Original research

Biallelic truncating variants in ATP9A cause a novel neurodevelopmental disorder involving postnatal microcephaly and failure to thrive

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ABSTRACT

Background Genes implicated in the Golgi and endosomal trafficking machinery are crucial for brain development, and mutations in them are particularly associated with postnatal microcephaly (POM).

Methods Exome sequencing was performed in three affected individuals from two unrelated consanguineous families presenting with delayed neurodevelopment, intellectual disability of variable degree, POM and failure to thrive. Patient-derived fibroblasts were tested for functional effects of the variants.

Results We detected homozygous truncating variants in ATP9A. While the variant in family A is predicted to result in an early premature termination codon, the variant in family B affects a canonical splice site. Both variants lead to a substantial reduction of ATP9A mRNA expression. It has been shown previously that ATP9A localises to early and recycling endosomes, whereas its depletion leads to altered gene expression of components from this compartment. Consistent with previous findings, we also observed overexpression of ARPC3 and SNX3, genes strongly interacting with ATP9A.

Conclusion In aggregate, our findings show that pathogenic variants in ATP9A cause a novel autosomal recessive neurodevelopmental disorder with POM. While the physiological function of endogenous ATP9A is still largely elusive, our results underline a crucial role of this gene in endosomal transport in brain tissue.

INTRODUCTION

Intellectual disability (ID) has a prevalence of approximately 1% in the general population. It is often diagnosed in childhood due to neurodevelopmental delay (NDD) and represents one of the most common paediatric conditions. Most ID/NDD disorders occur in combination with additional malformations or other clinical features, such as behavioural abnormalities, epilepsy and microcephaly. Using exome sequencing (ES), a causative genetic variant can be detected in about 40%–60% of cases. In particular, the discovery of new disease genes has markedly increased the diagnostic yield in recent years. Currently, more than 1300 genes are listed as primary ID-associated genes (ID-AGs, SysID database) and approximately 25% of these genes are associated with microcephaly. Proteins encoded by microcephaly-associated genes play a role in diverse biological processes and molecular pathways such as transcriptional regulation, DNA repair, microtubule organisation and endosome regulation. Genes encoding proteins of the Golgi and endosomal trafficking machinery are of particular interest because they are crucial for brain development, and mutations in these genes are associated with postnatal microcephaly (POM).

The endosomal genes include the family of P4-ATPases, which regulates asymmetric membrane lipid distribution in eukaryotic cells by ATP-dependent translocation of phospholipids from the exofacial to the cytosolic leaflet. Active lipid remodelling of the plasma membrane and intracellular membranes is a critical organisational prerequisite for various cellular processes such as vesicle trafficking, cell signalling and neuronal cell survival. The P4-ATPase-mediated flipping of phospholipids initiates vesicle biogenesis and facilitates the formation of various transport carriers. The human genome encodes 14 members of the P4-ATPase family that differ in substrate specificity and tissue expression and are divided into five subclasses. So far, three P4-ATPases (ATP8A2, ATP8B1 and ATP11C) have been linked to genetic diseases. Pathogenic variants in ATP8A2 cause autosomal recessive cerebellar ataxia, mental retardation and dissequilibrium syndrome 4 (MIM: 615268); ATP8B1 is associated with autosomal recessive and dominant cholestasis (MIM: 243300, MIM: 147480 and MIM: 211600), and mutations in ATP11C have been shown to be causal for X-linked haemolytic anaemia (MIM: 301015). Using ES, we identified biallelic truncating variants in ATP9A (ATPase phospholipid transporting 9A, HGNC:13540) in three children affected with POM and ID in two unrelated families. ATP9A and ATP9B in humans and its orthologues TAT-5 (c. elegans) and Neo1 (S. cerevisiae) form the P4-ATPase subclass. Recent studies using yeast demonstrated that the P4-ATPase family comprises two distinct subclasses: the P4-ATPase-a subclass and the P4-ATPase-b subclass, which share a common folding pattern and are catalytically active in translocating phospholipids.
ATP9A is located on chromosome 20q13.2 (GRCh37/hg19). The canonical transcript (ENST00000338821.5, NM_006045.3) consists of 28 exons, encodes a 1047 residue protein and is mainly expressed in the brain. Detailed knowledge about the function and subcellular distribution of endogenous ATP9A in physiologically relevant tissue is lacking. In HeLa cells, overexpressed ATP9A localises to early/recycling endosomes and the trans-Golgi network (TGN) and is required for endocytic recycling of the transferrin receptor to the plasma membrane. In contrast to ATP9A, ATP9B contains a specific N-terminal region and localises exclusively to the TGN. ATP9A as its orthologues TAT-5 and Neo1 form a highly conserved complex with DOP1B (DOP1 leucine zipper like protein B, HGNC:21194) and MON2 (MON2 homologue, regulator of endosome-to-Golgi trafficking, HGNC:29177) and are functionally intertwined with the SNX3-retromer (SNX3, sorting nexin 3, HGNC:11174). ATP9A knockdown cell line showed a significant upregulation and downregulation of 75 and 50 genes, respectively, where ARPC3 (actin-related protein 2/3 complex subunit 3, HGNC:706) was one of the most strongly upregulated genes (3.5-fold overexpression) and CORO1A (coronin 1A, HGNC:2252) was the most significantly downregulated (2.0-fold). In addition, as a result of its role in endosome trafficking pathways, ATP9A appears to inhibit the secretion of exosomes at the plasma membrane, possibly due to structural alteration of the actin cytoskeleton.

