A novel syndrome of abnormal striatum and congenital cataract: evidence for linkage to chromosomes 11


We report a consanguineous family of three girls and one boy affected with a novel syndrome involving the lens and the basal ganglia. The phenotype is strikingly similar between affected siblings with cognitive impairment, attention deficit hyperactivity disorder (ADHD), microcephaly, growth retardation, congenital cataract, and dystonia. The magnetic resonance imaging showed unusual pattern of swelling of the caudate heads and thinning of the putamina with severe degree of hypometabolism on the [18F] deoxyglucose positron emission tomography. Furthermore, the clinical assessment provides the evidence that the neurological phenotype is very slowly progressive. We utilized the 10K single-nucleotide polymorphism (SNP) microarray genotyping for linkage analysis. Genome-wide scan indicated a 45.9-Mb region with a 4.2353 logarithm of the odds score on chromosome 11. Affymetrix genome-wide human SNP array 6.0 assay did not show any gross chromosomal abnormality. Targeted sequencing of two candidate genes within the linkage interval (PAX6 and B3GALTL) as well as mtDNA genome sequencing did not reveal any putative mutations.

Conflict of interest

We, authors, would like to state that we do not have any commercial association for conducting or publicizing the study described in the manuscript that might pose or create a conflict of interest with the information presented in the manuscript.

Congenital cataracts are an important cause of visual impairment in children, with an estimated prevalence in developed countries of 6.31/100,000 newborn infants. Etiopathologically, mutations of different developmental genes involved are found in 25% of cases (1). Substantial amount of locus and allelic genetic heterogeneity exists in inherited cataracts (2). There are numerous genetic diseases in which lenticular
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Opacities are prominent features like aniridia–Wilms tumor association, Hallermann–Streiff syndrome, Rothmund–Thompson syndrome, Walker–Warburg syndrome, galactosemia (untreated), and galactose kinase deficiency. PAX6, a member of the paired box gene family encodes the PAX6 protein, a transcription factor, playing a key role in oculogenesis (3). Heterozygous PAX6 mutations are associated with isolated aniridia. In the rare cases of homozygous PAX6 mutation, severe craniofacial abnormalities, anophthalmia, absent or malformed nose, absent adrenal glands, and central nervous system (CNS) malformations have been previously reported (4, 5). By contrast, the identification of genes that are responsible for pathophysiological phenotypes of striatal neurons is less advanced (6). Basal ganglia may be affected in many neurometabolic conditions, such as organic acidurias, respiratory chain enzymatic defects, GM2 gangliosidosis, Wilson disease, pantothenate kinase-associated neurodegeneration, neuroferritinopathy, and aceruloplasminemia (7, 8).

With the availability of large number of single-nucleotide polymorphisms (SNPs) and high-density SNP arrays, it is now possible to identify critical regions and genes linked to unknown syndromes in families with autosomal recessive mode of inheritance in highly inbred societies. In this study, we identify four affected siblings (three girls and one boy) with a syndrome of cognitive impairment, microcephaly, striatal abnormalities, congenital cataract, and attention deficit hyperactivity disorder (ADHD) and provide linkage to a large pericentromeric region on chromosome 11.

Materials and methods

Patients

Four patients and the unaffected members from a large family from the central region of the Saudi Arabia were included in this study. The healthy parents are first cousins. The project was approved by our local IRB (RAC# 2040042). The adult patients and their parents provided informed consent for the study and the photographs.

DNA isolation, PCR, mtDNA and targeted gene sequencing

Five milliliter of whole blood from the consented patients was collected into ethylenediaminetetraacetic acid tubes and used for the genomic DNA isolation using PureGene DNA Purification Kit (Gentra Systems, Inc., Minneapolis, MN) according to the manufacturer’s instructions. DNA was amplified by polymerase chain reaction (PCR) using intronic primers designed to amplify the coding exons of PAX6 and B3GALTL. Primers sequences for both genes and others are available as an online document (Table S1, Supporting Information). The entire coding region of the mitochondrial genome was amplified and sequenced as described elsewhere (9). PCR for nuclear genes was performed according to standard protocols. Direct sequencing of PCR products was performed on an ABI 3100 Automated DNA Sequence Analyzer (Applied Biosystems, Foster City, CA) according to the manufacturer’s recommendations.

Affymetrix 10K mapping assay and data analysis

Genotyping was undertaken using Affymetrix GeneChip® Human Mapping 10K Array Xba 142 SNP Assay (Affymetrix Inc., Santa Clara, CA). The assay preparation, chip hybridization, washing, scanning, and primary data analysis were all performed according to the manufacturer’s protocols and manual (Affymetrix Inc.). Pedigree check and linkage analysis were done by PedCheck (10), GeneHunter (11) and Allegro (12) using Easy Linkage software (13).

