RESEARCH ARTICLE

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UBE2A Deficiency Syndrome: Mild to Severe Intellectual Disability Accompanied by Seizures, Absent Speech, Urogenital, and Skin Anomalies in Male Patients

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We describe three patients with a comparable deletion encompassing *SLC25A43*, *SLC25A5*, *CXorf56*, *UBE2A*, *NKRF*, and two non-coding RNA genes, *U1* and *LOC100303728*. Moderate to severe intellectual disability (ID), psychomotor retardation, severely impaired/absent speech, seizures, and urogenital anomalies were present in all three patients. Facial dysmorphisms include ocular hypertelorism, synophrys, and a depressed nasal bridge. These clinical features overlap with those described in two patients from a family with a similar deletion at Xq24 that also includes *UBE2A*, and in several patients of Brazilian and Polish families with point mutations in *UBE2A*. Notably, all five patients with an Xq24 deletion have ventricular septal defects that are not present in patients with a point mutation, which might be attributed to the deletion of *SLC25A5*. Taken together, the *UBE2A* deficiency syndrome in male patients with a mutation in or a deletion of *UBE2A* is characterized by ID, absent speech, seizures, urogenital anomalies, frequently including a small penis, and skin abnormalities, which include generalized hirsutism, low posterior hairline, myxedematous appearance, widely spaced nipples, and hair whorls. Facial dysmorphisms include a wide face, a depressed nasal bridge, a large mouth with downturned corners, thin vermilion, and a short, broad neck.

Key words: *UBE2A*; deficiency; deletion; intellectual disability; syndrome

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INTRODUCTION

Genomic rearrangements including losses and gains are frequently associated with a syndromic phenotype that comprises intellectual disability (ID). Often it is not clear which gene or genes are accountable for the clinical features observed in the patients with an imbalance comprising multiple genes. Only rarely, one gene can be held responsible for the major phenotypic characteristics observed in these patients. On the X chromosome, duplications encompassing specifically *MECP2* result in the *MECP2* duplication syndrome characterized by severe ID, hypotonia, seizures, and recurrent infections in male patients [Van Esch et al., 2005; Lugtenberg et al., 2006].

UBE2A is an X-chromosomal gene, which encodes an ubiquitin-conjugating enzyme that is involved in ubiquitination of proteins thus targeting them for degradation through the proteasome or changing their activity or localization [Ye and Rape, 2009]. Ubiquitination is important for numerous cellular processes including cell proliferation, signal transduction, apoptosis, transcriptional regulation, receptor modulation, and endocytosis. Although ubiquitination requires the concerted action of ubiquitin activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s), and ubiquitin ligases (E3s), the conjugating enzymes are thought to be the key mediators of ubiquitin chain assembly [Ye and Rape, 2009].They regulate chain length and establish the topology of assembled chains, thereby determining the consequences of ubiquitination for the modified proteins. Three point mutations: one premature stop mutation and two missense mutations, have been identified in *UBE2A*, which resulted in a syndromic form of X-linked ID (XLID) characterized by moderate to severe ID primarily accompanied by seizures, severely impaired/absent speech, facial dysmorphisms, small penis, and hirsutism [Nascimento et al., 2006; Budny et al., 2010]. More recently, one deletion in Xq24 that included *UBE2A* amongst nine other genes has been described in a male patient with similar features, additionally presenting with congenital heart disease [Honda et al., 2010].

Here, we describe three *UBE2A* encompassing deletions in Xq24 in three patients with syndromic XLID. We argue that the deletion of *UBE2A* is sufficient to cause the *UBE2A* deficiency syndrome characterized by mild to severe ID, seizures, absent speech, urogenital anomalies, and skin abnormalities. Other features, in particular congenital heart defects, may be caused by a deletion of *UBE2A* flanking genes.

PATIENTS AND METHODS

Patients

Written informed consent was obtained for all patients and our research project was approved by the local ethics committee (Commissie Mensgebonden Onderzoek Regio Arnhem-Nijmegen) according to the World Medical Association Declaration of Helsinki. Karyotypes at a resolution of at least 550 bands were normal. All DNA samples were isolated from whole blood by the salting out method as described by Miller et al. [1988].

