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Expending the Mutational Spectrum of Xia-Gibbs and Bosch-Boonstra-Schaaf Optic Atrophy Syndromes

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Abstract

Cytogenetics and dysmorphology have allowed the definition of a variety of syndromes involving Intellectual Disability (ID). Whole Exome Sequencing (WES) has become a very powerful method to identify *de novo* variants, especially those associated with neurodevelopmental abnormalities. Here we explore the utility of WES to identify novel causal variants in a Tunisian patient with severe ID associated to dysmorphic facial features. We identified, after a personalized filtering, two de novo variants in genes with functional significance that are plausibly relevant to ID. The first heterozygous missense mutation, c.3164G>A (p.Arg1055His), was found in the only encoding exon in the *AHDC1* gene which is known to cause the Xia-Gibbs Syndrome (XGS). The second variant is a heterozygous missense mutation c.1178T>C (p.Leu393Ser), was found in the third exon of *NR2F1* gene mostly described in the Bosch-Boonstra-Schaaf Optic Atrophy Syndrome (BBSOAS). Our data expand the phenotypic and genetic spectrum associated to these two syndromes. Identification of two de novo variants in genes of known or plausible clinical significance for abnormal brain development suggests that WES helps in the diagnosis and the genetic counseling of ID.

Keywords: Genetics; Medical; Genotype; Missense mutation; Phenotype; DNA sequence analysis

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Introduction

Specific populations of people with Intellectual Disability (ID) have particular health risks such as motor and speech delay and facial dysmorphia [1]. The associated syndromes implicate a variety of gene defects, duplications, translocations and deletions on several chromosomes [2]. Today, a rich data harvest involves more than 700 genes. Finding a diagnosis for each individual with ID remains a considerable challenge due to genetic variability and the phenotypic overlap in the majority of syndromes, new syndromes or "like syndromes".

In this context of multiple etiologies of ID and dysmorphia, the objective of this work consists on identifying the molecular defect in a Tunisian patient with severe ID associated to physical (essentially facial dysmorphia) and behavioral abnormalities.

Material and Methods

Patient

The study concerns a 34 old year woman, born at term from non affected and non consanguineous parents. This patient showed some abnormalities including severe disabilities on intelligence, motor and behavioral functioning that has become complicated gradually before adulthood. None of these signs is reported among siblings and parents. This work was approved by Farhat Hached Hospital ethic committee and written consent was given by the mother's patient (father died) for data publication.

Methods

The patient was examined in the Genetic Department at Farhat Hached University Hospital of Sousse, Tunisia. Appropriate genetic tests were done: Standard banding karyotype, Comparative Genome Hybridization (CGH, Agilent, with a 4X180K resolution) to search for additional/deletional defaults, Whole Exome Sequencing (WES) using a 17 genes panel (libraries loaded onto a NextSeq Illumina sequencer) to search for gene coding mutations. The data was processed *via* alignment with the reference genome (GRCh37). WES results were verified by direct Sanger sequencing (ABI

Prism 3130, Qiagen).

Numerous bioinformatics analyses were done

Face2gene software used for facial and body photos analyses [3], SIFT (v2.2.0), Polypen 2 and Mutation taster software used for the *in silico* prediction of the phenotypic variant's effect, Ion Reporter Software 5.12 used to measure the evolutionary conservation of the mutated site, confirmed by multiple sequence alignment using Clustal Omega software, the Combined Annotation Dependent Depletion (CADD) for scoring the deleteriousness of single nucleotide variants, the Genome Aggregation Database (gnomAD) to search for the previous descriptions of the variants found. In addition, the patient underwent an ophthalmological fundus examination and brain computed tomography.

Results

Clinical features

The phenotypic signs were, in addition to ID, dysmorphia and many developments, psychomotor, and behavioral abnormalities (Figure 1A and Table 1).

Face2gene analysis based on three patient photos revealed a set of 30 syndromes potentially related to facial signs.

Cytogenetic analysis

The karyotype showed no number or apparent structural abnormalities. This result eliminates syndromes related to chromosomal abnormality suggested by Face2gene analysis. The CGH array analysis showed no additional or deletional genetic materials on patient's chromosomes.

