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## Gonadal Mosaicism in *ARID1B* Gene Causes Intellectual Disability and Dysmorphic Features in Three Siblings

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### Abstract

The gene encoding the AT-rich interaction domain-containing protein 1B (*ARID1B*) has recently been shown to be one of the most frequently mutated genes in patients with intellectual disability (ID). The phenotypic spectrums associated with variants in this gene vary widely ranging for mild to severe nonspecific ID to Coffin–Siris syndrome. In this study, we evaluated three children from a consanguineous Emirati family affected with ID and dysmorphic features. Genomic DNA from all affected siblings was analyzed using CGH array and whole-exome sequencing (WES). Based on a recessive mode of inheritance, homozygous or compound heterozygous variants shared among all three affected children could not be identified. However, further analysis revealed a heterozygous variant (c.4318C>T; p.Q1440\*) in the three affected children in an autosomal dominant ID causing gene, *ARID1B*. This variant was absent in peripheral blood samples obtained from both parents and unaffected siblings. Therefore, we propose that the most likely explanation for this situation is that one of the parents is a gonadal mosaic for the variant. To the best of our knowledge, this is the first report of a gonadal mosaicism inheritance of an *ARID1B* variant leading to familial ID recurrence.

### Keywords

*ARID1B*; non-Mendelian inheritance; whole-exome sequencing; gonadal mosaicism

## INTRODUCTION

Intellectual disability (ID), also called intellectual development disorder (IDD), is a neurodevelopmental disorder defined by significant impairment of cognitive and adaptive

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functions in early childhood. To date, many genes and loci across the genome have been implicated in ID. Haploinsufficiency for the AT-rich interaction domain-containing protein 1B (ARID1B) has been reported to be responsible for non-syndromic ID (ARID1B-related ID, (MRD12) OMIM 614562), and Coffin–Siris syndrome [Hoyer et al., 2012; Santen et al., 2012]. *ARID1B* encodes a component of the Brahma-associated factor (BAF) complex, also known as the mammalian SWItch/sucrose non-fermentable (SWI/SNF) complex. The BAF-complex is an ATP-dependent chromatin remodelling complex, which modifies chromatin structure and facilitates access of transcription factors to DNA [Hurlstone et al., 2002; Nie et al., 2003; Hargreaves and Crabtree, 2011]. Recent discoveries demonstrated a crucial role for the BAF complex in neurodevelopment and cancer [Lessard et al., 2007; Singhal et al., 2010; Flores-Alcantar et al., 2011; Santen et al., 2012; Kadoch and Crabtree, 2013; Ronan et al., 2013; Wu and Roberts, 2013; Biegel et al., 2014; Santen et al., 2014]. Mutations and chromosomal abnormalities affecting genes encoding subunits of the BAF complex were found to be responsible for several syndromic and non-syndromic forms of ID and cancers [Hoyer et al., 2012; Santen et al., 2012; Ronan et al., 2013; Wu and Roberts, 2013; Biegel et al., 2014; Santen et al., 2014]. In this study, we report a novel variant in the *ARID1B* gene explaining a sporadic occurrence of ID and dysmorphic features in three siblings with consanguineous Emirati parents likely due to gonadal mosaicism in one of the parents.

## PATIENTS AND METHODS

### Patients and Ethics Statement

We ascertained a consanguineous Emirati family with three affected children showing intellectual disability and dysmorphic features. This study has been approved by Al-Ain Medical Human Research Ethics Committee according to the national regulations (protocol number 10/09). The parents in this family provided a signed informed written consent and agreed in writing for the use of photographs in medical publication.