Array Analysis

The genome of Patient A was screened for copy number variations by using 105 K Agilent array analysis (Agilent Technologies, Santa Clara, CA). Patient B was analyzed by using a Nimblegen 385 K whole genome oligonucleotide array (Roche Nimblegen, Madison, WI). Patient C was analyzed by using an Affymetrix *Nsp*I 250 K SNP array (Affymetrix, Santa Clara, CA). All SNP array experiments were performed according to the respective manufacturer's protocols. Copy number estimates were determined using DNA analytics (Agilent Technologies), Nimblescan software (Roche Nimblegen), or the CNAG software package (v2.0) [Nannya et al., 2005] in case of respectively Agilent, Nimblegen, or Affymetrix array analysis.

Genomic Real-Time Quantitative PCR (Genomic QPCR)

Genomic SYBR Green-based real-time quantitative PCR analysis was performed as described before [Marcelis et al., 2008]. Primers were designed using Primer Express Version 2.0 (Applied Biosystems, Foster City, CA) or by the primer3 program (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi) [Rozen and Skaletsky, 2000] (see supporting information Table I which may be found in the online version of this article) and validated as previously described [Marcelis et al., 2008]. Copy numbers were measured relative to *CFTR*. All comparative threshold cycle (C_t) values were within the range of DNA dilutions used to validate the primers. The melting curves of all PCR products showed a single product. All controls were negative. DNA copy number differences between two samples were calculated by the C_t or $2^{\Delta\Delta C_t}$ method [Livak and Schmittgen, 2001; Pfaffl, 2001].

PCR

The deletion in Patient B was mapped by conventional PCR. Eleven sets of PCR primers that tiled the deletion and surrounding genes (see supporting information Table I which may be found in the online version of this article) were designed by using Primer3 software [Rozen and Skaletsky, 2000]. DNA from Patient B or from a normal male was used as a PCR template for each primer pair, and the presence or absence of products of the expected size (~500 bp) was determined by agarose gel electrophoresis.

X-Inactivation Testing

In the mothers of Patients A and C, X-inactivation was investigated by examining the methylation status of the *AR* locus [Allen et al., 1992]. In brief, 1 µg DNA from carrier females and a male control was digested overnight at 37°C with either 40 U *Bam*HI (Westburg, Leusden, The Netherlands) and 20 U of the methylation-sensitive restriction enzyme *Hha*I (Westburg), or 40 U *Bam*HI alone as a control in NEB buffer 4 (Westburg) in a total volume of 35 µl. To ensure complete digestion, an additional 20 U *Bam*HI and 10 U *Hha*I or 20 U *Bam*HI were added to the respective reaction mixtures, which was then incubated for 4 hr at 37°C. Enzymes were inactivated at 65°C for 20 min. The CAG repeat was amplified from 2.5 µl digestion mixture by using 1.5 U AmpliTaq polymerase (Applied Biosystems) in AmpliTaq buffer (Applied Biosystems), 8% DMSO, 0.25 mM dNTPs (Invitrogen, Breda, The Netherlands), and 2 µM forward and

5′-FAM-labeled reverse primer (see supporting information Table I which may be found in the online version of this article) in a total volume of 30 µl. PCR cycling conditions consisted of (1) denaturation at 95°C for 2 min, (2) 30 cycles of amplification by denaturation at 95°C for 30 sec, annealing at 55°C for 30 sec and elongation at 73°C for 30 sec, followed by (3) final elongation at 73°C for 7 min. PCR products were analyzed by the ABI PRISM 3730 DNA analyzer (Applied Biosystems) and differences in repeat length determined with Genemapper (Applied Biosystems). Complete digestion of one of the two alleles was confirmed by the absence of a PCR product in the *Bam*HI/*Hha*I digested DNA of the hemizygous male control, whereas in all other samples at least one allele was amplified. In the mother of Patient B, X inactivation was analyzed by using a two-color FISH/late replication assay as described by Wei et al. [2001].

