

# An overview of the Prince Salman Center for Disability Research scientific outcomes

*Ali N. Al-Odaib, PhD, Sultan T. Al-Sedairy, PhD.*

---

## Introduction

The Prince Salman Center for Disability Research (PSCDR) was established to address the needs of persons living with disabilities. In addressing those needs, the PSCDR has set its goal as the promotion, conduct, and support of scientific research and the application of new knowledge to the benefit of persons with disabilities and their families. The mission of PSCDR is to prevent disabilities and improve the quality of life of the disabled. To accomplish its mission, PSCDR developed strategies, initiatives, and programs that effectively address many of the common problems facing the disabled community. By focusing on activities that promote an “enabling” environment, PSCDR believes that persons living with disabilities will be able participate fully in society. To guide its work, PSCDR is committed to adhering to the following core values:

- Pursuing knowledge that benefits mankind;
- Team-building and the sharing of knowledge and resources;
- Promoting a culture of integrity, professionalism, and compassion.

The PSCDR carries out and supports various research programs and projects aiming to enhance services provided to people with disability and to provide suitable environments to facilitate their access to utilities, services, communications, interaction, and participation so that the person with disability is an efficient member of society. Attaining these goals entails integrated work and launching local, regional, and international partnerships so that they have a positive effect, and to be a science benefiting people. This article highlights the scientific achievements of the PSCDR throughout the past 20 years.

## Projects and programs

### *1) The provision code for persons with disabilities in the Kingdom of Saudi Arabia*

In realization of the importance of persons with disabilities, the first Saudi disabled children’s association conference was held during the period 13-16/5/1413H (8-11/11/1992) to discuss this important issue. The recommendation of this conference was approved by the Royal Court. Under the direction of HRH Prince Sultan Bin Salman Bin AbdulAziz and after collecting required information, data, regulations, and rules related to people with disabilities in the Kingdom, the PSCDR center prepared an integrated and comprehensive proposal for a national system for people with disabilities. All the aspects of this proposal have been studied by expert bodies in the Council of Ministers. The work team was assigned to prepare the Provision Code for Persons with Disabilities. The main code consists of 16 articles. The 16 articles are summarized as follows:

---

*From the Prince Salman Center for Disability Research, and the Research Center, King Faisal Specialist Hospital & Research Center, Riyadh, Kingdom of Saudi Arabia.*

*Address correspondence and reprint request to: Dr. Ali N. Al-Odaib, Deputy Executive Director for Research Affairs, Prince Salman Center for Disability Research, PO Box 94682, Riyadh 11614, Kingdom of Saudi Arabia. Tel. +966 (11) 4884401. E-mail: odaib@pscdr.org.sa*

*Article 1:* Includes terms definition.

*Article 2:* Includes governmental guarantee for welfare, prevention, healthcare, education, training, and habilitation services, employment, social participation, and sports facilities for persons with disabilities.

*Article 3:* Includes coordination of the Supreme Council with authorities to abide regulations for architectural specifications required to provide easy access for movement and transportation for persons with disabilities.

*Article 4:* Includes coordination of the Supreme Council with authorities to provide manpower for education and training - nationally and internationally - in the field of disability and to promote experience exchange with other countries.

*Article 5:* Includes loan awarded by the government for person with disabilities to establish occupational or commercial employments suitable to their abilities.

*Article 6:* Includes customs exemption for technical aids and devices used by persons with disabilities.

*Article 7:* Includes establishment of a trust fund under the control of the Supreme Council for depositing all endowments, donations, and revenues from fines, which will be used for providing care for persons with disabilities.

*Article 8:* Includes the establishment of a Supreme Council of the Affairs of Persons with Disabilities and associated with a Prime Minister.

*Article 9:* Includes authorization of the Supreme Council to formulate the strategy and organization of the Affairs of Persons with Disabilities.

*Article 10:* Includes submission of an annual report by the Supreme Council to the Prime Minister regarding the services provided for persons with disabilities.

*Article 11:* Biannual meetings should be conducted.

*Article 12:* Includes organization of staff appointment by the Supreme Council in accordance with the regulations of the civil service.

*Article 13:* The Supreme Council shall form a working group and determine and specify the group's expertise and work methodology.

*Article 14:* The Supreme Council shall have a budget that will be subject to the general rules and provisions of the Kingdom's budget.

*Article 15:* All pre-existing codes, policies, procedures, decisions, and instructions to persons with disabilities shall be modified according to this Code within 3 years of the date of its publication.

*Article 16:* Publication of this code in all official newspapers, and should be valid and in effect 180 days from the date of publication.

***Aim of the study:*** To prepare the Provision Code for Persons with Disabilities.

***Results:*** This code was issued according to the Royal Decree (NO. M/37) dated 23/9//1421H that approved the decision of the Council of Ministries (NO. 224) dated 15/9/1421H authorizing the Code. However, this code is now being revised and a new addition is under process.

## ***2) National research project to study childrens' disability in the Kingdom of Saudi Arabia***

The study covered demographic as well as epidemiological aspects, causes of disabilities and their relation to congenital and environmental factors, identification of social and economical factors, as well as rehabilitative, preventive, and therapeutic aspects, and services rendered to people with disability. This underscores the necessity of benefiting from the coordinative and integrative efforts in the field of disability. Research results also included some recommendations on care, rehabilitation, and preventive procedures to lower disability rates and train human resources, encourage research in the field of disability, and participate in laying out suitable and applicable plans in this field.

***Results:*** Results of studies conducted, through this research, showed that the number of children with disabilities was 3838 out of the research sample of (60630 children), in different regions of the Kingdom, which amounts to 6.3%.

### 3) *Pre-implantation genetic diagnosis for the prevention of genetic diseases*

The incidence of many recessive genetic diseases is 40-80 times higher in Saudi Arabia than other places in the world due to high rates of consanguineous marriages. For some of these disorders, effective, and non-costly treatment procedures are available whereas for some other disorders, the treatment is either ineffective or very costly. Therefore, this project will focus on the use of the pre-implantation genetic diagnosis (PGD) technique in preventing the occurrence of some of the frequently encountered disorders, which have a known gene structure and mutation that cause significant morbidity and requires lifelong intensive and expensive treatment. In this technique, embryos are generated by in vitro fertilization (IVF) and the affected embryos are detected during the cleavage stage embryo. This will permit the transfer of only unaffected embryos thereby eliminating the need for abortion following the prenatal diagnosis in case of an affected fetus.

#### *Aims of the study:*

- Select initially a group of diseases, in which the parents will be offered the option of PGD.
- To initially implement PGD in 5 selected disorders.
- To establish a microarray DNA containing the mutations discovered during the period of this project for future use in pre-marital screening.
- To apply the experience gained in PGD to other genetic disease.