### Molecular Analysis

Peripheral blood samples were collected from members of the affected family in EDTA tubes. DNA samples were analyzed first by CGH array. The whole exome capture and next-generation sequencing, including library construction, DNA capturing, sequencing, and data analysis, were carried out by Baylor-Hopkins Center for Mendelian Genomics ([www.mendeliangenomics.org](http://www.mendeliangenomics.org)) and the variant filtering analysis was performed using the PhenoDB Variant Analysis tool [Sobreira et al., 2015]. We captured the CCDS exonic regions and flanking intronic regions totaling ~51 Mb by using the Agilent SureSelect XT kit and performed paired end 100 bp reads with the Illumina HiSeq2500 platform. We aligned each read to the 1000 genomes phase 2 (GRCh37) human genome reference with the Burrows–Wheeler Alignment (BWA) version 0.5.10-tpx [Li and Durbin, 2009]. Local realignment around indels and base call quality score recalibration were performed using the Genome Analysis Toolkit (GATK) [McKenna et al., 2010] version 2.3-9-ge5ebf34. Variant filtering was done using the Variant Quality Score Recalibration (VQSR) method [DePristo et al., 2011]. For SNVs the annotations of MQRankSum, HaplotypeScore, QD, FS, MQ, ReadPosRankSum were used in the adaptive error model (six max Gaussians allowed, worst 3% used for training the negative model). HapMap3.3 and Omni2.5 were used as training

sites with HapMap3.3 used as the truth set. SNVs were filtered to obtain all variants up to the 99th percentile of truth sites (1% false negative rate). For indels the annotations of QD, FS, ReadPosRankSum were used in the adaptive error model (four max Gaussians allowed, worst 12% used for training the negative model, indels that had annotations more than 10 standard deviations from the mean were excluded from the Gaussian mixture model). A set of curated indels obtained from the GATK resource bundle ([Mills\\_and\\_1000G\\_gold\\_standard.indels.b37.vcf](#)) were used as training and truth sites. Indels were filtered to obtain all variants up to the 99th percentile of truth sites (1% false negative rate). The mean percentage of the target bases with at least 30× coverage was 90.5%. Sanger DNA sequencing was carried out to evaluate the segregation of the variants identified by WES. Primers for all potential causative variants were designed using Primer3 version 0.4.0 (<http://primer3.ut.ee/>). Amplified PCR products were cleaned up using EXO-SAP-IT and sequenced using the BigDye Terminator kit v3.1 (Applied Biosystems, USA) on a the ABI 3130xl Genetic Analyzer (Applied Biosystems, USA). DNA chromatograms were inspected and analyzed based on cDNA sequence in accordance with the GenBank entry NM\_004933.2 for *CDH15* and NM\_020732.3 for *ARID1B* using the Sequencing Analysis<sup>®</sup> 5.3 software (Applied Biosystems) and ClustalW2 algorithms (<http://www.ebi.ac.uk/Tools/msa/clustalw2/>).

## RESULTS

### Clinical Data

The parents are second cousins Emirati nationals of Baloushi origin (Fig. 1A). They have six children, three of them are affected. The parent's appearances are normal and they have a normal IQ. There is no family history of similar problem.

**Patient 1**—A 14 year-old female (Fig. 1A\_V-3), product of normal pregnancy and term normal vaginal delivery. Her birth weight was 2,420 g (3rd centile) and head circumference 34 cm (25th centile). During the first few weeks of life, parents noted that she was hypoactive with feeding difficulties. She was seen in the Paediatric clinic at the age of 8 months due to delayed developmental milestones. She weighed 6 kg (below 3rd centile) and had a head circumference of 43 cm (50th centile). She has dysmorphic features including brachycephaly, narrow forehead, low hair line, long eyelashes, and low set ears. There was alternating squint but detailed eye examination was normal. She was unable to sit or roll over, there was severe head lag, axial hypotonia with exaggerated reflexes. There was feeding and sucking problems. Chromosome analysis was normal. MRI brain showed complete agenesis of corpus callosum. Renal ultrasound was normal. She was evaluated in the genetic clinic at the age of 10 years. She was noticed to have global developmental delay with delayed speech (says few words only) and autistic behavior. Parents reported that she did not like loud sound and tends to put her hands on her ears when there is any loud noise. She was dysmorphic with narrow forehead and low anterior hair line, thick eyebrows with medial flare, long eyelashes, broad nasal tip, wide mouth with thick lower lip, low set prominent ears, and wide big toes. She had hypertrichosis over her entire body. She had autistic behavior with aggressive tendency.