CLINICAL REPORTS

Patient A is of Dutch origin (Fig. 1A; Table I). He was born spontaneously after an uneventful pregnancy of 37 weeks and 4 days duration with a birth weight of 2,920 g. The patient was referred to the hospital at the age of 3 days because of neonatal seizures due to severe hypoglycemia for which he was treated. The hypoglycemia resolved spontaneously after several weeks. At the age of 1 year, he had microcephaly, congenital cataracts, bilateral cryptorchidism, hypospadias, and cerebral white matter lesions and cysts as shown by brain MRI. He also presented with severe hypotonia, persisting epilepsy and severe developmental delay. When he was 1 week old, cardiac investigation showed transient septal hypertrophy, possibly due to hyperinsulinism for which a direct cause was not found, and a muscular ventricular septal defect, which had closed spontaneously at the last assessment when he was 3 years of age. He had a history of recurrent respiratory infections requiring hospital admission, but no immune deficiencies were detected. Extensive metabolic screening including a muscle biopsy did not show any abnormalities. No other affected family members were reported.

Patient B is from Texas (Fig. 1B; Table I). He was born at 38 weeks gestation via elective caesarian (due to a prior caesarian) after an uneventful pregnancy. His birth weight was 3,600 g and length 50.8 cm. The patient was referred to the hospital at age 3 months because of three small left kidney stones, which passed spontaneously. He also had bilateral duplicated kidneys, bilateral inguinal cryptorchidism, and a normal penis without hypospadias. In addition, developmental delay, bilateral inguinal hernia, bilateral congenital cataracts, moderate to severe sensorineural deafness, a right preauricular pit, small atrial and ventricular septal defects with spontaneous closure, patent ductus arteriosus requiring ligation, simian creases, hypotonia, and cerebellar hypoplasia were observed. Family anamnesis did not reveal consanguinity or additional affected family members except for some with adult onset kidney stones and cataract. These latter traits were not linked to the X chromosome as they showed male-to-male transmission.

Patient C is of Irish origin (Fig. 1C; Table I). He was born after 37 weeks of gestation, weighing 2,500 g, and he is the first child of unrelated, healthy Irish parents. He had microcephaly, a ventricular septal defect, a persistent vitello-intestinal duct, 11 pairs of ribs, and glandular hypospadias. He was noted to be dysmorphic, with hypertelorism, synophrys, and abnormal external ears. He had recurrent bacterial pneumonia, and associated failure to thrive. He showed moderate to severe developmental delay. He was found to be neutropenic, with hypogammaglobulinemia, and a low B cell count. He started regular intravenous immunoglobulin therapy at 1 year of age, with a major improvement in his infections and in his growth. He had surgery for his ventricular septal defect at 15 months of age. Cranial MR scan did not show any abnormalities. He developed seizures at the age of 6 years. At his most recent assessment, age 10 years, he remains hypotonic, and is wheelchair bound, unable to walk and has no speech, and is not toilet trained. He is on 5th centile for weight and height.