**Results:** This project resulted in the discovery of several novel mutations identified in: Niemann-Pick disease type-B: The new mutation detected was in the 6 coding exons of the SMPDI gene. The mutation was caused by a thymidine to cytosine substitution (W533R).<sup>1</sup> Gaucher disease: A novel compound heterozygote mutation comprising L444P on the paternal allele, and F397S on the maternal allele was identified.<sup>2</sup> Propionic academia: The largest novel deletion in the propionyl CoA carboxylase in its alpha subunit (PCCA) of ~73kb extending from intron 16 to intron 19, and an 18bp insertion at the distal end of the deletion in PCCA gene was identified.<sup>3</sup> Canavan disease: A novel deletion in the aspartoacylase enzyme gene extending from introns 2 and 3 comprising the full exon 3 and extending 3346bp was detected in 2 patients.<sup>4</sup> During the course of this project, and for the first time, the multiple displacement amplification (MDA) technique was used to overcome some of the technical limitations facing PGD regarding chromosomal abnormalities and single gene disorders. The MDA technique was used to amplify minute amounts of DNA in clinical samples to a reasonable quantity that suits microarray analysis or the diagnosis of any known single gene disorder by a standard polymerase chain reaction (PCR) technique.<sup>5</sup> This project was expanded into a diagnostic technical service to help families suffering from recessive genetic diseases to have normal offspring.

### 4) *Spinal muscular atrophy: Heterozygote (carrier) screening in Saudi Arabia*

Spinal muscular atrophy (SMA) is an autosomal recessive inherited disease that results in the loss of motor neurons in the spinal cord and lower brainstem leading to symmetrical progressive paralysis with muscle atrophy. It represents the second most common lethal autosomal recessive disorder after cystic fibrosis. Previous reports have indicated that the incidence of SMA is 20 times higher in the Saudi population compared with other ethnic groups due to the high degree of consanguineous marriages. The duplication of the SMA locus makes the detection of carriers in the general population difficult. In light of this observation, it is essential to develop a sensitive method for screening carriers in the Saudi population that will facilitate the screening of SMA patients who harbor a single SMN1 gene (heterozygote).

#### *Aims of the study:*

- To study the prevalence of SMA carriers in a representative sample of Saudi volunteers (university, college, and military college students) in Riyadh.
- To re-establish the sensitivity and specificity of SMA carrier screening method by examining the parents of SMA patients.

- To develop a policy for increasing awareness of SMA among the Saudi population depending on the carrier screening results.

**Results:** To achieve the goals of this project, an easy, inexpensive, and highly sensitive quantitative multiplex PCR method using dried blood spot on filter paper was developed for determination of the SMN1 copy number in the human genome.<sup>6</sup> This method includes the isolation of the genomic DNA from the blood spot sample then the detection of the SMN1 copy numbers in an individual DNA sample using a multiplex PCR assay. A total of 187 Saudi healthy control subjects and 62 parents of SMA patients (carriers of this disease) were analyzed. The results showed that 92% of parents have carrier status. Furthermore, out of 187 controls, 9 individuals had carrier status. This makes the carrier frequency 5%, or one in 20 individuals; which is almost 2.5 to 4 times higher than in other ethnic groups.

### *5) Stroke in Saudi children: Clinical features, etiology, risk factors, and prognosis*

Strokes are considered to be among the main causes of children's disability throughout the world. Among those children who live after having a stroke, 75-100% suffer from some kind of disability such as motor disability, epilepsy, mental retardation, and communication disorders. Etiology and risk factors of strokes vary according to age and demographic variables. Stroke studies, conducted on Saudis, were concentrated on adults and, so far, no comprehensive study addressing strokes in Saudi children has been conducted. Results of this study are expected to establish the cornerstone of proper intervention plans to prevent disability. This retrospective and prospective study, which spanned 10 years and 7 months, is one of the largest cohorts of children with stroke at one medical center worldwide.

**Aims of the study:** This study intends to describe types of strokes affecting Saudi children, in a strategic way, to identify causes and risk factors of strokes, especially those related to congenital aspects. The study will assess the results of strokes along with identifying the factors that could produce positive results in Saudi children.

**Results:** During the combined study periods of 10 years and 7 months, 117 children (61 males, and 56 females, aged one month-12 years) were evaluated; the majority (89%) of these were Saudis. The calculated annual hospital frequency rate of stroke was 27.1/100,000 of the pediatric (1 month-12 years) population. The mean age at onset of the initial stroke in the 104 Saudi children was 27.1 months (SD = 39.3 months) and median was 6 months. Ischemic strokes accounted for most cases (76%). Large-vessel infarcts (LVI, 51.9%) were more common than small-vessel lacunar lesions (SVLL, 19.2%). Five patients (4.8%) had combined LVI and SVLL. Intracranial hemorrhage was less common (18.2%), whereas sinovenous thrombosis was diagnosed in 6 (5.8%) patients. A major risk factor was identified in 94 of 104 (89.4%) Saudi children. Significantly more hematologic disorders and coagulopathies were identified in the prospective study group compared with the retrospective study group ( $p=0.001$ ), reflecting a better yield following introduction of more comprehensive hematologic and coagulation laboratory tests during the prospective study period. Hematologic disorders were the most common risk factor (46.2%), presumed perinatal ischemic cerebral injury was a risk factor in 23 children (22.1%), and infectious and inflammatory disorders of the circulatory system in 18 (17.3%). Congenital and genetic cerebrovascular anomalies were the underlying cause in 7 patients (6.7%), and cardiac diseases in 6 (5.8%). Six patients (5.8%) had Moyamoya syndrome, which was associated with another disease in all of them. Inherited metabolic disorders (3.8%) included 3 children with Leigh syndrome, and a 29-month-old girl with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. Systemic vascular disease was a risk factor in 3 children (2.9%) including 2 who had hypernatremic dehydration; and post-traumatic arterial dissection was causative in 3 cases (2.9%). Several patients had multiple risk factors, whereas no risk factor could be identified in 11 (10.6%) children.<sup>7</sup>

### *6) Longitudinal study of prenatal and postnatal lead exposure and early cognitive development in Al-Kharj, Kingdom of Saudi Arabia*

Many studies have confirmed that low-level lead exposure in early life can be associated with deficits in neurobehavioral-cognitive performance during childhood and adolescence. Our previous studies confirmed the

transfer of lead from the mother to the fetus as well as the effect of low lead exposure on neuropsychological behavior in school children. These results encouraged us to design a longitudinal survey to evaluate the effect of prenatal and/or postnatal lead exposure on early cognitive development among a selected group of children from birth to 2 years of age.

*Aims of the study:*

- To assess the effect of prenatal and postnatal lead exposure upon early cognitive development of infants using the Bayley Scales of Infant Development at the ages of 6, 12, 18, and 24 months in a longitudinal study.
- To determine the risk of exposure to lead through a detailed questionnaire.
- To identify prevention factors that should be taken into consideration by public health authorities.

