfsX9</td>
</tr>
<tr>
<td>Kosovo (Polok A)</td>
<td>2</td>
<td>1</td>
<td>7 and 14 years</td>
<td>0:2</td>
<td>No</td>
<td>c.1312dupC/c.1312dupC</td>
<td>p.Leu438ProfsX9</td>
</tr>
<tr>
<td>Kosovo†</td>
<td>1</td>
<td>1</td>
<td>9 years</td>
<td>1:0</td>
<td>No</td>
<td>c.1312dupC/c.1312dupC</td>
<td>p.Leu438ProfsX9</td>
</tr>
<tr>
<td>Unknown (Polok C)</td>
<td>1</td>
<td>1</td>
<td>38 years</td>
<td>0:1</td>
<td>No</td>
<td>c.971T &gt; C/c.971T &gt; C</td>
<td>p.Leu324Pro</td>
</tr>
<tr>
<td>Turkey</td>
<td>2</td>
<td>1</td>
<td>5 and 6 years</td>
<td>0:2</td>
<td>Yes</td>
<td>c.586T &gt; C/c.586T &gt; C</td>
<td>p.Ser196Pro</td>
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<tr>
<td>Iran</td>
<td>4</td>
<td>2</td>
<td>NA</td>
<td>2:2</td>
<td>Yes</td>
<td>c.1?_1403+?del/c.1?_1403+?del</td>
<td>NA</td>
</tr>
<tr>
<td>Guatemala</td>
<td>5</td>
<td>1</td>
<td>NA</td>
<td>5:0</td>
<td>No</td>
<td>c.2149C &gt; T/c.62_145 del</td>
<td>p.Gln717X/p.Leu21HisfX185</td>
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<tr>
<td>Scotland</td>
<td>1</td>
<td>1</td>
<td>NA</td>
<td>1:0</td>
<td>No</td>
<td>c.971T &gt; C/c.1690C &gt; T</td>
<td>p.Leu324Pro/p.Gln564X</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>4</td>
<td>1</td>
<td>47–54 years</td>
<td>1:3</td>
<td>Yes</td>
<td>c.1555C &gt; T</td>
<td>p.R519X</td>
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<tr>
<td>Unpublished</td>
<td>6</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>One compound heterozygous for a new mutations, the remainder are homozygous for new/known mutations</td>
<td></td>
</tr>
</tbody>
</table>

*aClinical presentation at onset as described by either the family or medical personnel.

†Based on the World Health Organization (WHO) categorization.21

‘Probable Saudi Arabian origin. Includes 30 examined patients, one screened but declined full examination and five cases lived abroad: two in Saudi Arabia, two in Algeria and one in Libya (correct in September 1987).

dVisual impairment was present but visual acuity was unreported.

Based on comment by the author of close resemblance to family Kosova A.

These patients were associated with neurofibromatosis of two separate alleles and Lisch nodules were present on both irises.