Here we show that individuals with biallelic truncating ATP9A variants display NDD, POM and failure to thrive. To the best of our knowledge, this is the first time that mutations in ATP9A are described as causative for a human phenotype.

### MATERIAL AND METHODS

#### ES and segregation analysis

Individual A-II-1 was included in TRANSLATE-NAMSE, an innovation project of the German Federal Joint Committee to improve the care of patients with rare diseases. Genomic DNA was isolated from peripheral blood and enriched with Sure-Select Human All Exon V6 (Agilent) for ES on an Illumina system. Reads were aligned to human genome build GRCh37/hg19. Sequence reads were called and analysed according to an in-house standard operating procedure using the VarFish platform. In brief, variants were filtered by minor allele frequency, mode of inheritance, predicted functional impact (i.e., missense, nonsense and splicing) and ranked by their gene-phenotype similarity score (exomiser: HiPhive) and pathogenicity score (CADD, MutationTaster).

In family B, genomic DNA from individual B-II-1 was used for library preparation (kit: Nextera DNA Flex). Subsequently, ES was performed on a NextSeq 550 (Illumina). Sequence alignment of raw fastq files to the human reference sequence (GRCh37/hg19 assembly) and variant calling was performed using the DRAGEN Germline Pipeline V3.2.8 on Illumina BaseSpace (https://basespace.illumina.com/). Variant annotation and filtering was performed using VarSeq V2.2 (Golden Helix, Bozeman, Montana, USA; www.goldenhelix.com).

Segregation analysis was performed via Sanger sequencing in family members of both families. The GeneMatcher tool allowed the identification of the two families.

### Homozygosity mapping

Due to the known parental consanguinity, homozygosity mapping was performed using AutozygosityMapper, an updated version of HomozygosityMapper. For homozygosity mapping, a joint variant calling was performed on the BAM files of the two individuals (A-II-1 and B-II-1). The resulting VCF file was analysed by AutozygosityMapper using the default settings. Different shared homozygous regions could be detected. Genome-wide runs of homozygosity and the genotypes surrounding the ATP9A gene are shown in online supplemental figure S1.

### Dermal fibroblasts, splice site analysis and mRNA expression

For RNA extraction, cells from the affected individuals and controls were seeded in a confluent status of 2 × 10^5 cells per well. After 3 days, cells were lysed in TRI Reagent, and total RNA was prepared using Direct-zol RNA Miniprep Kit (Zymo Research). Total cDNA was reverse transcribed by RevertAid H Minus First Strand cDNA Synthesis Kit (Fermentas). Quantitative PCR (qPCR) was performed using EVAGreen (Solis BioDyne) on a QuantStudio V3 Real-Time-PCR System (Thermo Fisher Scientific). ATP9A, ARPC3 and SNX3 expression levels were measured using the comparative C\text{\text{ }}, method in comparison to GAPDH. Primer sequences for qPCR and reverse transcription PCR (RT-PCR) are provided in online supplemental tables S1 and S2.