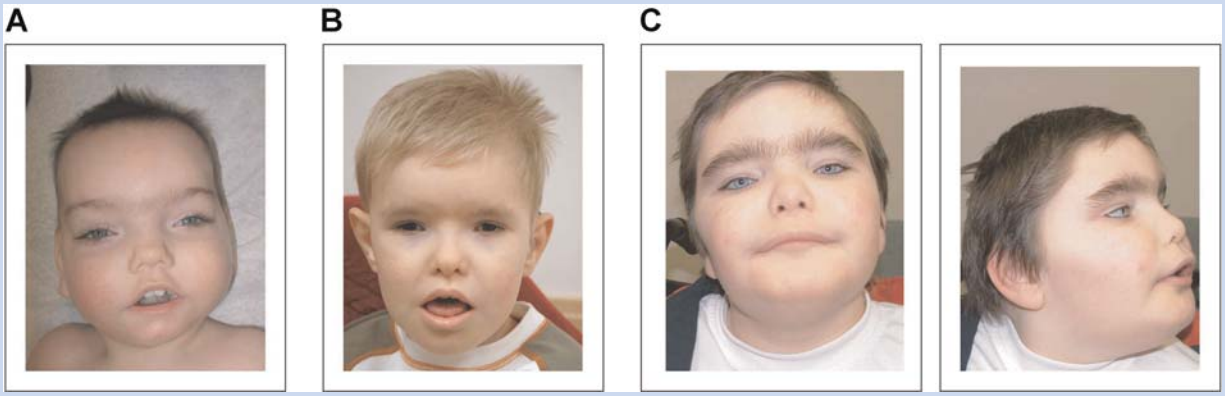

FIG. 1. Photographs of the three patients with an *UBE2A* deletion described in this report. A: Patient A at the age of 8 months years showing synophrys, ocular hypertelorism, low nasal bridge, and short broad neck. B: Patient B at the age of 5 years and 9 months, who presented with synophrys, ocular hypertelorism, and a depressed nasal bridge. C: Patient C at the age of 10 years. Note the wide face, midface hypoplasia, synophrys, upslanted palpebral fissures, ocular hypertelorism, depressed nasal bridge, large mouth with downturned corners, and thin vermilion of the lips, short broad neck, and low posterior hairline.

TABLE I. Clinical Descriptions of the ID Patients With an *UBE2A* Deletion [This Report] [Honda et al., 2010] and the p.Q128X, p.G23R, and p.R11Q Mutations in UBE2A [Nascimento et al., 2006; Budny et al., 2010]

				Honda et al.		Nascimento et al.			Budny et al.					
Patiënt	**A**	**B**	**C**	**II-1**	**II-2**	**II-3**	**III-2**	**III-3**	**V:2**	**IV:13**	**III:12**	**IV:3**	**II:3**	**Total (%)**
Mutation	*UBE2A* deletion					p.Q128X			p.G23R				p.R11Q	
General														
Age of last examination (years)	3	5.8	9	5	2	46	19	5	10	21	43	29	43.5	–
Birth weight (centile)	50th	>95th	50th	85	10	50th	90–97th	> 97th	25–50th	>95th	NA	50–75th	NA	–
Height (centile)	25th	NA	50th	10th	<3th	<3rd	10–25th	10th	10–25th	<3th	<3th	<3th	3th	–
Weight (centile)	50th	50th	50th	10	<3	>97th	90th	>97th	90–97th	>97th	75–90th	25–50th	75–90th	–
Head circumference (centile)	<3rd	<5th[a]	50th	3th	NA	>98th	>98th	50th	75th	90th	>97th	90–97th	90th	
Psychomotor retardation	+	+	+	+	+	+	+	+	+	+	+	+	NA	100
Age of walking (years)	>3	5	Nw	NA	NA	Nw	3	2	NA	2	1	1.5	NA	–
Severely impaired speech	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Hypotonia	+	+	+	–	–	–	–	–	+	–	–	+	–	38
Recurrent infections	+	–	+	–	–	–	–	–	–	–	–	–	–	15
Craniofacial														
Synophrys	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Large mouth with down-turned corners and thin lips	+	–	+	+	+	+	+	+	+	+	+	–	+	85
Short, broad neck	+	–	+	+	+	+	+	+	–	+	+	–	+	77
Wide face	–	–	+	+	+	–	+	+	+	+	+	–	+	69
Low posterior hairline	–	–	+	+	+	+	+	+	–	+	+	–	+	69
Depressed nasal bridge	+	+	+	+	+	–	+	+	–	+	–	–	–	54
Ocular hypertelorism	+	+	+	+	+	–	+	–	–	–	–	–	–	46
Up-slanted palpebral fissures	–	–	+	+	+	+	+	+	–	–	–	–	–	46
Midface hypoplasia	–	–	+	+	+	–	+	+	–	–	–	–	–	38
Neurological														
Mild to severe ID	+	+	+	+	+	+	+	+	+	NA	+	+	+	100
Seizures	+	+	+	+	+	+	+	+	+	+	–	+	–	85
White matter hypodensity	+	+	–	+	+	NA	+	+	–	NA	NA	–	NA	67
Hypoplastic cerebellum	–	+	–	–	–	–	–	–	–	NA	NA	+	NA	20
Cerebral palsy	–	–	–	–	–	NA	–	–	–	–	–	+	–	8
Urogenital														
Small penis	+	–	+	+	+	+	+	+	–	+	+	+	+	85
Cryptorchidism	+	+	–	–	–	–	–	–	–	–	–	–	–	15
Hypospadias	+	–	+	–	–	–	–	–	–	–	–	–	–	15
Galbladder lithiasis	–	–	–	–	–	+	+	–	–	–	–	–	–	15
Duplicated kidneys	–	+	–	–	–	–	–	–	–	NA	NA	NA	NA	11
Horseshoe kidney	–	–	–	–	–	–	–	–	+	NA	NA	NA	NA	11
Hydronephrosis	–	+	–	–	–	–	–	–	–	–	–	–	–	8
Nephrolithiasis	–	+	–	–	–	–	–	–	–	–	–	–	–	8
Skin														
Marked generalized hirsutism	–	–	+	+	+	+	+	+	+	+	+	–	+	77
Myxedematous appearance	–	–	–	+	+	+	+	+	+	+	+	–	+	69
Widely spaced nipples	+/–	–	–	NA	NA	+	+	+	+	+	+	–	+	65