CBS, cystathionine beta-synthase domain; cNMP, cyclic nucleotide monophosphate; DUF21, domain of unknown function; NA, not available; TM1, transmembrane domain 1; TM2, transmembrane domain 2.
<table>
<thead>
<tr>
<th>Affected domain</th>
<th>Presentation*</th>
<th>Visual acuity†</th>
<th>Refraction</th>
<th>Night blindness</th>
<th>Photophobia</th>
<th>Macular phenotype</th>
<th>Macular degeneration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TM2</td>
<td>Photophobia, nystagmus and visual impairment</td>
<td>1−5</td>
<td>Low myopia to high hyperopia</td>
<td>No</td>
<td>Yes</td>
<td>Maculopathy</td>
<td>Bull's eye to excavation</td>
<td>7, 9, 14</td>
</tr>
<tr>
<td>cNMP-binding domain</td>
<td>Teeth anomalies and visual impairment</td>
<td>2−3</td>
<td>+5.00</td>
<td>No</td>
<td>Yes</td>
<td>Normal macular morphology</td>
<td>Normal morphology</td>
<td>9, 14</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>+3.00 average</td>
<td>No</td>
<td>Yes</td>
<td>Normal morphology</td>
<td>Maculopathy</td>
<td>9, 20</td>
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<tr>
<td>DUF21</td>
<td>Photophobia, night blindness and nystagmus at 2 years.</td>
<td>Visual impairment‡</td>
<td>High hyperopia‡</td>
<td>Yes</td>
<td>Yes</td>
<td>Maculopathy</td>
<td>Atrophic macular degeneration with pigment mottling</td>
<td>13</td>
</tr>
<tr>
<td>CBS domain</td>
<td>Photophobia, nystagmus and teeth anomalies</td>
<td>3</td>
<td>Moderate to high hyperopia</td>
<td>Yes</td>
<td>Yes</td>
<td>Maculopathy</td>
<td>Yes, macular pigment mottling and atrophy</td>
<td>12, 14</td>
</tr>
<tr>
<td>CBS domain</td>
<td>Photophobia and nystagmus</td>
<td>3−4</td>
<td>High hyperopia</td>
<td>Yes</td>
<td>Yes</td>
<td>Maculopathy</td>
<td>Atrophic macular degeneration with pigment mottling</td>
<td>13</td>
</tr>
<tr>
<td>CBS domain</td>
<td>Photophobia, nystagmus and visual impairment</td>
<td>4</td>
<td>Low myopia</td>
<td>No</td>
<td>Yes</td>
<td>Maculopathy</td>
<td>Bull's eye</td>
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<tr>
<td>DUF21</td>
<td>Photophobia and night blindness at 2 years and nystagmus at 2 months</td>
<td>4</td>
<td>Low myopia</td>
<td>Yes</td>
<td>Yes</td>
<td>Maculopathy</td>
<td>Bull's eye</td>
<td>13</td>
</tr>
<tr>
<td>TM2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal macular morphology</td>
<td>Normal morphology</td>
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</tr>
<tr>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal morphology</td>
<td>NA</td>
<td>14</td>
</tr>
<tr>
<td>–/TM1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal macular morphology</td>
<td>Normal morphology</td>
<td>14</td>
</tr>
<tr>
<td>DUF21/</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Normal macular morphology</td>
<td>Normal morphology</td>
<td>14</td>
</tr>
<tr>
<td>Between CBS and cyclin box domains</td>
<td>Nystagmus and severe enamel dysplasia</td>
<td>2−3</td>
<td>Myopia</td>
<td>NA</td>
<td>NA</td>
<td>Maculopathy</td>
<td>NA</td>
<td>10</td>
</tr>
</tbody>
</table>

* Presentation: Photophobia, nystagmus, visual impairment, teeth anomalies, maculopathy.
† Visual acuity: 1−5 low myopia to high hyperopia.
‡ Visual impairment: Normal to high hyperopia.

References: 7, 9, 14
form, was found to be associated with a severe infancy-onset form of the syndrome with progressive macular lesions, while the c.1813C > T (p.Arg605X) mutation was associated with a relatively less severe form of childhood onset with normal fundi. The former mutation has been found to affect one of the transmembrane domains in the ACDP family, while the latter inserted a stop mutation in the cNMP-binding domain. These observations prompt us to suggest that the transmembrane helix domains within the protein have an important functional role to play, which may be associated with the formation of transmembrane ion channels facilitating transport of metal ions. This hypothesis is strengthened by the observation that other patients with mutations in the transmembrane domains also show a more severe form of the syndrome (Table 1).

Jalili suggested the possibility that high fluoride levels in the groundwater of the Gaza Strip, as well as in the regions where the reported cases of Jalili syndrome originated, may have a role to play in establishing the original mutation. There is some evidence to suggest genotoxic effects from long-term exposure to fluoride in drinking water. It is possible that this high fluoride level in the groundwater, together with increased water intake in hot climates and low calcium intake due to malnutrition, could have triggered the mutagenesis in the index cases. Spread of this mutation resulted in a proportionally higher number of patients in an extended family suffering from Jalili syndrome and can be attributed to the high level of consanguinity and the high fertility rate in the population. The rate of consanguinity in the extended Jalili A family was 91% and is very similar to the consanguinity rate of 92% among parents of Palestinian Arabs suffering from autosomal recessive genetic disorders. The remainder of families reported with Jalili syndrome can also be traced back to regions recognized for their high fluoride levels in groundwater or from neighbouring regions. This hypothesis calls for further investigations including analysing the effects of other water contaminants.

