ORIGINAL ARTICLE

Non-syndromic intellectual disability and cataract in a patient with dual molecular diagnosis of *SRD5A3* and *PITX3*-related diseases

Naif A.M. Almontashiri[1,2,3*], Samar A. Al-Swailem[4], Reham M. Balahmar[1], Essa Alharby[1], Manar M. Almuntashri[5], Ali Alasmari[6]

ABSTRACT

Objectives: Our objective was to identify the genetic cause in a patient with intellectual disability and bilateral cataracts.

Methods: The genetic, neurological, and ophthalmological evaluations were performed. DNA samples were provided from the patient, parents, and unaffected sibs to perform whole exome sequencing (WES) and Sanger confirmation. Biochemical testing on the serum sample was performed to ascertain the clinical significance of the WES finding.

Results: The proband presented with intellectual disability, subtle dysmorphic features, and bilateral cataracts. WES and segregation studies using Sanger sequencing revealed a homozygous missense variant of uncertain significance (VUS) in *SRD5A3* and a *de novo* pathogenic frameshift variant in *PITX3* in the proband. Biochemical analysis of serum carbohydrate-deficient-transferrin (CDT) to ascertain the significance of the VUS in *SRD5A3* was consistent with a glycosylation defect and confirmed type 1, N-glycosylation defect.

Conclusion: This case has a dual molecular diagnosis. The *SRD5A3* variant with confirmed biochemical abnormality accounts for intellectual disability and subtle dysmorphic features, whereas the *de novo* pathogenic *PITX3* variant accounts for bilateral cataracts. This case expands the severity spectrum of *SRD5A3* disorder and represents a milder form. It also highlights the importance of clinical correlation and reverse phenotyping.

Keywords: CDG1Q, congenital disorder of glycosylation, type Iq, CDT, carbohydrate-deficient-transferrin.

Background

The steroid 5 alpha-reductase type 3 deficiency (SRD5A3) is critical for N-glycosylation during the early assembly process in the dolichol-linked glycosylation (1). It is necessary for the conversion of polyprenol to dolichol in human and other species such as mouse and yeast, to act as a polyprenol reductase, indicating that during N-glycosylation, the reduction of polyprenol is a major pathway for dolichol biosynthesis (1). SRD5A3 knockout (k/o) in mice resulted in early embryonic lethality, smaller embryos, failure of axial rotation, dilated hearts, and open neural tube (1). Transcriptomic analysis of the SRD5A3 k/o mice embryos showed a significant upregulation of genes involved in the unfolded protein response, highly suggesting that SRD5A3 is required for ER protein folding, consistent with the developmental role of N-glycan.

Correspondence to: Naif A.M. Almontashiri
*Center for Genetics and Inherited Diseases, Taibah University, Almadinah Almunwarah, Saudi Arabia; Faculty of Applied Medical Sciences, Taibah University, Almadinah Almunwarah, Saudi Arabia; and Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia.
Email: nmontashri@taibahu.edu.sa
Full list of author information is available at the end of the article.
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Biallelic pathogenic variants in the *SRD5A3* gene are known to cause congenital disorder of glycosylation, type Iq (CDG1Q, OMIM#612379). CDG1Q is an ultra-rare disease and is mainly associated with severe and variable ophthalmological abnormalities (early-onset retinitis pigmentosa, retinal dystrophy, colobomas, and optic nerve hypoplasia) and neurological features [e.g., intellectual disability (ID) and ataxia]. Other features may include ichthyosiform skin lesions, skeletal abnormalities, gastrointestinal and endocrine abnormalities, brain malformations, dysmorphic features, and coagulation defects (1). Milder cases of CDG1Q are yet to be described.

Hauntologically, patients develop microcytic anemia, coagulation abnormalities, and decreased antithrombin III (1). Biochemically, the patients may show elevated liver enzymes and laboratory studies of transferrin showed a type 1 glycosylation defect (2). The biochemical functional studies showed that the metabolic defect happened early in the N-glycosylation pathway, interfering with the synthesis or transfer of the glycan component of the lipid-linked oligosaccharide to the recipient proteins. Some of the patients with documented SRD5A3 deficiency showed no abnormality in the transferrin studies (3).

Here, we present a milder case of CDG1Q with subtle dysmorphic features and ID due to a homozygous missense variant in a highly conserved domain in *SRD5A3* with glycosylation abnormality of type 1, N-glycosylation defect.