Affymetrix genome-wide human SNP array 6.0

Sample and assay preparation were done according to Affymetrix’s guidelines. Samples from father, mother and one of the patients were included to this experiment. Genotyping and copy number calculations were done using GENOTYPING CONSOLE (GT Console, Version 3.0.1.) and visualized by GTC Browser using default settings as recommended.

Results

Clinical reports

Patient 1

The proband is a 29-year-old girl (Fig. 1a). Birth history was unremarkable. Early gross motor milestones revealed mild delay as she walked at 16 months. She had significant visual problems and was found to have bilateral cataracts at the age of the 4 years. She developed glaucoma at the age of 8 years with subsequent corneal opacity involving the left eye. Height, weight, and occipitofrontal circumference (OFC) were below the third percentile. The heart, chest, and abdominal examination were normal. Detailed CNS examination revealed that she was not able to count from 10 to 1. She was able to repeat three digits only and failed to repeat four digits. Memory skills for immediate recall were within normal limits as well as remote memory. She carried three-step commands with no difficulty. She had a grade 4 level of reading, and she had difficulty with holding a pen and writing. She had articulation difficulties. Cranial nerve examination revealed that the left eye was blind with leukocoria. The right eye pupil was distorted, abnormal in shape because of previous lens surgery. She had full extraocular movements. Visual field on the right eye was normal. She had a myopathic face and was not able to bury her eyelids. She had normal facial sensation and corneal reflex as well as hearing. Her muscle bulk was normal. She had a combination of rigidity with cogwheel pattern associated with mild fixed contractures at the elbow and the metatarsal joints. Power was 5/5 in all muscle groups. She had dystonic posturing when she performed
Fig. 1. Patient photos. Photographs of patient 1 (a), patient 2 (b), patient 3 (c) and patient 4 (d) showing the facial appearance with nondysmorphic facies. Note: the leukocoria of the left eye in patient 1 with myopathic face. Hand dystonic posturing is shown in (e). The axial brain magnetic resonance imaging images (f, g, h, and i) in patients 1, 2, 3, and 4, respectively, show small putamina and relatively large caudate nuclei (arrows). Transaxial slices of the brain [18F] deoxyglucose positron emission tomography (j, k) reveal bilateral severe hypometabolism of the putamina in patients 1 and 3.

Patient 1
An action. All deep tendon reflexes were brisk at +4 with clonus. Plantars responses were upgoing. She had normal sensation and cerebellar function. Her gait was quite fast in short steps, with some spastic component. Neuropsychological assessment revealed severe linguistic delay, and moderate ADHD mainly of the motor type. She had marked dysarthria and marked visual-motor perceptual dyspraxia. The intelligence quotient (IQ) was 77.

Patient 2
The second affected sibling is an 18-year-old girl (Fig. 1b), whose antenatal history was unremarkable. She had congenital cataract. Initial milestones showed mild global delay. Her IQ was 80, and she had significant dysarthria and linguistic delay, visual perceptual problems, and moderate ADHD mainly of the motor type. Her height, weight, and head circumference were below the third percentile. Facial examination revealed no dysmorphic features. There was mildly increased tone in all four extremities with brisk deep tendon reflexes (3+) gait difficulty due to the dystonic posturing. Dystonia was evident on action tasks (Fig. 1e).

Patient 3
The third affected child is a 14-year-old girl (Fig. 1c), who had congenital cataract, severe linguistic delay, dysarthria, mild hypertonicity with hyperreflexia, dystonic posturing, clumsy gait, and moderate ADHD mainly of the mixed type. Her height and OFC were below third percentile. The weight was at the 10th centile. She had an IQ of 84.

Patient 4
The fourth affected child is a 10-year-old boy (Fig. 1d), who had bilateral lens opacity that recently required extraction surgery. His IQ was equal to 89. He had linguistic delay and severe ADHD mainly of the motor type. All his growth parameters were below third

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Table 1. Summary of clinical features of the four affected patients in the family

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Growth parameters</td>
<td>&lt;third centile</td>
<td>&lt;third centile</td>
<td>&lt;third centile, (weight at 10th centile)</td>
</tr>
<tr>
<td>Linguistic delay</td>
<td>Severe</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>IQ</td>
<td>77</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ADHD (years)*</td>
<td>(3)</td>
<td>(2–3)</td>
<td>(2–3)</td>
</tr>
<tr>
<td>Cataract</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Dystonia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Putamen</td>
<td>Thinning</td>
<td>Thinning</td>
<td>Thinning</td>
</tr>
<tr>
<td>Caudate head</td>
<td>Swelling</td>
<td>Swelling</td>
<td>Swelling</td>
</tr>
<tr>
<td>Hypometabolism of putamina</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; IQ, intelligence quotient.