Molecular exploration and *In silico* analysis

WES showed two de novo mutations in heterozygous state (Figure 1B). These variants were absent in the mother. The first variant observed, c.3164G>A; p.Arg1055His, is found within the single coding exon 6 of the *AHDC1* gene (AT-hook DNA-binding motif-containing protein 1). *AHDC1* gene is located at 1p36.11-p35.3 and encodes a protein of 1,603 amino acids, containing two conserved regions. The first shows 2 AT-hooks, and the second contains a carboxy-terminal PDZ binding domain consensus sequence. The variant found in this case lies in the proximity of the second conserved region (Figure 1C).

The second variant found in the present case: c.1178T>C; p.Leu393Ser is located on the *NR2F1* gene (nuclear receptor subfamily 2 group F member 1) which is located on 5q15 and encodes the Coup transcription factor protein 1. Coup TF1 protein shows two regions: DNA Binding Domain (DBD) and Ligand Binding Domain (LBD).

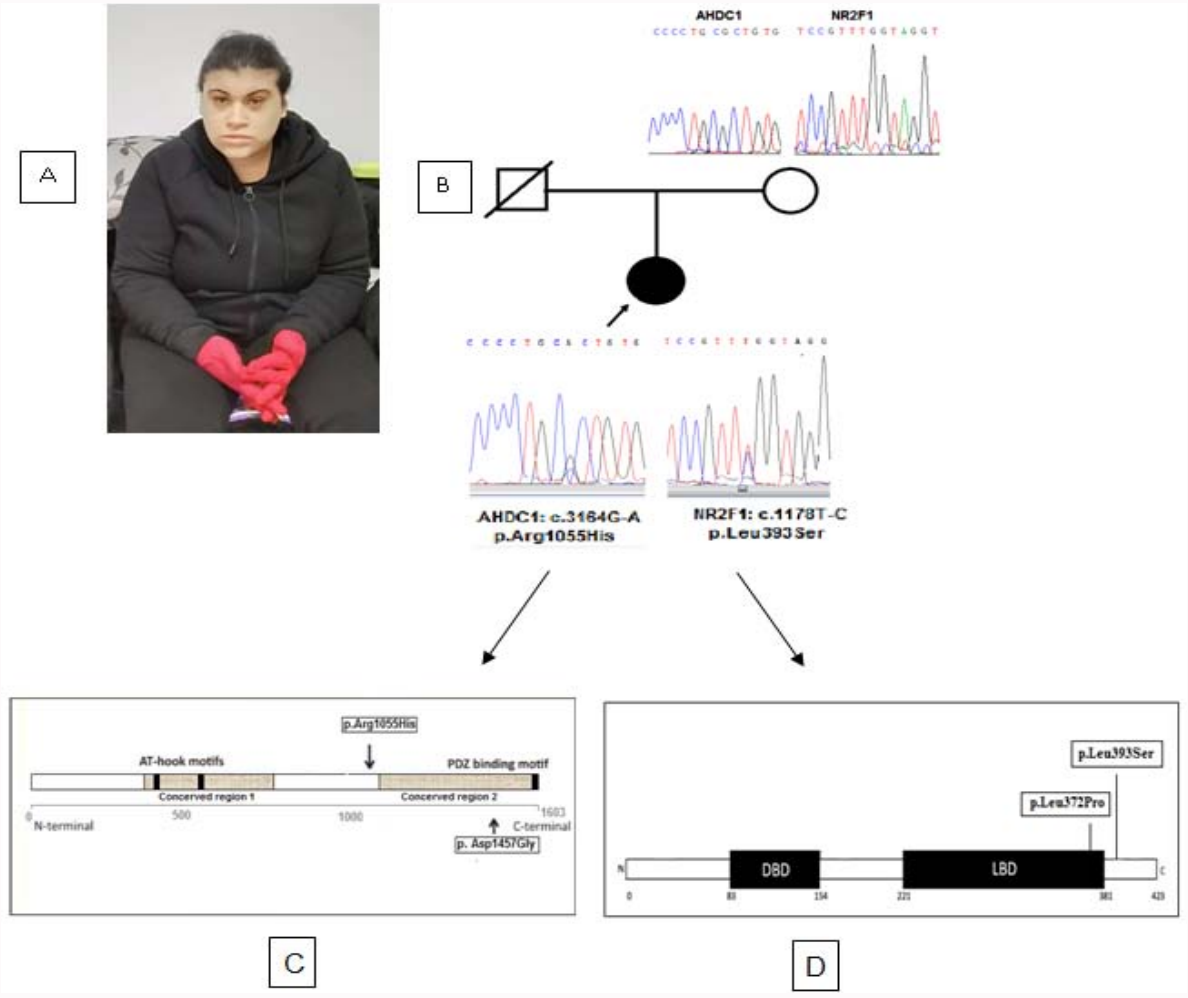

Figure 1: Phenotype and genotype findings. A: Patient's photo showing the facial dysmorphia, the obesity and the cross-linking fingers behavior; B: Molecular findings showing the *AHDC1* and the *NR2F1* heterozygous variants in the patient (arrow) and not in the mother, C and D: This study variant position compared to another missens mutation on the *AHDC1* and *NR2F1* genes respectively.

Table 1: Patient's phenotype compared with those of XGS and BBSOAS due to missense mutations.

	XGS patient	This study	BBSOAS patient
Variant on *AHDC1* gene	c.4370A>G p.Asp1457Gly in PDZ	c.3164G>A p.Arg1055His	
Variant on *NR2F1* gene		c.1178T>C p.Leu393Ser	c.1115T>C p.Leu372Pro in LBD
Signs	Developmental delay; brain anomalies; laryngomalacia; craniosynostosis, constipation; electrolyte imbalance.	Intellectual disability; motor and speech delay; generalized hypotonia; short stature (-2.2 SD); obesity (+1.41 SD); microcephaly (-0.64 SD); curved back, dependent and jerky walking; larynx problem (snoring and feeding difficulties); constipation; hearing impairment; autistic traits (repetitive gestures, unexplained laughter); convulsive seizures with loss of consciousness; flat feet; facial dysmorphia including dental malformation; upslanted palpebral fissures; wide flat nose; depressed nasal bridge; thin upper lip; slightly curled ears on the left; narrow forehead; short palpebral slit; short phyltrum; short neck.	Severe developmental delay; hypotonia; motor and speech delay; repetitive motion behavior; optic atrophy; mild dysmorphia with slight hypertelorism; prominent synorphrys; simplified cupped ear helices; large head.
Reference	[6]		[14]