**Patient 2**—A 10-year-old boy is the product of normal pregnancy and term delivery (Fig. 1A\_V-4). No birth measurements are available. He was kept in NICU for 13 days due to irregular heart beat and echocardiography revealed a small VSD. He was assessed by a neurologist at the age of 6.5 months because of developmental delay. He had head lag with axial hypotonia and hyperreflexia and reasonable social interaction. There was a soft systolic murmur at the left sternal edge. His developmental milestones as following: he started to sit alone at 14 months of age, stand at 2 years of age, and walk at 27 months of age. Brain CT scan showed corpus callosum dysgenesis, hearing test and vision assessments were normal. Karyotype, amino acids chromatography, echocardiography, and skeletal surveys were all normal. He was evaluated in genetic clinic at the age of 6 years. His weight was 22 kg (>50th centile), height 110 cm (25th centile) and head circumference 50 cm (25th centile). He had dysmorphic features including brachycephaly, narrow forehead with low anterior hair line, thick eyebrows with medial flare, broad nasal tip, prominent philtrum, wide mouth with thick lower lip, and low set prominent ears. He had short fingers, broad big toes, and hypertrichosis over his entire body. He had moderate intellectual disability with delayed speech (says 2–3 word sentences). Microarray and fragile X mutation analysis were normal.

**Patient 3**—A 9-year-old boy the product of normal pregnancy and delivery (Fig. 1A\_V-5). His birth weight was 2,430 g (>3rd centile) and head circumference 33 cm (10th centile). He was assessed in the pediatric clinic at the age of 2 months because of slow sucking, and failure to gain weight. He was found to have facial dysmorphic features with low anterior hair line, low set ears, high arched palate, hypotonia with head lag, and hyperreflexia. Echocardiography showed bicuspid aortic valve. Amino acid chromatography, urine organic acid chromatography, MRI brain, ultrasound kidney, and karyotyping were all normal. Ophthalmology examination and hearing assessment were normal. He was evaluated in genetic clinic at the age of 5 years. His weight was 18 kg (50th centile), height 105 cm (>10th centile) and head circumference 50 cm (40th centile). He had developmental delay and delayed speech (no words) with dysmorphic features including brachycephaly, narrow forehead with low anterior hairline, medial flare of the eyebrows, wide nasal tip, prominent philtrum, thick lips, low set ears, short fingers, broad big toes, and hypertrichosis over his entire body.

### **Whole-exome Sequencing Revealed a Novel Heterozygous Variant in *ARID1B* With Gonadal Mosaicism Segregation**

Due to consanguinity and absence of phenotype in the parents, we assumed an autosomal recessive mode of inheritance in this family. However, filtering the whole-exome sequencing variants data failed to identify any homozygous or compound heterozygous variant that is in agreement with a recessive inheritance model. By accepting a dominant inheritance model, we were able to identify two heterozygous variants in known disease-causing genes, *CDH15* and *ARID1B*. The variant in *CDH15* is a known SNP (rs201368808) in exon 14 leading to the substitution of an arginine residue with glutamine at position 775 (c.2324G>A/p.R775Q). This variant has a minor allele frequency of A = 0.0018/9 in the 1000 Genomes Project database and 0.001154 in the ExAC database (<http://exac.broadinstitute.org>). In addition, Sanger sequencing showed that this variant is heterozygous in all three affected children, their mother (IV-2) and one unaffected sibling (V-2). SIFT, PROVEN, and

Mutation Taster predicted this variant to be neutral while PolyPhen2 predicted it to be possibly damaging. Collectively, these findings strongly suggest that this variant (rs201368808) is benign without any clinical significance. The second variant is a novel single nucleotide substitution (c.4318C>T) detected in exon 18 of the *ARID1B* gene. Sanger sequencing validated the segregation of this deletion in the studied family showing that both parents and all unaffected siblings were homozygous for the wild-type allele while all three affected children were heterozygous (Fig. 2A). This variant results in a nonsense mutation with introduction of premature termination codon at amino acid position 1440 (p.Q1440\*) of this 2249 amino acid protein. This mutation is not described in the exome variant server (<http://evs.gs.washington.edu/EVS/>), dbSNP database, 1000 Genomes project database, or in the ExAC database. In addition, p.Q1440\* was absent in 200 ethnically matched normal control chromosomes which confirmed the novelty of this variant.