Materials and Methods

Standard protocol approvals, registrations, and patient consents

Whole exome sequencing (WES) studies were indicated based on the phenotype and family history. Genetic testing and disclosure consents were obtained from all participants as per an approved institutional review board protocol (TU MLT-2019-07).

Whole exome sequencing

DNA from whole blood samples collected in EDTA tubes was extracted, and then, the DNA libraries were prepared and sequenced using the SureSelect Kit (Agilent, Santa Clara, CA) and Hiseq2000 platform (Illumina, San Diego, CA), respectively. The Genome Analysis Toolkit was used for variant calling. Variants were classified as per the American College of Medical Genetics (ACMG) guidelines (4). The identified variants were confirmed by Sanger sequencing.

Carbohydrate-deficient-transferrin analysis

Separation of the serum transferrin isoforms was performed by a College of the American Pathologists-accredited commercial diagnostic laboratory using high-performance liquid chromatography (HPLC) as the current reference method of carbohydrate-deficient-transferrin (CDT) analysis (5).

Results

Case presentation

An 8-year-old girl (II: 3, Figure 1A) was referred for genetic evaluation due to delayed speech with only a few words, ID, aggressive behavior, vision abnormality, and subtle dysmorphic features. The parents are first cousins with two other healthy daughters. She started to walk at the age of 3 years and is currently attending a special school. On examination, her head circumference was on the 50th centile, height and weight were below the 3rd centile. She had subtle dysmorphic features of hypertelorism, thick broad nose, long philtrum, strabismus, and low-set ears (Figure 1B and C). She was wearing distance glasses to correct nearsightedness (myopia). An ophthalmological examination revealed a bilateral blue dot cataract. Neurological evaluation revealed ID, delayed speech, normal tunes, reflexes, and power with no autistic features or signs of attention deficit hyperactivity disorder. Her slightly aggressive behavior could be explained by her frustration due to language impairment. Other systemic examinations were unremarkable.

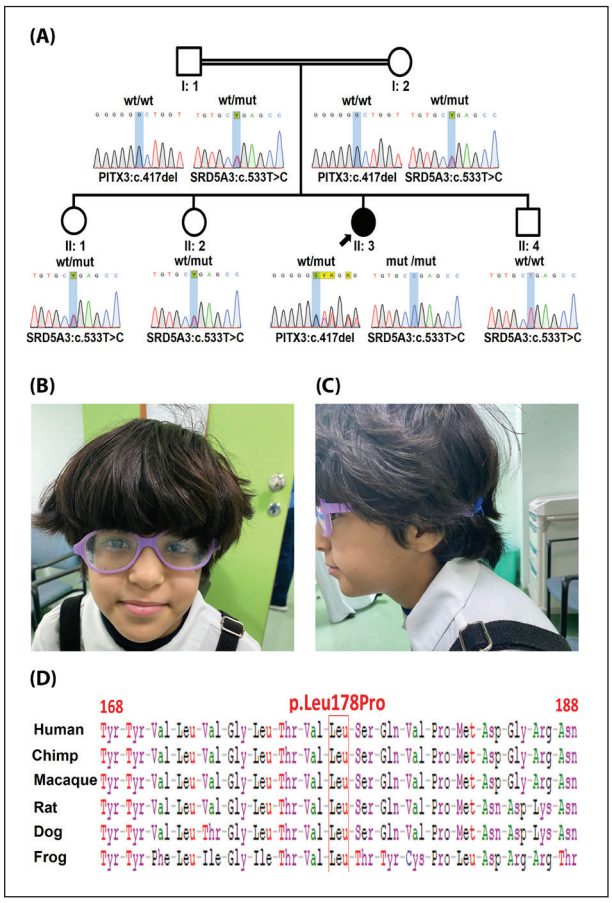

Fig. 1. *Variants segregation and dysmorphic features. SRD5A3 and PITX3 variants complete co-segregation with disease in the proband (II:3) using Sanger sequencing (A). Facial images of the proband showing hypertelorism, thick broad nose, long philtrum, squint (B), and low-set ears (C). Multiple sequence protein alignments highlighting the conservation of the substituted amino acid residue in SRD5A3 (D). wt/mut indicates heterozygous, mut/mut homozygotes for the mutant allele, and wt/wt homozygotes for the reference allele.*

Brain magnetic resonance imaging was unremarkable. Laboratory investigations including liver function, coagulation profile, complete blood, and renal function tests were unremarkable.