The variant found in this case lies in the proximity of the LBD (Figure 1D).

Bioinformatic analyses of the *AHDC1* c.3164G>A variant revealed a PhyloP score of 4.95, showing that G nucleotide is highly conserved over species. This result was confirmed by multiple sequence alignment. The gnomAD revealed a previous description of this variant only once in two populations: African and Latino without relation to any phenotype. SIFT, PolyPhen and Mutation Taster software predicted deleterious, pathogenic and disease causing respectively. The CADD score was of 32 showing that the variant is among the top 0.1% of deleterious variants in the human genome.

For the *NR2F1* c.1178 T>C variant, the PhyloP score was of 5.13 showing the very high evolutionary conservation of T allele. The multiple sequence alignment confirmed this conservation. This variant is not reported in any of the major population databases (gnomAD, ESP, ExAC, 1000 Genomes, dbSNP) confirming its novel finding. SIFT and Polyphen predicted a deleterious and pathogenic effect respectively, with a CADD score of 33.

Discussion

The presence of two mutations in our patient on 2 different genes let us wonder about the involvement share of each mutation in the appearance of the phenotypic signs. To address this issue, first, we analyzed the genotype-phenotype correlation separately for the two mutations and then attempted to synthesize their combined implication.

The effect of AHDC1 variant

Mutations in the *AHDC1* gene are mostly revealed in patients with Xia-Gibbs Syndrome (XGS) described for the first time by Xia et al. [4]. XGS is defined as a rare and syndromic intellectual disability with autosomal dominant inheritance (OMIM: 615829) and low prevalence (<1/1000000). It is characterized by ID, developmental delay, hypotonia, absent or severely delayed speech development, obstructive sleep apnea, mild dysmorphic facial features and behavioral abnormalities. Epilepsy, ataxia and nystagmus have also been reported [5]. All these signs except nystagmus are present in our patient.

XGS encompasses a wide range of clinical phenotypes which result essentially from de novo mutations within the *AHDC1* gene. Fewer than 50 patients with XGS have been noticed [6]. According to ClinVar database and literature, 28 variants are described on *AHDC1*, 23 with XGS phenotype [4,7-9]. The more severely affected individuals showed truncating nonsense or frameshift mutations, especially within the AT hook region, or deletions in *AHDC1*. It has been suspected that a reduction in the amount of functional *AHDC1* protein prevents normal brain development, leading to intellectual disability, speech problems, and other neurological syndrome features [7,10].