**Results:** Lead levels were measured in 653 umbilical cord blood samples taken from healthy Saudi mothers delivering at King Khalid Hospital, Al-Kharj, Kingdom of Saudi Arabia. Based on the results of lead levels in the collected cord blood samples, infants were classified into 3 groups for neuropsychological assessments as follows:

- Low group: the lower 10th percentile of lead levels ( $\leq 1.045$   $\mu\text{g}/\text{dl}$ ).
- High group: the upper 10th percentile of lead level ( $\geq 3.466$   $\mu\text{g}/\text{dl}$ ).
- Mid group: in between the high and low groups ( $> 1.045$ - $< 3.466$   $\mu\text{g}/\text{dl}$ ).

At 6, 12, 18, and 24 months, the Bayley Scales of Infant Development were administered and venous blood lead levels were measured. Demographic, environmental, and socio-economic information was obtained for each infant. The mean blood lead concentrations in the infants increased from 3.36  $\mu\text{g}/\text{dl}$  at the age of 6 months to 4.451  $\mu\text{g}/\text{dl}$  at the age of 24 months, but the standardized Mental Development Index (MDI) and Psychomotor Development Index (PDI) decreased from 99.26 and 98.13 at the age of 6 months, to 93.29 and 82.52 at the age of 24 months. Adjustment for a large number of confounding variables was performed, and then it was found that prenatal lead exposure was significantly and inversely associated with the standardized MDI and PDI scores at the age of 6 months old. A borderline significant effect of prenatal lead exposure was also seen on standardized PDI scores at the age of 24 months. On the other hand, no relationship was found between postnatal blood lead levels and concurrent cognitive development scores. Such observation is not conclusive because of low statistical power due to small sample size.<sup>8</sup>

*7) Characterization of the molecular basis of hereditary hearing loss in Saudi Arabia*

Recessively inherited diseases are more prevalent in populations where consanguineous marriages are common, like Saudi Arabia. Deafness is the most common sensory deficit in humans (1:1000 child births) with both genetic (50%) and environmental (50%) etiologies. Our study hopes to define the genetics of deafness in this population. Families with profound congenital deafness and an autosomal recessive mode of inheritance are a powerful resource for genetic linkage studies of recessively inherited deafness.

*Aims of the study:*

- To identify known and novel genes causing hereditary hearing loss in the Saudi Arabian population.
- To provide a primary platform for the design, validation, and implementation of molecular diagnostic testing for inherited diseases to help lay the foundation for preventive measures including carrier testing, prenatal diagnosis, pre-implantation genetic diagnosis, and pre-marital screening.

**Results:** Individuals from 200 families of Saudi Arabian tribal origin diagnosed with an autosomal recessive non-syndromic sensorineural hearing loss (NSHL) were screened for mutations at the DFNB1 locus by direct sequencing. If negative, genome-wide linkage analysis or homozygosity mapping were performed using AffymetrixGeneChip® Human Mapping 250K/6.0 arrays (Affymetrix, Santa Clara, CA, USA) to identify regions

containing any known-deafness causing genes that were subsequently sequenced. Our results strongly indicate that DFNB1 only accounts for 3% of non-syndromic hearing loss in the Saudi Arabian population of ethnic ancestry. The overall results of this study are highly suggestive that the underlying molecular basis of autosomal recessive non-syndromic deafness in Saudi Arabia is very genetically heterogeneous. In addition, we report that the preliminary results indicate that there does not seem to be any common or more prevalent loci, genes, or mutations in patients with autosomal recessive non-syndromic hearing loss in patients of Saudi Arabian tribal origin.<sup>9</sup> During the course of this project, an SNP array-based whole-genome homozygosity mapping approach in search of the causative gene was used in a consanguineous Saudi family with 5 affected individuals presenting severe to profound congenital NSHL. A single shared block of homozygosity was identified on chromosome 19p13.3 encompassing GIPC3, a recently identified hearing loss gene. Subsequently, a novel mutation c.122 C>A (p.T41K) in GIPC3 was found. The presence of the GIPC3 mutations in only one of 100 Saudi families with congenital NSHL suggests that it appears to be a rare cause of familial or sporadic deafness in this population.<sup>10</sup> Also, a novel p.S243X truncating mutation in USH1G that segregated with the disease phenotype and was not present in 300 ethnically matched normal controls was identified. Additionally, novel retinal findings and the outcome of cochlear implantation in the affected individuals was reported.<sup>11</sup>

### 8) *The rights of the handicapped in Islam*

This project was a PhD thesis. This work tackles one of the novel topics; namely, disability in Islam, in one of the promising fields of research; namely, religion and disability. Academic studies in this field in general are still scarce and concerning the religion of Islam in particular; they are almost absent.

**Aims of the study:** To explore the position of people with disabilities and their rights in Islam as a contribution to a better understanding regarding the needs of, and provisions for people with disabilities in the norms of the Islamic religion.

**Results:** Every part of this dissertation represents a new scholarly contribution in this field. This study consists of the following parts, Part I (Islam Theology) and Part II (Islamic Jurisprudence). The author tried to find a balance between early and modern Muslim scholars when discussing ideas regarding people with disabilities and their rights in the Islamic tradition. It was noticed that the early Muslim scholars were more prominent in some parts of this study than the modern ones. The terminology used by classical sources to denote people with disabilities was discussed thoroughly by the author. For instance, in Islamic theology, people with disabilities fell within the board category of ‘people with afflictions’(ahl-al bala) whose common characteristic was affliction. In Islamic jurisprudence, people with disabilities also fell into the board category of “people with excuse” (ahal-al-adhar) whose common characteristic was having a valid excuse for exemption from specific religious obligations. Also, in the adab works, people with disabilities were presented as part of a large group of those mainly characterized by their “abnormality “and weirdness”. Additionally, in this study, intensive discussions took place among Muslim scholars on the rights of this group to have paid work, medical treatment, and financial aid when they needed it. The debates among these scholars on the ethics of writing regarding people with disabilities were elaborated in the thesis, and bear witness to the fact that the human rights dimension was not absent from the discussions of these scholars.<sup>12</sup>

### 9) *Hunting for one of the autism genes that might be linked to osteopetrosis with renal tubular acidosis*

Osteopetrosis with renal tubular acidosis (OPRTA) is an autosomal recessive disease caused by mutations in the CA2 gene (8q22) encoding carbonic anhydrase II. It is considered one of the most common cerebral degenerative diseases of infancy in Saudi Arabia. The disease is sub classified into classical OPRTA (OPRTA-C), OPRTA with autism (OPRTA-AUT), and OPRTA with mental retardation (OPRTA-MR). Out of all known associations of classical autism, 2 translocation abnormalities have been associated with the region around CA2. Reviewing the OPRTA patient files at King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia indicates the presence of at least 33 patients with OPRTA under current follow-up, and another 4 patients in addition were found to have classical autism bringing the total to 37. It is reasonable to hypothesize that there must be a putative autism gene in the region where carbonic anhydrase II is located.

**Aims of the study:** The main aim of this project is to investigate 30 patients with OPRTA some of whom were also found to be autistic. A region of 180Kbp where carbonic anhydrase II will be studied for:

- Polymorphic markers.
- Carbonic anhydrase II gene mutations.
- Inversion within the region.
- Possible micro-deletion in the region.