## DISCUSSION

Heterozygous pathogenic variants and cytogenetic abnormalities involving *ARID1B* are considered the leading cause of Coffin–Siris syndrome (CSS) being found in 68–83% of cases [Santen et al., 2013; Wieczorek et al., 2013; Santen et al., 2014; Tsurusaki et al., 2014]. These abnormalities are also found in 0.9% of unselected intellectual disability (ID) patients [Hoyer et al., 2012]. All the reported disease-producing variants in *ARID1B* are truncating and predicted to result in haploinsufficiency of the protein product [Santen et al., 2014]. The phenotypic features of the syndromic *ARID1B* haploinsufficiency are variable ranging from mild to severe ID associated with speech delay and facial features that include low anterior hair line, coarse face, thick eyebrow, broad nasal tip, large mouth with thick lower lip. There is usually hypertrichosis, corpus callosum abnormalities, and hypoplasia of the nails of fifth fingers/toes. A recent review of 60 patients with *ARID1B* mutations from several CSS cohort studies in the literature concluded that there is a broad variation in the phenotype and speculated on the possibility of unidentified genetic factors that may modify the phenotype and determine the severity of phenotype in affected patients [Santen et al., 2014]. This study also concluded that the major features of the *ARID1B* phenotype, present in almost all patients with prior CSS diagnosis are: intellectual disability (100%), speech delay (100%), coarse features (90%) and hypertrichosis (95%) while minor features present in a smaller but significant fraction of patients such as small 5th finger or toe nails (81%), short 5th finger (73%), feeding difficulties (65%), agenesis of corpus callosum (35%), seizures (23%), and growth delay (19%). The authors suggested that patients with 2/3 major features and at least two minor features should be tested for *ARID1B* gene mutations [Santen et al., 2014]. Mari et al. [2015] suggested that other hand and feet anomalies, including broadening of distal phalanges and broad hallux, might be present in this syndrome [Mari et al., 2015]. All reported cases so far have been sporadic suggesting high rates of new mutations in this gene [Santen et al., 2014].

The family we describe here is consanguineous with three of six children affected with moderate degree of ID and dysmorphic features. All three children had low anterior hair line with thick eyebrows, broad nasal tip, large mouth with thick lower lip and hypertrichosis. In addition, two of them had hypoplastic corpus callosum. There was no hypoplasia of the nails of 5th fingers or toes but there were broad halluces in all of them. The parents were

completely phenotypically normal. The presence of consanguinity with three affected children of both sexes and phenotypically normal parents suggests autosomal recessive inheritance in this family. However, WES failed to identify a homozygous or compound heterozygous variant that could explain the etiology of the phenotype in this family. We then considered autosomal dominant inheritance with incomplete penetrance or highly variable expressivity [Beratis et al., 1971; Russell et al., 1995]. However, careful examination of the parents and absence of the variant in their constitutional DNA ruled this possibility out. Therefore, we conclude the most likely explanation is that one of the parents is a germline mosaic. Germline mosaicism has been reported in several autosomal dominant conditions [Ng et al., 2004; Chiang et al., 2010; Barbaro et al., 2012; Danda et al., 2014; Hufnagel et al., 2014; Armaroli et al., 2015] and gives the impression of autosomal recessive inheritance when there is recurrence of an autosomal dominant trait among offspring of phenotypically normal parents. This possibility should be considered when analyzing exome sequencing data.