*Age of onset of ADHD (The diagnosis of ADHD was made through a formal neuropsychological testing).

percentile. The patient had some dystonic posture of his extremities with walk test and had some difficulty in performing tasks with action. The other parts of neurological examination were unremarkable.

The Laboratory investigations in the affected members revealed normal complete blood count, renal, liver and thyroid function tests, urinalysis, urine reducing substances, mucopolysaccharide screen, plasma immunoglobulin concentrations, serum lactate, tandem mass spectrometry, urine organic acid analysis, very long chain fatty acid analysis, plasma amino acids analysis, serum biotinidase assay, galactose-1-phosphosphate uridyltranferase assay, and chromosomal analysis. DMPK gene analysis showed 17 CTG repeats in both alleles of the gene. All the important features in the four patients are provided in Table 1.

Neuroradiological evaluation

In all patients, the brain magnetic resonance imaging (MRI) (Fig. 1f,g) showed unusual pattern of thinning of the lentiform nucleus predominantly involving the putamina with evidence for some hyperintensity on T2, and with some swelling in the caudate heads bilaterally. [18F] deoxyglucose positron emission tomography (FDG PET) scan (Fig. 1h,i) indicated moderate to severe hypometabolism involving the putamina bilaterally with the presence of only a rim of mild FDG uptake. The distribution of FDG within the thalami, caudate lobes, cerebral cortex, and the cerebellar hemispheres was within normal limits.

SNP genotyping, targeted gene and mtDNA sequencing, and CNV analysis

Genotypes of the four affected children and other healthy members in the family (Table S2) were generated using SNP-based chip arrays. Genome-wide linkage analysis was performed by GENEHUNTER and ALLEGRO algorithms using EASY LINKAGE SOFTWARE. Parametric multipoint logarithm of the odds (LOD) score analysis was performed with sets of 75 markers, a disease allele frequency of 0.0001% with minor allele frequencies and no phenocopies. A dominant peak was attained on chromosome 11 with an LOD score of 4.2353 (Fig. 2a). The region of interest on chromosome 11 is actually extending from the p arm to the q arm spreading over the centrome and appears as two branches (c).
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chromosome 11 extends approximately 45.9 megabases region starting from the cytogenetic bands p14.3 (chromosome genome coordinates: 23348262) to 11q13 including the centromeric region (chromosome genome coordinates: 69261965) (Fig. 2b,c). The region contains more than 850 genes based on NCBI MapViewer 3.2 Build including PAX6 and B3GALTL that were selected as candidate targets based on their function and annotation to be screened for probably mutations. Besides the well-annotated RefSeq genes, there are 228 pseudogenes, 45 hypothetical genes and 16 miRNA coding regions.

The entire coding region of the mitochondrial genome was amplified in 24 separate PCRs for the patients, certain family members, and controls. Sequencing results were analyzed as mentioned elsewhere (14). No putative changes were identified after the mutation analysis.

Affymetrix Human SNP Array 6.0 assay was utilized to determine genome-wide malignant copy number variations (CNVs) among the parents and one of the affected patients. We paid a special attention to any detectable gross changes within the linkage interval using Affymetrix' Genotyping Console. Compared to parents and ethnically matched controls, there were no pathological CNV detected at this interval or elsewhere in the genome.

Discussion

Among children and adults with intellectual disability, cataract was the fourth most frequent ocular pathology seen in 10% of them (15). In patients with early-onset cataract and known neurologic disease, myotonic dystrophy (16), and cerebrotendinous xanthomatosis represent the two most common causes (17). The presence of four affected siblings with three girls and one boy in this consanguineous family indicates that the autosomal recessive is the most likely mode of inheritance. Beside the microcephaly, cognitive delay and congenital cataract, our patients do not have dysmorphism or microphthalmia. The most striking finding in this family is the specific involvement of the striatum with thinning of the putamina and prominently globular caudate heads on brain MRI, and hypometabolism of the putamina on FDG PET. These peculiar neuroradiological abnormalities were consistent in all affected siblings. There is lack of seizure, white matter changes or posterior fossa abnormalities in these patients. Neurologically, the eldest patient (patient 1) seems to be the most cognitively impaired and the most seriously affected with the dystonic movement, whereas the youngest boy (patient 4) appears to be the least, which may be indicative of the slowly progressive nature of the neurologic disease. There is lack in the literature, to the best of our knowledge, of reports about the association of congenital cataract and the striatal disease that our patients exhibit.