It is anticipated that a gene, or genes, linked to autism will be thus identified and should contribute to the research on autism-associated gene markers.

**Results:** Blood samples were collected from 31 consented patients. Out of 31 patients, only 7 cases were subjected to microarray based gene expression studies using Affymetrix GeneChip® in where whole-genome mRNA expression profile in lymphoblasted cells from 7 OPRTA with normal intelligence, 7 OPRTA patients with mental retardation, and 5 OPRTA patients with autism in addition to 8 non-autistic controls were presented. To find genes that were differentially expressed across the 3 different subject groups of OPRTA, the expression of the lymphoblasted cells were subjected to analysis of variance (ANOVA). The ANOVA identified 1093 probes (759 known genes) with  $p < 0.001$  significantly modulated across the 3 subjects groups. Those significantly modulated genes were subjected to principal component analysis (PCA) in where the 3 dominant PCA components that contained 81.6% of the variance in the data matrix clearly separated the individuals based on their genetic etiology. The hierarchical clustering using 1093 probes clearly classified individuals based on their genotype. Each disease specific genes were subjected to Expression Analysis Systematic Explorer (EASE) analysis to identify potential biological themes associated with each OPRTA disease type. Genes were categorized by using Gene Ontology (GO) categories belonging to the ontologies of molecular function, biological process, and cellular component. The EASE analysis revealed that genes belonging to “cytokinesis,” “cell-cell signaling,” morphogenesis,” “cellular process,” “receptor binding,” “signal transducer activity,” “cell communication,” and “development” are among the most significantly overrepresented ontologies (EASE score  $< 0.05$ ) for the OPRTA with autism up regulated genes. Genes related to “intracellular,” “spliceosome assembly,” “cell,” “RNA binding,” “cytoskeleton,” “cell organization and biogenesis,” “mRNA metabolism,” and “cell growth and/or maintenance” are among the overrepresented categories for the OPRTA with autism down regulated genes. For the OPRTA with mental retardation, genes related to “spindle,” “mitosis,” “microtubule cytoskeleton,” and “nuclear division” were significantly overrepresented GO categories for the up regulated cluster, whereas “cellular process,” “olfaction,” “cyclase activity,” “cell fraction,” “cell communication,” “cell motility,” “cell growth and/or maintenance,” and “cell-cell signaling” were overrepresented in the down regulated cluster of genes specific to OPRTA with mental retardation. The EASE analysis for the OPRTA with normal IQ discriminatory genes enriched in the following GO categories: “cytoplasm,” “intracellular,” protein binding,” “physiological process,” “calmodulin binding,” and “signal transduction”. During this project a case report was published describing the occurrence of autism in a child suffering from propionic acidemia, a metabolic disease, where affected individuals are known to suffer from intellectual disabilities.<sup>13</sup> Additionally, another publication was released identifying a novel Xq12-q13.3 duplication in an extended family all maternally related.<sup>14</sup>

### *10) Mitochondrial DNA genotyping in Arab patients with various optic neuropathies*

The number of mitochondria in a cell and the amount of mitochondrial DNA (mtDNA) per mitochondrion together constitute the mtDNA content of the cell. Cells carefully regulate the mtDNA content, but they also seem able to adjust relative (to nuclear DNA) mtDNA content upward by duplication of mitochondria or proliferation of mtDNA as compensation for reduced ATP synthesis. For example, relative mtDNA content increases in certain tissues as respiratory function declines with age and oxidative stress. Non-arteritic anterior ischemic optic neuropathy (NAION) and Leber’s hereditary optic neuropathy (LHON) are clinically distinct types of optic neuropathies, but they share certain clinical characteristics, including simultaneous or sequential subacute optic nerve injury with swelling of the optic disc, most often without pain or recovery of vision. Mitochondrial abnormalities might be a risk factor for such optic neuropathies. This study highlights the importance of identifying

mtDNA mutations that may be specific to the Saudi population, and explores the possible link between mtDNA mutations with LHON, NAION, and other optic nerve diseases, such as glaucoma. When the link between mitochondrial DNA mutation, mitochondrial functional disturbance, and optic nerve injury is better understood, this may help in assessing possible treatment options. This may be particularly important in glaucoma, where tens of thousands of Saudi's are affected and current treatment is frequently inadequate to prevent profound visual loss.

#### *Aims of the study:*

- Determine the possible association between different types of optic nerve injury and mitochondrial DNA mutations and/or mitochondrial respiratory dysfunction.
- Determine the spectrum of mitochondrial mutations in the Saudi population associated with various optic nerve diseases.

**Results:** The entire mtDNA coding region in a group of 19 patients with NAION and in 100 controls was sequenced. Synonymous and non-synonymous nucleotide changes were more common in NAION patients ( $p < 0.001$ ). Twelve of these (11 novel) were potentially pathologic, 9 of which altered moderately or highly conserved amino acids in the functional domain of the affected protein. Mitochondrial malfunction may be a risk factor for NAION.<sup>15</sup> Implying that mitochondrial abnormalities might be a risk factor for this optic neuropathy, a decision was made to investigate whether those NAION patients also have changes in relative mtDNA content. Therefore, in another study, those same 19 NAION patients were compared to 32 controls matched for age, gender distribution, and ethnicity. Results showed that the mean relative mtDNA content in controls (0.93 [SD 0.11]; 95% confidence interval [CI] 0.89 to 0.97) was significantly less than in NAION patients (2.40 [SD 1.05]; 95% CI 1.90 to 2.91;  $p < 0.001$ ). Relative mtDNA content was negatively correlated with Snellen visual acuity (Spearman's rho;  $r = -0.37$ ;  $p = 0.022$ ). Increased relative mtDNA content in NAION patients may imply a response to oxidative stress, possibly in part because of mitochondrial respiratory chain defects. Significantly more non-synonymous mtDNA nucleotide changes, significantly increased relative mtDNA content, and a significant association between relative mtDNA content and visual acuity all imply that mitochondrial abnormalities may be a risk factor for NAION.<sup>16</sup>