It has been suggested that missense mutations in *AHDC1* do not cause disease [11]. In 2020, Gumus described the first heterozygous missens mutation, c.4370A>G; p.Asp1457Gly in the PDZ region (Figure 1C) with a less severe phenotype of XGS. Symptoms may be related to the dysfunction of the PDZ binding motifs [6]. In this study, we report the second yet described missens mutation in the 5' side of PDZ motif. All the signs reported by Gumus were present in our patient (Table 1), except craniosynostosis and structural brain anomaly (normal brain computed tomography), thus extending the phenotypic spectrum of XGS. The slight difference between the two phenotypes may be due to the nature of amino acid changes. In fact, PDZ domain proteins coordinate several biological processes by recognizing short amino acid motifs at the carboxyl termini of target proteins. Missing these functional domains may compromise brain development and function.

The effect of *NR2F1* variant

Multiple mutations in *NR2F1* are described in patients with a series of phenotypic signs called for the first time Bosch-Boonstra-Schaaf Optic Atrophy Syndrome (BBSOAS). This syndrome is defined as a rare disorder, (prevalence: <1/1000000), with autosomal dominant inheritance (OMIM: 615722). BBSOAS was first characterized by developmental delay, intellectual disability, and significant visual impairment [12]. Other common clinical signs and symptoms are described, such as hypotonia, oromotor dysfunction, seizures, autism spectrum disorder, repetitive behaviors, structural changes of brain morphology, and dysmorphic facial features which are variable and nonspecific [5]. The majority of these signs, except the visual impairment (normal ophthalmological fundus) and the brain morphology changes are present in our patient. Visual impairment is not a constant sign in BBSOASS [13]. In our patient, the heterozygous p.Leu393Ser missens mutation found in a high conserved site of the *NR2F1* protein strengthens the hypothesis of BBSOAS.

According to ClinVar database on NCBI and previous studies, 31 patients and 41 variants on *NR2F1* gene have been reported in this syndrome, the majority are missens mutations [12-15].

BBSOAS encompasses a broad range of clinical phenotypes.

The *NR2F1* gene encodes a conserved orphan nuclear receptor and transcriptional regulator [16]. *NR2F1* is found to be expressed in 27 tissues where the brain takes the fourth position [17].

Analysis on the functional effect of the c.1178T-C mutation was not possible to test in our laboratory. However, we compared with the nearest previously described mutation: Leu372Pro missens variants [14], in approximately the same LBD region of *NR2F1* gene (Figure 1D) as the phenotypic signs are almost similar to those of our patient (Table 1). Kaiwar et al. [14] used homology-based molecular modeling and molecular dynamic simulations which supported the pathogenicity of Leu372Pro variant for BBSOAS. This mutation was found to disrupt the dimerization interface of the LBD domain. In our patient, mutation in approximately the same region of *NR2F1* may have an effect on the decrease of transcriptional activity of *NR2F1* expressed in the brain leading to the disturbance in the intellectual, psychomotor and language expression.

The combined effect analysis

Using Biogrid tool [18], no direct interaction, neither physical nor genetic between *AHDC1* and *NR2F1* genes was found. This allows us to suggest that these genes act individually in the appearance of our patient's phenotype.

In this study, the patient seems to have the majority of the two syndromes signs. The composite heterozygous mutated status may explain her highly severe phenotype. The two concerned genes have been described to be implicated in the brain development of [19,20].

Some signs are twice present in the two syndromes, making difficult their attribution to one of the two mutations. Further reports and *in-vivo/in-vitro* experimentations would make possible knowing the individual and the combined effect of these mutations.

Conclusion

Using the WES technique, we have reported two de novo missens mutations in a Tunisian patient: c.3164G>A on the *AHDC1* gene and c.1178T>C (first description) on the *NR2F1* gene. The features described in the present patient share great similarities with those in previously reported cases of XGS and BBSOAS thus expanding the mutational spectrum of these two syndromes. This study has allowed the identification of the molecular default in the patient and thus a genetic counseling in the family. Further experimental studies should be conducted to demonstrate the pathogenicity of these novel variants and to better establish the full genotype-phenotype correlation.

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