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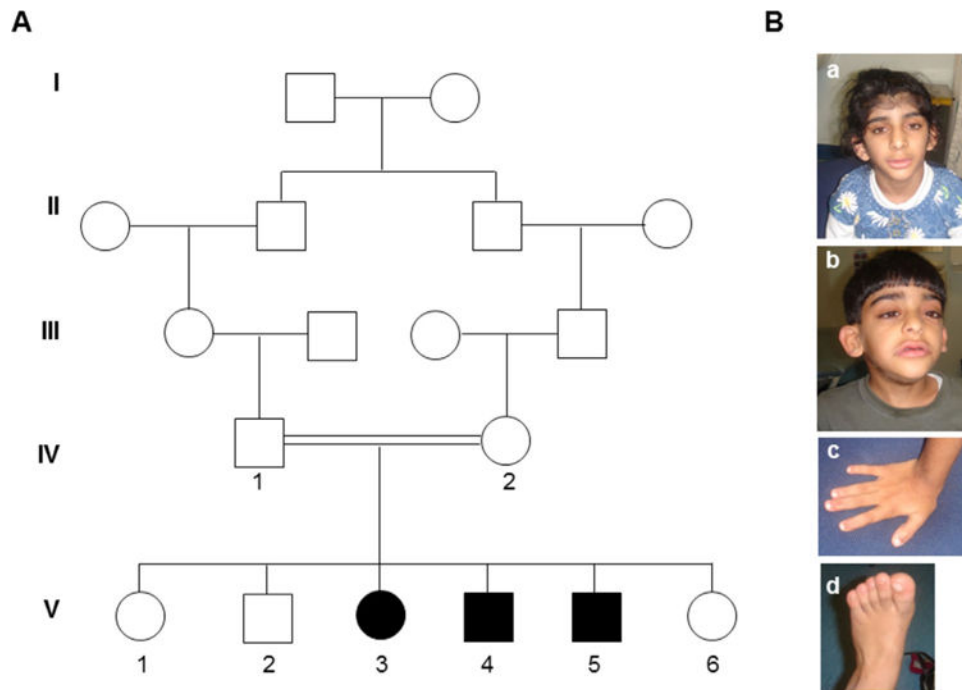
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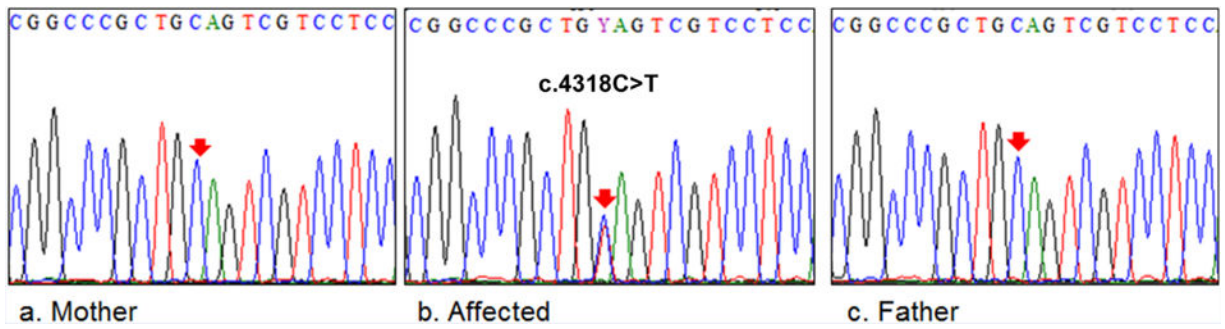
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**FIG. 1.** Pedigree of consanguineous family with three intellectually disabled children. A: Pedigree of consanguineous family showing three affected children with intellectually disabled and dysmorphic features. Circles and squares denote females and males respectively, filled symbols represent affected members, double lines denote consanguineous marriage, roman numbers indicate the first generation until their offspring, arabic numbers depict all participants in this study. B: Pictures of affected children showing the typical feature of ARID1B-related ID. B.a,b: showing abnormal head shape and low-set, posteriorly rotated, and abnormally shaped ears, low anterior hair line with thick eyebrows, broad nasal tip, large mouth with thick lower lip and hypertrichosis. B.c: shows shows short fingers. B.d: shows broad big toe. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmga>]

**FIG. 2.**

Molecular analysis of patients with *ARID1B* mutation. A: DNA chromatograms of *ARID1B* mutation compared to wild-type sequence. A.b: shows the heterozygous nonsense mutation (c.4318C>T) detected in the affected patients. A.a,c: show normal chromatograms in the parents. [Color figure can be seen in the online version of this article, available at <http://wileyonlinelibrary.com/journal/ajmga>]