During this research period, the case of a 76-year-old man suffering from NAION with mitochondrial nt-9957 mutation was studied to assess the functional significance of the nt-9957 mutation as this mutation has been previously reported in association with mitochondrial encephalopathy, lactic acidosis, and stroke-like events (MELAS). Results showed that this man had optic nerve disease bilaterally and seizures, but no clinical or radiological evidence of MELAS. He had no mitochondrial DNA mutation other than the 9957. Functional testing revealed a severe defect in mitochondrial complex III activity. It seems quite likely that this mutation may be responsible for optic nerve and brain injuries.<sup>17</sup> While conducting this research, a case report of a patient with LHON plus dystonia who had a severe complex I respiratory defect with no pathological mtDNA mutation was described. This provides presumptive evidence of a mitochondrial abnormality of nuclear origin.<sup>18</sup> Additionally, throughout the course of this research work, the evaluation of 29 patients with pseudoexfoliation glaucoma (PEG) for the presence of mitochondrial abnormalities and nuclear gene mutations associated with various types of glaucoma (MYCO, OPTN, WDR36, and CYP1B1) and certain inherited optic neuropathies (OPA1 and OPA3) was conducted. The nuclear genes MYOC, OPTN, WDR36, CYP1B1, OPA1, and OPA3 were sequenced in PEG patients. The entire mtDNA coding region was also sequenced, relative mtDNA content was investigated, and mitochondrial respiration was assessed. Results showed that no novel or previously reported mutations were present in the nuclear genes MYOC, OPTN, CYP1B1, WDR36, OPA1, or OPA3 in 29 PEG patients. Twenty-six patients (89.7%) had no pathological or potentially pathological mtDNA mutation(s); however, 3 patients (10.3%) had potentially pathologic mtDNA nucleotide changes not found in controls. The PEG patients did not differ significantly from controls in relative mitochondrial content ( $p = 0.98$ ) or in mitochondrial respiratory activity ( $p = 0.18$ ). These findings conclude that these PEG patients had no mutations in nuclear genes associated with other types of glaucoma, or other inherited optic neuropathies, and there was little evidence of mitochondrial abnormalities. These results imply that the nuclear genes and mitochondrial parameters evaluated here are less important determinants of PEG than other factors related to the presence of pseudoexfoliation material.<sup>19</sup>



While conducting this project, and considering the fact that primary open-angle glaucoma (POAG) is the second most common cause of blindness and was linked to mutations in MYCO and OPTN genes, although mutations have been found in less than 5% of patients, and given the fact that all major risk factors for POAG have not yet been identified and that known nuclear genetic abnormalities are associated with only a small fraction of patients, an investigation of a possible link between mitochondrial abnormalities and patients with POAG was initiated. In this research, 27 patients with definite POAG, the MYOC, and OPTN genes were sequenced, the entire mitochondrial mtDNA coding region was sequenced, relative mtDNA content was investigated, and mitochondrial respiratory function was assessed. Results revealed that only 3 benign polymorphisms were identified in MYOC and OPTN in patients with POAG and in control subjects. Conversely, 27 different novel non-synonymous mtDNA changes were found, only in patients with POAG (not control subjects), 22 of which (found in 14 patients) were potentially pathogenic. Unlike LHON, most mtDNA sequence alterations in patients with POAG were transversions-sequence changes that alter the purine/pyrimidine orientation and imply oxidative stress. The mtDNA content was relatively increased in 17 patients with POAG compared with age-matched control subjects, also implying a possible response to oxidative stress. Mean mitochondrial respiratory activity was decreased by 21% in patients with glaucoma compared with control subjects ( $p < 0.001$ ). These results reveal a spectrum of mitochondrial abnormalities in patients with POAG, implicating oxidative stress and implying that mitochondrial dysfunction may be a risk factor for POAG. This concept may open up new experimental and therapeutic opportunities.<sup>20</sup>

As glaucoma prevalence can vary geographically and ethnically, which suggests that a genetic element could play a significant role and the studies investigating the role of various mitochondrial haplogroups in the pathogenesis of glaucoma are scarce, an investigation of the possible association of mitochondrial haplogroups with the pathogenesis of the 3 common types of glaucoma (POAG, primary angle-closure glaucoma [PACG], and PEG) prevalent in Saudi Arab population was studied. A comparison between the prevalence of different mitochondrial haplogroups in 107 glaucoma patients (49 with POAG; 29 with PACG; and 29 with PEG) and 552 maternally unrelated normal controls was conducted. All patients and controls were Saudi Arabs. Results showed that there was no statistically significant difference between patients and controls for all mitochondrial haplogroups tested except for PACG patients with mitochondrial haplogroup preHV1 (odds ratio=4.9; 95% CI 2.3-10.5;  $p=0.00002$ ). This suggests that patients with preHV1 mitochondrial haplogroups are at higher risk of developing PACG. However, due to the relatively small studied group, further studies with more patients in other populations are needed to confirm this interesting finding.<sup>21</sup>

### *11) National genetic and birth defect registry*

Saudi Arabia has an inordinately large number of genetic diseases, particularly autosomal recessive diseases are encountered frequently more than in the West. This is probably due to high rates of consanguineous and tribal marriages. In Saudi Arabia, cousin marriages account for around 60%, with half involving first cousins, and one fourth involving double first cousin marriages. Currently, there is no comprehensive database for genetic diseases registry in the Kingdom. In the face of such a public health problem that afflicts a significant segment of the population requiring chronic care, the most important policy decision is to design a preventive health system to combat the problem. One of which is to start the establishment a formal genetic defect registry. This project was established to register dysmorphic patients, chromosome abnormalities, and patients with inherited metabolic diseases, as well as children with diverse inherited neuro-metabolic diseases.

#### *Aims of the study:*

- To establish the infrastructure of a comprehensive database to cover all the aspects related to genetic and birth defect disorders.
- To register patients from the clinics of King Faisal Specialist Hospital & Research Center (KFSH&RC) with known or proven genetic and metabolic diseases.
- To enter those patients registered into the database.
- To analyze data as proposed in the initial proposal.

**Results:** A comprehensive database was designed and established with a close collaboration between the departments of Biostatistics, Epidemiology and Scientific Computing, Genetics, and Medical Genetics. The database covers the following:

- Patient's demographics (name, age, gender, national number...)
- Patient's tribe, and sub-tribe
- Family history and pedigree
- Clinical diagnosis
- Biochemical diagnosis
- Molecular diagnosis
- Clinical visits
- Emergency room visits
- Treatments (medication, supplements, diet...)

### *12) Universal accessibility program*

Prince Salman Center for Disability Research promotes research projects that focus on the needs of the persons with disabilities, and the results of these projects contribute to improving the lives of persons with disabilities and the science benefiting people. One of these projects is the universal accessibility program. Easy universal accessibility simply means designing products, buildings, and outdoor spaces that can be used by all people as much as possible. This also includes designing technology, information, and a communication environment, along with provision of programs, services, and activities. The universal accessibility program was launched to confirm the accommodation of persons with disabilities in aspects of public life, and to support them in all areas so that they can exercise their normal lives as indicated in the provisions of Disability Code.

**Aims of the study:** The overall goal of this research program is to create a barrier-free environment that facilitates full participation for all members of society, especially those with disabilities by creating a comprehensive system of standards and assessment based on international standards and best professional practices. Standards for building environments, transportation, and tourism are to be formulated, adopted, launched, disseminated, and implemented by key stakeholders in the Kingdom.