To analyse the consequence of the splice site variant in B-II-1, RT-PCR amplicons were Sanger sequenced.

### RESULTS

#### Clinical report

In this study, we report on three affected individuals from two unrelated, consanguineous families. The clinical features of the affected individuals are summarised in table 1 and illustrated in figure 1A.

**Proband A-II-1** was delivered at term by C-section after an uneventful pregnancy as the first child of healthy consanguineous Syrian parents. Birth parameters were not available. The boy showed psychomotor developmental delay and growth retardation. He was able to speak his first words at the age of 18 months and walked unaided at 24 months. Microcephaly was first documented at the age of 7 years when the family moved to Germany. The ophthalmic evaluation showed visual impairment with hyperopia and astigmatism. X-ray examination of the hand showed a delayed bone age. A developmental test (Snijders-Oomen non verbal-R2-7) at 8 years of age revealed a score in the range of 50–60, representing mild ID. He attends a special needs school. Parents reported frequent emesis and epigastric pain. Esophagogastroduodenoscopy (EGD) at the age of 11 years and 5 months revealed antrum gastritis. Although Helicobacter pylori eradication therapy was initiated, recurrent vomiting continued. At the last physical examination (12 years and 5 months), he showed deficits in coordination and fine motor skills. Furthermore, he had attention deficit, motor restlessness and sleep disturbance. Anthropometric measurements were as follows: weight, 26.3 kg (−2.95 SD); length, 125 cm (−3.71 SD); and head circumference (OFC), 49.5 cm (−3.10 SD). An MRI of the brain, performed at 11 years, was normal. Karyotype, array CGH and transferrin electrophoresis were unremarkable, thus excluding congenital disorders of glycosylation (CDG syndromes).

**Proband A-II-2** is the third child of family A. He was born at term by C-section. Apgar scores were 9/10/10. Birth measurements were normal: weight, 3492 g (0.36 SD); length, 56 cm (2.08 SD); and OFC, 34.5 cm (−0.33 SD). Microcephaly was first documented at the age of 6 weeks. Echocardiography revealed an atrial septal defect (ASD) II and a left ventricular...
Table 1 Clinical features of affected individuals with biallelic ATP9A pathogenic variants

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Proband</th>
<th>HP:0002360</th>
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<tbody>
<tr>
<td>Gender</td>
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<td>Male</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>125 cm</td>
<td>121 cm</td>
</tr>
<tr>
<td>Weight (kg)</td>
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<td>Neurodevelopment</td>
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<tr>
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<td>+</td>
</tr>
<tr>
<td>Speech delay</td>
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<td>+</td>
</tr>
<tr>
<td>Fine motor impairment</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
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<td>+</td>
<td>+/−</td>
</tr>
<tr>
<td>ID, severe HP:0010864</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Sleep disturbance HP:0002360</td>
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<td>−</td>
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</table>

Table 1 Continued

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<th>Delayed myelination</th>
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<th>n.d.</th>
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<tr>
<td>Nausea and vomiting</td>
<td>+</td>
<td>+</td>
<td>+/−</td>
</tr>
<tr>
<td>Gastro-esophageal reflux</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Failure to thrive HP:0001508</td>
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</table>

ATP9A (NC_000020.1, NM_006045.3, NP_006036.1) genotypes and variant description

gDNA | g.50292679G>A | g.50310546C>T |
|------|---------------|---------------|
cDNA | c.868C>T      | c.642+1G>A    |
| RNA  | n.a.          | r.547_642del (exon7) |
| Protein p.(Arg290*) | p.(Ser184Profs*16) |
| Genotype | Homozygous | Homozygous |
| gnomAD frequency | Absent | Absent |

+ indicates presence; − indicates absence; +/- means features might be present.

HP: Helicobacter pylori; ID: intellectual disability; n.a., not applicable; n.d., not determined; OFC, head circumference.

The boy was born at 41+2 weeks of gestation by C-section with polyhydramnios. Polyhydramnios was diagnosed in pregnancy. The boy was noted to have severe cognitive impairment. At the age of 1 year, OFC was 43.3 cm (−3.01 SD). At the age of 9 years and 7 months, his body height was 120.8 cm (−3.10 SD); his weight was 19.6 kg (−4.01 SD); and his OFC was 48 cm (−3.33 SD). Weekly emesis and feeding difficulties due to gastritis despite therapy with proton-pump inhibitors persisted.