Hair whorls	−	−	−	+	NA	+	+	+	−	−	+	+	+	58
Dry skin	+/−	−	−	+	+	+	+	+	−	−	−	−	−	42
Onychodystrophy	−	−	−	−	+	+	+	−	+	−	+	−	−	38
Other														
Small, flat feet, dorsum swelling	−	NA	+	+	+	+	+	+	−	−	−	−	−	67
Digital anomalies	−	−	−	+	+	−	−	−	+	+	+	+	+	54
Heart defect	+	+	+	+	+	−	−	−	−	−	−	−	−	38
Congenital cataract	+	+	−	−	−	−	−	−	−	−	−	−	−	15
Preauricular pit	−	+	−	−	−	−	−	−	−	−	−	+	−	15
Profound sensorineural deafness	−	+	−	−	−	−	−	−	−	−	−	−	−	8
Biochemical														
Hypogammaglobulinaemia	NA	−	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	50
Neonatal hypoglycemia	+	−	−	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	33

Total occurrence of a specific feature is given as percentage of the examined patients. NA, not available; Nw, not walking.

[a]Measured at birth.

RESULTS

Xq24 Deletions in All Three Patients

Genome-wide array CGH analysis showed a 350 kb deletion at Xq24 in Patient A from 118.38 to 118.73 Mb (UCSC Human Genome Browser, hg18), which was confirmed by gQPCR (Fig. 2). The deletion encompasses *SLC25A43*, *LOC100303728*, *SLC25A5*, *CXorf56*, *UBE2A*, *NKRF*, and *SEPT6*. The mother carried the deletion as well and showed complete skewing of X-inactivation. Patient B had a 240 kb deletion at Xq24 from 118.35 to 118.59 Mb (UCSC Human Genome Browser, hg18). Conventional PCR established that the deletion extended slightly further distally: the first deleted proximal gene is *SLC25A43*, and *NKRF* is the most distal deleted gene. Metaphase FISH analysis using bacterial artificial chromosome (BAC) probes that span ~66% of the deleted region (RP11-54K19 and RP3-404F18) showed that the deletion was also present in his mother. The deleted X chromosome was inactivated in 90% of the mother's peripheral blood lymphocytes. Patient C had a comparable deletion of 360 kb at Xq24 (118.30–118.66 Mb; UCSC Human Genome Browser, hg18) with SNP_A-4223220 and SNP_