Genetic testing

Trio WES with copy number variants analysis was indicated and performed. Interestingly, WES revealed a homozygous variant of uncertain significance (VUS) in *SRD5A3* (NM_024592.5:c.533T>C;p.(Leu178Pro)) in a highly conserved residue (Figure 1D) and a pathogenic frameshift variant in *PITX3* (NM_005029.4:c.417delG;p.(Leu140fs)). The p.(Leu178Pro) variant in *SRD5A3* is predicted to be damaging by multiple *in silico* prediction tools, including CADD score (score of 25.3), Phred, Align GVGD, PolyPhen-2, SIFT, and MutationTaster. The frameshift variant in *PITX3* is expected to result in the introduction of a premature stop codon, subjecting the transcript to nonsense-mediated decay and loss of function. Both variants were predicted to be deleterious and not found in the gnomAD control database.

Follow-up segregation studies for parents and siblings using Sanger sequencing showed complete segregation of both variants with the disease and confirmed the *de novo* status of the *PITX3* variant (Figure 1A).

CDT analysis

To examine the biochemical consequence and clinical significance of the homozygous VUS in *SRD5A3*, serum CDT analysis using HPLC was performed and showed increased disialotransferrin (26.1%, upper limit reference range (ulRR) 2%), asialotransferrin (2%, usually undetectable), and CDT (28.1%, ulRR 1.2), confirming N-glycosylation defect, type 1.

Discussion

This patient has a dual molecular diagnosis of autosomal recessive and dominant diseases due to variants in two genes: *SRD5A3* and *PITX3*. The first molecular diagnosis is the congenital disorder of glycosylation, type Iq (CDG1Q, MIM# 612379) due to the homozygous *SRD5A3* variant as supported by the segregation studies and CDT analysis.

Our patient presented with non-syndromic developmental delay and subtle dysmorphic features with no other known features of CDG1Q such as ocular coloboma, ichthyosis, structural brain malformation, coagulation defects, and endocrine abnormalities, likely representing a relatively milder form of CDG1Q (1,6). Increased di- and asialotransferrin and CDT, abnormal coagulation profile, low IGF1, and IGFBP3 are reported in patients with SRD5A3 deficiency (1). This case only presented with a CDT abnormality signature of the N-glycosylation defect, type 1. The variant segregated perfectly in the family, predicted to be deleterious, and absent from gnomAD (v4.1.0). Taken together, according to the variants classification guidelines by the ACMG, the classification of this variant was upgraded to likely pathogenic (4).

The second molecular diagnosis was due to the *de novo* pathogenic frameshift variant in *PITX3*. It is predicted to introduce an early stop codon and be subjected to nonsense-mediated decay and therefore, loss of function. Mono- and biallelic variants in *PITX3* are associated with non-syndromic and syndromic cataracts (MIM# 610623), respectively (7). The recessive syndromic cataract includes a neurodevelopmental disease. Thus, the monoallelic *PITX3* variant detected in our case explains the cataract phenotype.

Conclusion

This case highlights the importance of clinical correlation and reverse phenotyping when interpreting exome or genome data. It also demonstrates the significance of proper and gene-specific follow-up testing through familial segregation and biochemical investigations in determining the clinical significance and pathogenicity of VUSs in metabolic and non-metabolic genes. Finally, this case presents a milder and non-syndromic form and extends the severity spectrum of CDG1Q.

List of Abbreviations

ACMG	American College of Medical Genetics
CDT	carbohydrate-deficient-transferrin
HPLC	high-performance liquid chromatography
SRD5A3	steroid 5 alpha-reductase type 3 deficiency
VUS	variant of uncertain significance
WES	whole exome sequencing

Declaration of conflicting interests
The authors declare that they have no conflict of interest regarding the publication of this article.

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Patient informed consent
The patient provided written consent.

Ethics approval
Genetic testing and disclosure consents were obtained from all participants as per an approved institutional review board protocol (TU MLT-2019-07).

Data availability
All data are available from the corresponding author upon request.

Author details
Naif A.M. Almontashiri[1,2,3], Samar A. Al-Swailem[4], Reham M. Balahmar[1], Essa Alharby[1], Manar M. Almuntashri[5], Ali Alasmari[6]

1. Center for Genetics and Inherited Diseases, Taibah University, Almadinah Almunwarah, Saudi Arabia
2. Faculty of Applied Medical Sciences, Taibah University, Almadinah Almunwarah, Saudi Arabia
3. Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia
4. Anterior Segment Division, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia
5. King Saud University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Medical city and Ministry of National Guard, Riyadh, Saudi Arabia

6. Section of Medical Genetics, Children's Specialist Hospital, King Fahad Medical City, Riyadh, Saudi Arabia

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