**Results:** Work in this project continued for more than 3 years and resulted in:

- Designing 4 guidelines for the universal accessibility program. These guidelines are: Universal Accessibility Built Environment Guidelines, Universal Accessibility Land Transportation Guidelines, Universal Accessibility Marine Transportation Guidelines, and Universal Accessibility Destinations and Places Accommodations. These guidelines are available at the PSCDR portal (<http://accessibility.pscdr.org.sa/>) (Figure 1).
- PSCDR advocates activating and applying the universal accessibility program.
- PSCDR raises the awareness among professional engineers, technicians, and administrators by holding orientation sessions for engineers and technicians in different engineering sectors and for those who are interested in universal accessibility.
- In cooperation with the competent authorities, PSCDR is currently designing professional courses for engineers to accredit them as universal accessibility engineers.

### *13) The effect of using technology based teaching to remedy dyslexic Saudi elementary stage pupils*

Learning difficulties that pupils encounter and may have a negative impact on their achievement, especially in their early educational years, are numerous. This research aims at identifying the effect of using some modern educational technologies such as computer and interactive video to remedy one of the learning difficulties; namely, dyslexia. To diagnose dyslexic students, some appropriate already made tools will be used as well as new tools that will be standardized to fit the Saudi context. A comprehensive survey for a large sample of Saudi elementary

الدليل الإرشادي  
للوصل الشامل في المملكة العربية السعودية  
١٤٣١ هـ - ٢٠١٠ م

مركز الأمير سلمان للأبحاث الإعاقة  
Prince Salman Center for Disability Research  
Science Enabling People  
علم يفتح آفاقاً

الدليل الإرشادي للبيئة العمرانية  
Universal Accessibility Built Environment Guidelines

اضغط هنا لقراءة الدليل الآن  
اضغط هنا لتنزيل الدليل

الدليل الإرشادي للوصول الشامل في مساحات النقل البرية  
Universal Accessibility Land Transportation Guidelines

اضغط هنا لقراءة الدليل الآن  
اضغط هنا لتنزيل الدليل

الدليل الإرشادي للوصول الشامل للوجهات السياحية وقطاعات الإيواء  
Universal Accessibility Destinations & Places Accommodations

اضغط هنا لقراءة الدليل الآن  
اضغط هنا لتنزيل الدليل

الدليل الإرشادي للوصول الشامل لمساحات النقل البحرية  
Universal Accessibility Marine Transportation Guidelines

اضغط هنا لقراءة الدليل الآن  
اضغط هنا لتنزيل الدليل

© 2010 مركز الأمير سلمان لأبحاث الإعاقة جميع الحقوق محفوظة

Figure 1 - The website of the Universal Accessibility Program Guidelines. Available from: <http://accessibility.pscdr.org.sa/>

stage pupils (9 to 12 year-old) from 5 different regions in the Kingdom of Saudi Arabia (about 3000 pupils), will be conducted to identify the dyslexic pupils in terms of: frequency, degree of dyslexia they suffer from, symptoms, causes, and effects. To remedy dyslexia, some educational programs will be designed with the aid of modern educational technologies to be used with dyslexic pupils who find difficulty in studying and learning concepts in Arabic, Mathematics, Science, and Social Studies at the Southern Region of Aseer in the Kingdom of Saudi Arabia. Some guidance programs for teachers and parents will also be devised and used alongside with those technologically based educational programs. The effect of those programs on the pupils' achievement of concepts, which were difficult for them to learn, will be measured using some criterion-referenced tests, prepared particularly for this purpose. Recommendations, suggestions, and mechanisms for implementing the programs to fully make use of the modern educational technologies to remedy the learning difficulties will be determined accordingly.

*Aims of the study:* The study attempts to achieve the following aims:

1. Identifying the common characteristics of primary stage Saudi dyslexic pupils who have learning difficulties related to dyslexia.
2. Determining the extent to which those learning difficulties are spread among a sample of Saudi primary stage pupils via surveying 5 different regions within the Kingdom of Saudi Arabia.
3. Diagnosing the difficulties that dyslexic pupils encounter when studying primary curricula particularly Arabic, Mathematics, Science, and Social Studies in Aseer Region.
4. Devising appropriate educational programs for the dyslexic pupils in which modern educational technologies (computer and interactive video) would be employed to remedy learning difficulties due to dyslexia, in addition to the supplementary guidance programs for teachers.
5. Applying the technology based programs to the dyslexic pupils on one hand and on teachers the other hand to measure the effect of using educational technology upon dyslexic pupils. This will be achieved via employing achievement tests in Arabic, Mathematics, Science, and Social Studies, which will help determine the effectiveness of technology based programs, if there are any.

*Results:* The results of the study can be summed in the following:

- Regarding the first hypothesis, the results revealed that the ratio of the dyslexia spread differs according to the region and the students' grades. The results showed that the largest ratio of dyslexia spread was in Riyadh region (30.6%) and in the sixth grade (14.2%). Generally, the results of this hypothesis refer to the fact that dyslexia spread in the Kingdom of Saudi Arabia is similar to the international rate.
- Regarding the second hypothesis, results revealed that dyslexics are characterized with incompetence in many of the behavioral characteristics and the basic reading skills compared with their ordinary peers.
- The results of the third hypothesis showed that dyslexics suffer from clear incompetence in auditory perception, word analysis, word meaning, sentence comprehension, paragraph, and text understanding compared with their ordinary peers.
- The results of the fourth hypothesis refer to the effectiveness of the study programs, especially the dyslexia remedial program, in curing reading difficulties of dyslexics (the study sample). The results of this hypothesis showed that there were significant differences favoring the post assessment as well as an effect volume ranging from 0.59 to 1.8, which clearly proves the accuracy, well planning and application of the program.

#### *14) Saudi newborn screening program for metabolic diseases*

The newborn screening program is a public health program implemented on August 20, 2005 to detect and prevent selected congenital and heritable disorders. These disorders cause severe mental retardation, illness, or death if not treated early in life. Numerous studies showed that early detection and early intervention may prevent these consequences. The selected disorders are: phenylketonuria (PKU), maple syrup urine disease (MSUD), argininosuccinase deficiency (ASL), citrullinemia (ASD), HMG-CoA lyase deficiency (HMG), isovaleric acidemia (IVA), methylmalonic acidemia (MMA), propionic acidemia (PA), beta-ketothiolase deficiency (BKT),

methylcrotonyl-CoA carboxylase deficiency (3MCC), glutaric acidemia type-I (GA-I), medium-chain acyl-CoA dehydrogenase deficiency (MCAD), galactosemia (GAL), congenital hypothyroidism (CH), congenital adrenal hyperplasia (CAH), biotinidase deficiency (BD). The first 12 of these diseases are screened for by tandem mass spectrometry; the last 4 disorders will be screened for by 4 different fluoroimmuno assays.