The association of congenital cataract and neurologic disease is seen in many syndromes, such as Marinesco–Sjögren syndrome (18), Warburg Micro syndrome (19), hypomyelination and congenital cataract syndrome (20). A comparison between these syndromes and the syndrome described in this report is provided in Table 2. Other autosomal recessive disorders include Martosolf syndrome (microcephaly, intellectual disability, short stature, cataract, and hypogonadism) (21), Smith–Lemli–Opitz syndrome (22), Walker–Warburg syndrome (23), Cockayne syndrome (24), and cerebrooculofacioskeletal syndrome-1 (25). X-linked disorders include Nance–Horan syndrome (congenital cataracts, dental anomalies, dysmorphic features, and in some cases intellectual disability)

Table 2. Comparison between the syndrome in this article and syndromes with congenital cataract and prominent CNS abnormalities

<table>
<thead>
<tr>
<th>Feature</th>
<th>Marinesco–Sjögren syndrome</th>
<th>Warburg micro syndrome</th>
<th>Hypomyelination and congenital cataract syndrome</th>
<th>This syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMIM</td>
<td>248,800</td>
<td>600,118</td>
<td>610,532</td>
<td>–</td>
</tr>
<tr>
<td>Inheritance</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
<td>AR</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>Cerebellar ataxia</td>
<td>hypoplasia corpus callosum and pachygyria/polymicrogyria</td>
<td>Ataxia</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Cataract</td>
<td>+</td>
<td>+</td>
<td>Progressive white matter atrophy</td>
<td></td>
</tr>
<tr>
<td>CNS abnormalities</td>
<td>Cerebellar atrophy</td>
<td>hypoplasia corpus callosum and pachygyria/polymicrogyria</td>
<td>Progressive white matter atrophy</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Myopathy and hypogonadism</td>
<td>Microphthalmia, optic atrophy, and hypogonadism</td>
<td>Peripheral neuropathy</td>
<td>ADHD</td>
</tr>
<tr>
<td>Gene (locus)</td>
<td>SIL1 (5q)</td>
<td>RA83GAP2 (2q)</td>
<td>FAM126A (7p)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

ADHD, attention deficit hyperactivity disorder; OMIM, Online Mendelian Inheritance in Man.
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(26), and Lowe oculocerebrorenal syndrome (bilateral cataract, intellectual disability and renal Fanconi syndrome) (27). There are hereditary syndromes of unknown etiology in which cataract and intellectual disability and/or growth retardation are prominent features such as CAMAK or CAMFAC (cataract, microcephaly, failure to thrive, arthrogryposis, and kyphoscoliosis) syndrome (28). Furthermore, a novel phenotype of postnatal growth failure, microcephaly, intellectual disability, cataracts, large joint contractures, cortical dysplasia, and cerebellar atrophy was reported (29). Another novel syndrome of cataract, intellectual disability, erythematous skin rash and facial dysmorphism was mapped to 1p35.3-p36.32 in an Australian aboriginal family (30). Hudson et al. (31) also reported a familial syndrome of congenital cataract, mental impairment, and severe neuronal loss in the hippocampal dentate gyrus. Finally, a syndrome of ataxia, microcephaly, and cataract was reported in a highly inbred Arab family (32).

More importantly, the linkage data that we have pinpoint clearly to a significant linkage interval of 45.9 Mb on chromosome 11. The region is prohibitively large that contains more than 800 genes making serial gene sequencing impossible. Two genes (PAX6 and B3GALTL) residing with the linkage interval were possible candidate genes. B3GALTL defect results in Peters plus syndrome, an autosomal recessive disease that causes anterior chamber eye anomalies in addition to disproportionate short stature, developmental delay, characteristic craniofacial features, and cleft lip and/or palate (33). The sequencing of the exons and exon/intron boundaries of PAX6 and B3GALTL genes did not yield any putative mutations for this particular phenotype.

In conclusion, we believe the presence of the congenital cataract and the distinctive striatal abnormalities in this family warrants the classification of the phenotype that the family in this report has as a novel syndrome that maps to Chromosome 11p14.3-q13.

Supporting Information

The following Supporting information is available for this article:

Table S1. Primers for the sequenced genes
Table S2. Pedigree of the family

Additional Supporting information may be found in the online version of this article.

Acknowledgements

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