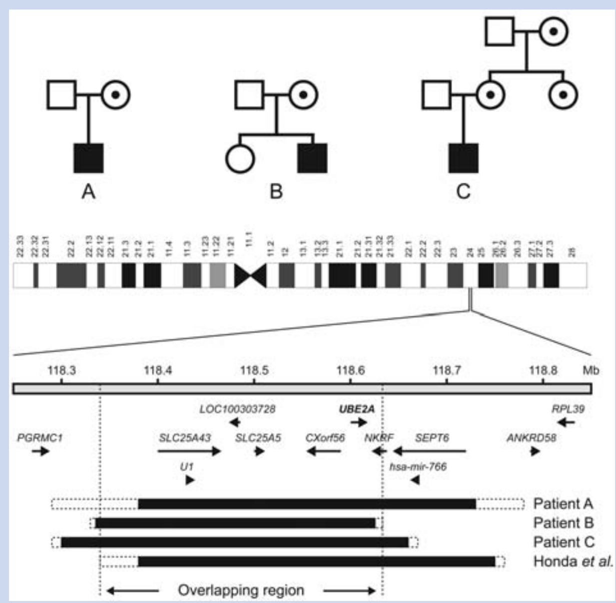

FIG. 2. Pedigrees of the families (upper panel) and schematic overview of the Xq24 genomic region (lower panel; UCSC Human Genome Browser, hg18) with the three deletions identified in our patients from the Netherlands (A), Texas, USA (B), and Ireland (C). Affected males are represented by filled squares. The presence of the deletion is indicated by a dot in the middle of the gender symbol. The carrier status of the sister of Patient B is not known. Black bars represent the extent of the deletions. The dotted lines indicate the breakpoint region between the last deleted genomic sequence and the first one present. Arrows indicate the position and orientation of all genes in the region. *UBE2A* is printed in bold. *U1*, *LOC100303728* and *hsa-mir-766* are non-coding RNA genes. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com]

A-2252277 as the delimiting SNPs as shown by 250 k SNP array analysis. Confirmation by gQPCR showed that the proximal breakpoint is located between *PGRMC1* and *SLC25A43* and the distal one within *SEPT6*. This deletion was also inherited from the mother who showed complete skewing of X-inactivation. In none of the patients was any other potentially causative copy number variation detected by the genome-wide array analysis.

DISCUSSION

Here, we describe three patients with a comparable deletion at Xq24 encompassing *SLC25A43*, *SLC25A5*, *CXorf56*, *UBE2A*, *NKRF*, and two non-coding RNA genes, *U1* and *LOC100303728*. *SEPT6* is (partially) deleted in two out of the three patients (A and C) and *hsa-mir-766* is deleted only in Patient A. In this region, no normal copy number variations have been described to our knowledge. In the three female carriers tested, X-inactivation was at least 90% skewed. Although similar, the breakpoints of each separate Xq24 deletion are different. Since there are also no low copy repeats in this area, non-allelic homologous recombination can be excluded as a molecular mechanism. However, the deletions may be a result of non-homologous end joining, or replication-error mechanisms, such as microhomology-mediated break-induced replication.

Moderate to severe ID, absent speech, seizures, and urogenital anomalies, most notably a small penis in two patients and renal abnormalities in one patient, are present in our three patients. These clinical features overlap completely with those described in two patients from a family with a deletion at Xq24 including *UBE2A* [Honda et al., 2010] and in patients with a point mutation in *UBE2A* [Nascimento et al., 2006; Budny et al., 2010]. Other characteristics that occur in more than half of the patients are facial dysmorphisms and skin abnormalities. The face of the patients is characterized by a wide face, a depressed nasal bridge, a large mouth with downturned corners, and thin vermilion of the upper lip, and a short, broad neck. Skin abnormalities include generalized hirsutism, low posterior hairline, myxedematous appearance, widely spaced nipples, and hair whorls. Other features that were reported in more than half of the patients are white matter hypodensity, small flat feet, dorsum swelling, and digital anomalies. The p.R11Q and p.G23R missense mutations are highly conserved amino acid residues in the UBCc domain (InterPro entry IPR000608) presumably resulting in reduced ubiquitination. The p.Q128X mutation result in a truncated protein that deletes the very last part of the UBCc domain. As the mutation is found in the last exon, it would not lead to nonsense-mediated decay and hence in reduced protein levels. The deletions remove *UBE2A* completely resulting in no expression and thus no enzyme activity at all. Despite the different consequences of the individual mutations for the UBE2A protein, the clinical features noted in more than half of the patients are similar, indicating that a loss of UBE2A activity in general results in a clinically well-recognizable syndrome.