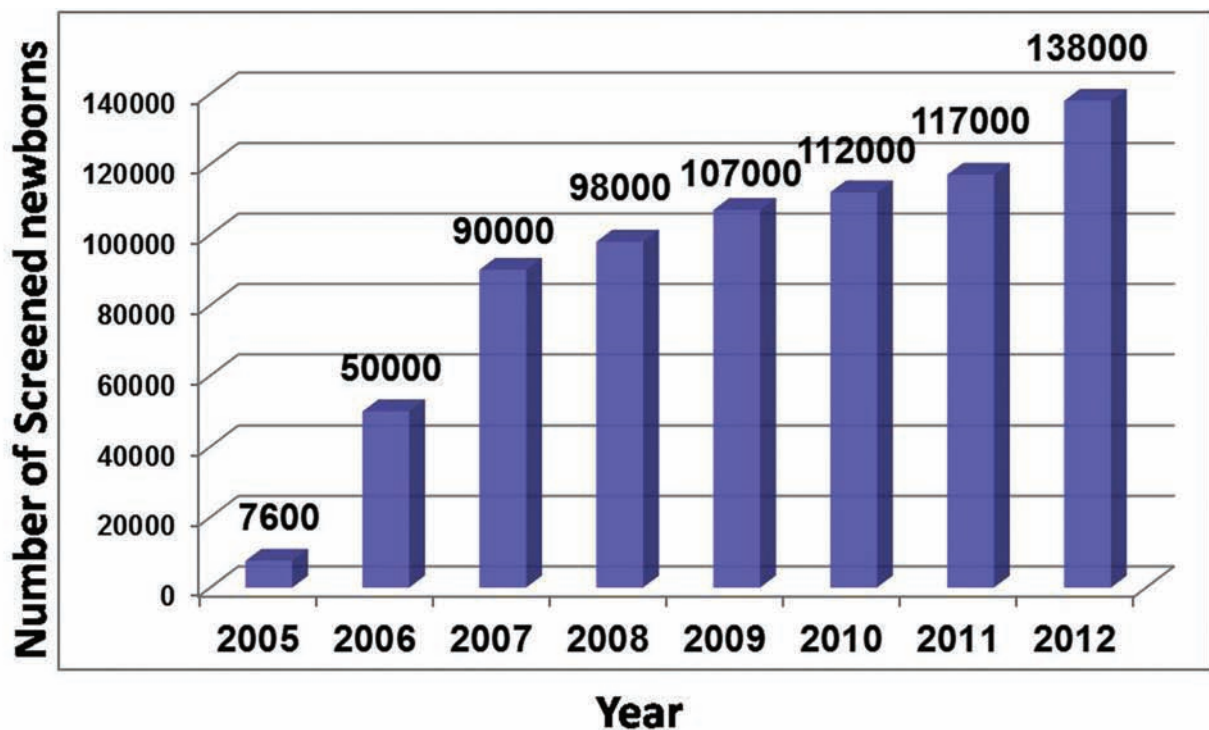
*Aims of the study:* Early detection and intervention of selected congenital and heritable disorders, which results in preventing the harmful consequences of such disorders.

*Results:* This is an ongoing program operated by PSCDR to facilitate the services to health care providers. The newborn screening program is implemented in more than 145 governmental and private hospitals. The total number of newborns screened since the establishment of the program is 792000 babies with a total number of 779 abnormal cases. The total number of newborns screened per year (from 2005 to 2012) is illustrated in Figure 2. The main partners in the program are: National Guard Health Affairs, Ministry of Defense Health Services, Ministry of Interior Health Services, University Affiliated Hospitals, Royal Commission for Jubail and Yanbu, some of the private hospitals, and King Faisal Specialist Hospital & Research Center (KFSH&RC).

### 15) Learning disabilities program

Learning disabilities are among the most common problems. It is estimated that the number of students who suffer from learning disabilities in Saudi Arabia is more than 300,000 students in public schools. The PSCDR sought to adopt research and training initiatives and projects aiming to provide success opportunities to students who suffer from learning disabilities through:

- Developing tools for early detection and diagnosis
- Developing strategies and teaching materials for learning disabilities
- Adapting curricula and using the supporting technology
- Training teachers and specialists



**Figure 2** - Total number of screened newborns / year (2005 to 2012).

**Aims of the study:** The main goal is to provide opportunities for the success of students suffering from learning disabilities through supporting research projects and training programs.

**Results:** 1) *Literacy Test Battery.* Development of these diagnostic tools has been prepared in conformity with the culture and language to accurately identify persons with learning disabilities (dyslexia and language-related disabilities) for the age group of preliminary stage to grade 6. This project is implemented in cooperation with: King AbdulAziz University, Saudi Arabia, Institute of Health Professions, Boston, Australian College of Kuwait.

This includes 4 key standards and 21 assisting tests:

*Visual test and dictation process:* includes discrimination, spell linking and spelling visual memory.

*Phonological process:* includes phonological awareness, deletion of sections and sounds, rapid naming of figures and letters and phonological memory, including repetition of unreal words.

*Measurements of reading and spelling:* include spelling, distinguishing letters, naming letters, reading unreal words, reading content, understanding words, understanding sentences, and understanding content.

*Verbal measurement of language:* includes verbal vocabulary, verbal phrases, and verbal configuration.

All tests have been developed based on logic theory rule for testing models for the academic year 2012-2013.

2) *Phonological awareness difficulties deduction battery.* In partnership with high-level authorities of the Gulf and international levels, the PSCDR designed an integrated set of diagnostic batteries for detecting learning, academic, and various disabilities, which codified according to the standards and regulations suitable for the Kingdom's environment. The phonological awareness difficulties deduction battery of students has been completed. Field personnel and specialists have been trained on the correct use of this battery. The trainees have been granted authorization certificates to use the battery in diagnosis and detection. Legalization of other sets of batteries is underway to explore other academic and learning disabilities, for example the dyslexia detection battery, and working memory battery. The first phase of the project was completed. The test was applied to the survey sample in schools of Riyadh.

### 16) *The Saudi national mental health survey*

Mental health disorders are a major public health problem worldwide, affecting people of all ages, cultures, and socio-economic status. It is estimated that 450 million people globally have mental disorders. Concerns regarding the disparity between mental health service demand, and supply led the World Health Organization (WHO) to start the World Mental Health (WMH) Survey Initiative in collaboration with Harvard University. For these reasons, The National Health and Stress Survey Program is one of the most important modern studies in the Kingdom, which is concerned with unveiling the most important reasons for psychological stresses, and understanding the most important factors resulting in complex psychological diseases to provide services enhancing the psychological health in the Kingdom. The PSCDR carries out the program with the participation of the Ministry of Health, King Faisal Specialist Hospital & Research Center, Central Department of Statistics & Information of Ministry of Economy and Planning, Ministry of Social Affairs, King Saud University, and in cooperation with international bodies, the most important of which are the WHO, Harvard University, and the University of Michigan.

**Aims of the study:**

- To identify the psychological problems in the Kingdom of Saudi Arabia.
- To learn how to treat these problems and explore methods used for that. Also, to identify obstacles that may obstruct accessing medical care and to measure the handicap resulting from these diseases for developing the necessary methods of care.