Proband B-II-1 is the first child of consanguineous parents of Turkish descent. Polyhydramnios was diagnosed in pregnancy. The boy was born at 41+2 weeks of gestation by C-section with a weight of 3570 g (−0.41 SD), a length of 50 cm (−1.37 SD) and an OFC of 34 cm (−1.47 SD). Apgar scores were 9/10/10. In the first weeks of life, the boy suffered from oral thrush. In the first year, insufficient weight gain was noted because of severe oesophageal reflux and a fundoplication was performed with 10 months and repeated with 15 months due to a paraesophageal hernia. Tube feeding was necessary for the first years of life and in the further course, a gastrostomy was placed. MRI of the brain at the age of 9 months showed a mild delay of myelination, mild widening of the temporofrontal ventricular system, and mild hypoplasia of the corpus callosum and the vermis. Hypotonia and motor delay were diagnosed in infancy. Sitting was achieved at 10 months, independent walking at about 2.5 years. He was noted to have severe cognitive impairment. At the age of 9 years and 7 months, his body height was 120.8 cm (−3.10 SD); his weight was 19.6 kg (−4.01 SD); and his OFC was 48 cm (−3.33 SD). Weekly emesis and feeding difficulties due to gastritis despite therapy with proton-pump inhibitors persisted.
He used only single words. Excessive salivation was treated with scopolamine. He showed mild scoliosis, foot malposition, a high palate, a long face with a smooth philtrum, and thin upper lip vermilion. Chromosomal analysis, array CGH and transferrin electrophoresis revealed normal results. His younger sister showed normal development.

ES and cosegregation

ES in individual A-II-1 revealed a homozygous variant in exon 10 of ATP9A (NM_006045.3:c.868C>T, NC_000020.10:g.50310546C>T) (figure 1B). Sanger sequencing confirmed homozygosity for the variant in the affected brother (A-II-2) and showed that the unaffected sister and the parents are heterozygous carriers (figure 1B).

Homozygosity mapping

These rare ATP9A variants map within a homozygous block of 4.42 Mb (chr20[GRCh37]:46279866–50705211) in the affected individual A-II-1 and 7.46 Mb (chr20[GRCh37]:47686723–55151240) in the affected individual B-II-1 (online supplemental figure S1), likely resulting from identity by descent due to parental consanguinity.

Splicing analysis

Direct sequencing of RT-PCR amplicons confirmed the loss of this splice site affected by the variant c.642+1G>A, resulting in skipping of exon 7 (figure 2A). This is predicted to result in a frameshift and premature stop of translation p.(Ser184Profs*16).

mRNA expression of ATP9A and interacting genes

We measured the ATP9A expression levels in dermal fibroblasts of individual A-II-2 and individual B-II-1 by qPCR, which revealed the downregulation of ATP9A mRNA expression down to 14% in cells of A-II-2 and to 4% in B-II-1 (figure 2B). In conclusion, both variants resulted in almost absent ATP9A mRNA expression in both affected individuals.

Previously, ATP9A knockdown experiments in HepG2 cells resulted in an increased gene expression of ARPC3 and downregulation of CORO1A.23 Furthermore, in HEK293T cells, ATP9A, MON2 and DOP1B have been shown to form a complex binding...
Microcephaly is a common feature of POM syndromes and can either be primary (i.e., congenital) or secondary to SNX3, a regulator of endosomal trafficking. We checked RNAseq data available from multiple control fibroblast lines for expression levels of the aforementioned putative interaction partners of ATP9A and verified them using qPCR. Unfortunately, CORO1A, DOP1B and MON2 are only poorly expressed in human fibroblasts (data not shown). Hence, we could only measure relative ARPC3 RNA expression, which was increased by 1.8-fold in individual A-II-2 and 1.5-fold in cells of individual B-II-1 (figure 3A), and SNX3 expression, which was increased by 1.5-fold in individual A-II-2 and 1.3-fold in individual B-II-1 (figure 3B).