The size of the deletion is almost identical in each of our three patients and the two patients from Japan [Honda et al., 2010] ranging in size from 275 to 371 kb. Although the core clinical features are the same, other symptoms can occur that do not seem to correlate with the specific genes inside the deletions. Even more so, our Patient B with the smallest deletion had the most severe phenotype including numerous features not present in the other four patients, such as hypotonia, hypoplastic cerebellum, severe kidney problems, congenital profound hearing impairment, and heart malformations. However, except for the heart defects and hearing impairment, these might be the result of clinical variability of the urogenital anomalies (kidney problems) or of the brain abnormalities (hypotonia/hypoplastic cerebellum). Although a deletion of *UBE2A* would be enough to explain the phenotype of our three patients, the minimal overlapping region of approximately 300 kb contains four protein coding genes and two non-coding RNA genes (Fig. 2), which could influence the phenotype. The non-coding RNA gene, *U1*, codes for a small nuclear RNA that is part of the spliceosome and thus essential for correct pre-mRNA splicing for most pre-mRNAs [Raponi and Baralle, 2008]. There are multiple copies of this gene throughout the human genome (UCSC Human Genome Browser, hg18), which can be found as isolated genes or in clusters, for example, in the chromosome 1p36.13 and 1q21.1 regions. Deletions of these complete clusters that each contain four *U1* copies have been found in normal control individuals [Zhang et al., 2006], indicating that deletion of one copy, such as in our patients, will not lead to splicing aberrations. Of the non-coding RNA gene *LOC100303728*, limited information is available; although it might code for a natural antisense transcript regulating the expression of *SLC25A5*. *SLC25A43* and *SLC25A5* are part of a large gene family that encode mitochondrial carriers that shuttle a variety of metabolites across the inner mitochondrial membrane [Palmieri, 2004]. Both have low expression levels in brain [Zhang et al., 2007] indicating that it is unlikely that deletions of these genes contribute to the neurological features, although *SLC25A43* seems to be specifically expressed in the olfactory bulb and part of cerebral cortex [Haitina et al., 2006]. However, a deletion of *SLC25A5* could be causative for the septal heart defect in our Patients A and B as well as in the patients from Japan, as Slc25a5 null mice die at day E14.5 due to massive cardiac septal defects (Douglas C. Wallace, personal communication). SLC25A5 is one of the four adenine nucleotide transporters involved in the translocation of ADP from the mitochondrial matrix into the cytoplasm [Lunardi et al., 1992; Stepien et al., 1992]. Humans with a deletion of *SLC25A5* may survive because of partial redundancy of function with SLC25A6, the one ANT protein that is not present in mouse [Ellison et al., 1996]. *NKRF* encodes NF-κB repressing factor that is involved in silencing of IFN-β, IL-8/CXCL8, iNOS, and HIV type 1 (*HIV-1*) long terminal repeat (LTR) suggesting a role in immune response to infection [Nourbakhsh and Hauser, 1999; Nourbakhsh et al., 2001; Feng et al., 2002; Dreikhausen et al., 2005]. Apparently, a deletion of this gene does not result in an impaired immune system in general, since only Patients A and C presented with recurrent infections. In addition, *Nkrf* knockout mice have a normal immune response as well [Froese et al., 2006]. The function of CXorf56 is unknown and *CXorf56* expression in brain, nervous tissue, and genitourinary system is very low, although it is expressed in kidney and heart [Zhang et al., 2007].

In conclusion, we show that deletions of *UBE2A* are sufficient to result in the *UBE2A* deficiency syndrome primarily characterized by mild to severe ID, absent speech, seizures, facial dysmorphisms,

urogenital anomalies, in particular a small penis, and skin abnormalities.

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