**Results:** Upon commencing the fieldwork for the Saudi National Mental Health Survey (SNMHS) in January 2013, data regarding mental health, which will be the foundation for planning future research in this field, started to be collected. The most important achievements during this period are as follows:

- The team supervising the program held many advanced courses for supervisors and data collectors. These courses were held in the Central, Eastern, and Western regions with the aim of focusing on the importance of the high quality of the collected data.
- The fieldwork of the SNMHS started in the Western Region (Mecca, Al Madinah Al Munawwarah and their suburbs), the Central Region (Riyadh and Al Qassim), and the Eastern Region.
- Program supervisors formed a team for daily follow-up and coordination with the field survey directors, supervisors, and data collectors. This procedure helped the director of programs communicate with the supervisors, survey quality control personnel as well as the collected data.
- The daily follow-up team provided help at any time and addressed any disabilities appearing before the survey-relevant teams during interviews, whether they were technical issues, pertaining to the protocol of study, or personal issues.
- The program supervision team developed and used programs tailored for this type of projects. These programs are able to instantly monitor and control information and data and allow daily progress of the survey activities. Results were always discussed.

### 17) *Daycare center assessment system (CAS)*

The day care center assessment system (CAS) program was developed for the Saudi Ministry of Social Affairs by a team from the PSCDR in Saudi Arabia, and the Academy for Educational Development (AED) in the USA, with input from many and diverse stakeholders. The system engages the Ministry of Social Affairs (the Ministry) and the day care centers in a process of assessment and continuous improvement to strengthen the programs and services to children with disabilities and their families. This program is an excellent example of science benefitting people. The impact of that process has been to bring together key personnel from the Ministry of Social Affairs, the PSCDR, and day care centers to identify and address the critical issues in serving children with disabilities and their families. There is agreement among all regarding the nature of the challenge and the value of an assessment system, and an improvement planning process to address those challenges.

**Aims of the study:** The goal of the CAS project is the development of a comprehensive system to assess the operations of private day care centers serving children with disabilities and to guide their improvements.

**Results:** The developed assessment tool for the day care centers program has been completed, and is ready to be submitted to the Ministry of Social Affairs.

## References

1. Hellani A, Schuchman EH, Al-Odaib A, Al Aqueel A, Jaroudi K, Ozand P, et al. Preimplantation genetic diagnosis for Niemann-Pick disease type B. *Prenat Diag* 2004; 24: 943-948.
2. Kaya N, Al-Zahrani F, Al-Odaib A, Rahbeeni Z, Al-Hassnan Z, Al-Sharif F, et al. Identification of Gaucher disease mutations found in Saudi Arabia. *Blood Cells Mol Dis* 2008; 41: 200-201.
3. Kaya N, Al-Owain M, Albakheet A, Colak D, Al-Odaib A, Imtiaz F, et al. Array comparative genomic hybridization (aCGH) reveals the largest novel deletion in PCCA found in a Saudi family with proipionic academia. *Eur J Med Genet* 2008; 51: 558-565.
4. Kaya N, Imtiaz F, Colak D, Al-Sayed M, Al-Odaib A, Al-Zahrani F, et al. Genome-wide gene expression profiling and mutation analysis of Saudi patients with Canavan disease. *Genet Med* 2008; 10: 675-684.
5. Hellani A, Coskun S, Benkhalifa M, Tbakhi A, Sakati N, Al-Odaib A, et al. Multiple displacement amplification on single cell and possible PGD applications. *Mol Hum Reprod* 2004; 10: 847-852.
6. Majumdar R, Rehana Z, Al-Jumah M, Fetaini N. Spinal muscular atrophy carrier screening by multiplex polymerase chain reaction using dried blood spot on filter paper. *Ann Hum Genet* 2005; 69: 216-221.
7. Salih MA, Abdel-Gader AM, Al-Jarallah AA, Kentab AY, Alorainy IA, Hassan HH, et al. Stroke in Saudi children. Epidemiology, clinical features and risk factors. *Saudi Med J* 2006; 27 Suppl 1: S12-S20.
8. Al-Saleh I, Shinwari N, Nester M, Mashhour A, Moncari L, El Din Mohamed G, et al. Longitudinal study of prenatal and postnatal lead exposure and early cognitive development in Al-Kharj, Saudi Arabia: a preliminary results of cord blood lead levels. *J Trop Pediatr* 2008; 54: 300-307.
9. Imtiaz F, Taibah K, Ramzan K, Bin-Khamis G, Kennedy S, Al-Mubarak B, et al. A comprehensive introduction to the genetic basis of non-syndromic hearing loss in the Saudi Arabian population. *BMC Med Genet* 2011; 12: 91.

10. Ramzan K, Al-Owain M, Allam R, Berhan A, Abuharb G, Taibah K, et al. Homozygosity mapping identifies a novel GIPC3 mutation causing congenital nonsyndromic hearing loss in a Saudi family. *Gene* 2013; 521: 195-199.
11. Imtiaz F, Taibah K, Bin-Khamis G, Kennedy S, Hemidan A, Al-Qahtani F, et al. USH1G with unique retinal findings caused by a novel truncating mutation identified by genome-wide linkage analysis. *Mol Vis* 2012; 18: 1885-1894.
12. Ghaly M. Islam and Disability: Perspectives in Theology and Jurisprudence. Oxon (UK): Routledge; 2010.
13. Al-Owain M, Kaya N, Al-Shamrani H, Al-Bakheet A, Qari A, Al-Muaigl S, et al. Autism spectrum disorder in a child with propionic acidemia. *JIMD Rep* 2013; 7: 63-66.
14. Kaya N, Colak D, Albakheet A, Al-Owain M, Abu-Dheim N, Al-Younes B, et al. A novel X-linked disorder with developmental delay and autistic features. *Ann Neurol* 2012; 71: 498-508.
15. Bosley TM, Abu-Amero KK, Ozand PT. Mitochondrial DNA nucleotide changes in non-arteritic ischemic optic neuropathy. *Neurology* 2004; 63: 1305-1308.
16. Abu-Amero KK, Bosley TM. Increased relative mitochondrial DNA content in leucocytes of patients with NAION. *Br J Ophthalmol* 2006; 90: 823-825.
17. Abu-Amero KK, Bosley TM, Bohlega S, Hansen E. Mitochondrial T9957C mutation in association with NAION and seizures but not MELAS. *Ophthalmic Genet* 2005; 26: 31-36.
18. Abu-Amero KK, Bosley TM, Bohlega S, McLean D. Complex I respiratory defect in LHON plus dystonia with no mitochondrial DNA mutation. *Br J Ophthalmol* 2005; 89: 1380-1381.
19. Abu-Amero KK, Bosley TM, Morales J. Analysis of nuclear and mitochondrial genes in patients with pseudoexfoliation glaucoma. *Mol Vis* 2008; 14: 29-36.
20. Abu-Amero KK, Morales J, Bosley TM. Mitochondrial abnormalities in patients with primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2006; 47: 2533-2541.
21. Abu-Amero KK, Morales J, Bosley TM, Mohamed GH, Cabrera VM. The role of mitochondrial haplogroups in glaucoma: a study in an Arab population. *Mol Vis* 2008; 14: 518-522.