One protein, many functions

Pleiotropy, a term coined by the German geneticist Ludwig Plate, is the phenomenon whereby a single gene affects two or more apparently unrelated phenotypic traits. A stricter definition involves a mutation in the gene affecting two or more wild-type traits. The phenomenon has been discussed in genetic circles since Mendelian times; however, support for the importance of this phenomenon was dealt a blow by the popularity of the one gene–one enzyme hypothesis during the previous century. It was only with the advent of the ‘molecular age’ that pleiotropic effects were understood more clearly, resulting in the current recognition of pleiotropy in higher organisms as the rule, rather than the exception.

Jalili syndrome offers an example of how a single mutation in a gene is capable of affecting two independent traits by causing a defect in a single protein that carries out essentially the same function in two different tissue types. The importance of metal ions in the depolarization of the retinal cells is well understood. The CNNM4 protein may be playing a key role in the maintenance of this state through transport of magnesium ions, which act as cofactors for several enzymes involved in the retinal transduction process; however, during development of the dentition, the enamel begins with a relatively high concentration of magnesium deposit, which is progressively removed, in order to aid the dental biomineralization process. A failure of removal of these ions could lead to hypomineralized teeth. The possible role of CNNM4 in magnesium transport could also explain how mutations in the gene may lead to dental abnormalities. The functional significance of the CNNM4 protein is further supported by histological studies that show the localization of the protein within the retina in the ganglion cell layers, inner and outer plexiform layers, the outer segments of the photoreceptors and in the ameloblasts as well as the odontoblasts of the teeth.

Interestingly, Zobor et al. recently described a Kosovan girl who presented with Jalili syndrome in association with type 1 neurofibromatosis. This can be considered a random association, with mutations in two different genes causing two unrelated conditions; however, although Jalili syndrome is a rare condition, the relatively high frequency of the mutant allele in the Kosovan population could explain this comorbidity. Cases such as this are more likely in populations with high rates of consanguinity, e.g. in Arab countries. Reproductive choices in such populations are biased towards the amplification of rare genetic disorders and there is a heightened tendency for more than one autosomal recessive gene disorder to simultaneously manifest itself. Comorbid conditions are therefore common in this region. In fact, the third Palestinian family with the affected singleton (the Jalili C subject),
described by Jalili, is also a highly inbred family and has multiple members affected with other genetic conditions, including subnormal intelligence, ptosis and buphthalmos.

Jalili syndrome is just one of nearly 1000 genetic conditions that are known to cause various forms of inherited disorders in Arab populations. This is in addition to several other new syndromes described among the Palestinian population. Of these conditions, a large majority of the 735 known genetic disorders are associated with well-documented gene pathologies, and include 71 disorders that have been clinically and genetically characterized in the last two decades under the influence of genetic pleiotropic events, including achalasia–addisonianism–alacrimia syndrome (triple-A or Allgrove syndrome); Bartter syndrome with sensorineural deafness; branchiogenic–deafness syndrome; chorioretinal dystrophy, spinocerebellar ataxia and hypogonadotropic hypogonadism; dysmyelinating leucodystrophy with oligodontia, El-Shanti syndrome; Rambam–Hasharon syndrome, which causes psychomotor retardation with short stature, defective neutrophil motility and Bombay phenotype; and Waardenburg–Hirschsprung disease.

Given that 274 inherited disorders, almost exclusively reported in Arab families, have no defined genetic aetiologies as yet, and with genome-wide association studies being increasingly carried out in the region, it is highly plausible that more conditions will be assumed to be manifestations of pleiotropy. The benefits that will be gained from such studies are twofold: the confirmation of the role of pleiotropy in the molecular aetiology of clinically complex disorders; therefore, facilitating correct diagnosis, and the perception that pleiotropy has possibly been an important evolutionary component that shaped the extreme variety of genetic conditions observed in the region.

References