DISCUSSION

Our study identified homozygous loss-of-function variants in ATP9A as the cause of a novel neurodevelopmental disorder associated with NDD/ID, POM, failure to thrive and gastrointestinal symptoms. Complex neurodevelopmental and behavioural disabilities, including poor fine motor skills, restricted expression of language, attention deficit, hyperactivity and abnormal sleep patterns are common features in children with POM. The affected individuals in this study displayed NDD/ID and POM of variable degrees. Individuals A-II-1 and A-II-2 had mild ID, whereas individual B-II-1 was severely affected. Individuals A-II-1 and A-II-2 showed impaired fine motor skills, an attention deficit, hyperactivity and sleep disturbances. All three patients had feeding difficulties in infancy, showed gastrointestinal abnormalities,33 cranial MRI signs and hyperactivity (MIM: 613192).37 In contrast to other syndromes associated with POM, we observed no impairment of ambulation, no movement disorder (ataxic gait and stereotypies) or epilepsy in our patients.

Notably, in the recently published Mouse Organogenesis Cell Atlas, sci-RNA-seq3 measured particularly strong expression of At9p9a in excitatory, inhibitory, granule and postmitotic premature neurons (online supplemental figure S2).41 At9p9a+/− mice show hyperactivity and attention deficit and thus resemble the neurobehavioural disabilities of the individuals reported here (www.mousephenotype.org).42 In this context, we demonstrate that the variants identified in the probands are also loss-of-function variants: the variant c.868C>T, detected in family A, causes a premature stop codon in exon 10. mRNA expression determined by qPCR was reduced by >85% in the affected individual A-II-2 compared with controls. The splice variant c.642+1G>A in family B leads to skipping of exon 7, resulting in a frameshift and the creation of a premature stop codon. Nearly absent mRNA expression in cells harbouring one of the described homozygous variants is likely due to nonsense-mediated mRNA decay. No antibody against endogenous ATP9A is available, a problem that has already been addressed by other researchers. Therefore, we cannot rule out the possibility that some mutant protein is still produced. However, both premature stop codons would presumably result in a truncated protein lacking many functional domains (figure 2C).

ATP9A is mainly expressed in neuronal cells (online supplemental figure S3), but there is still limited knowledge about the subcellular localisation and physiological function of endogenous ATP9A in humans. In HeLa cells, overexpressed ATP9A localises to the early/recycling endosomes and is crucial for the endocytic recycling of the transferrin receptor and glucose transporters 1 from the endosome to the plasma membrane. Recently, Jyoti Naik and colleagues demonstrated that shRNA-mediated ATP9A knockdown in HepG2 cells resulted in enhanced exosome release and structural changes of actin fibres. It is speculated that this is secondary to induced ARPC3 and reduced coronin1A activity as well as to altered actin nucleation.23 We could only study the expression of ARPC3 because CORO1A is not sufficiently expressed in fibroblasts. Our qPCR data also show a significant upregulation of ARPC3 in fibroblasts of individuals A-II-2 and B-II-1 (figure 3A), supporting the hypothesis that ATP9A impacts the endocytic recycling of proteins that regulate cytoskeletal structures such as the docking sites of multivesicular late endosomes.
ATP9A, MON2 and DOP1B form an evolutionarily conserved endosome associated complex and interact with the SNX3-retromer, which orchestrates vesicular trafficking within the endosomal network. Because MON2 and DOP1B are not adequately expressed in fibroblasts, we studied SNX3 expression, which was also shown to be upregulated in the fibroblasts of the subjects of this study (figure 3B). Thus, our data provide further evidence that ATP9A is functionally involved in the regulation of the endocytic system. We hypothesise that loss of ATP9A impairs diversifying secretory routes, which would be in line with previous reports. It remains unclear whether ATP9A is localised to a specialised microdomain of early and recycling endosomes and whether ATP9A actively participates in translocation of phospholipids. Thus, the role of ATP9A in membrane composition and its involvement in vesicular transport carrier formation and exosome release needs to be further elucidated. For further studies, the examination of neuronal tissue (mice or induced pluripotent stem cell)erived) would be beneficial.

In conclusion, this work describes a novel neurodevelopmental disorder caused by biallelic truncating variants in ATP9A. Identification of further individuals affected by pathogenic variants in this gene will help to expand the molecular and phenotypical spectrum of this disorder.

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