

Novel truncating variants in *FGD1* detected in two Danish families with Aarskog–Scott syndrome and myopathic features

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Abstract

Aarskog–Scott syndrome (AAS) is a developmental disorder, caused by disease-causing hemizygous variants in the *FGD1* gene. AAS is characterized by dysmorphic features, genital malformation, skeletal anomalies, and in some cases, intellectual disability and behavioral difficulties. Myopathy has only been reported once in two affected siblings diagnosed with AAS. Only few adult cases have been reported. This article reports four adults with AAS (three male cases and one female carrier) from two unrelated Danish families, all males presented with variable features suggestive of myopathy. All four carried novel hemizygous pathogenic variants in the *FGD1* gene; one family presented with the c.2266dup, p.Cys756Leufs*19 variant while the c.527dup; p.Leu177Thrfs*40 variant was detected in the second family. All males had some mild myopathic symptoms or histological abnormalities. Case 1 had the most severe myopathic phenotype with prominent proximal muscular fatigue and exercise intolerance. In addition, he had multiple deletions of mtDNA and low respiratory chain activity. His younger nephew, case 3, had difficulties doing sports in his youth and had a mildly abnormal muscle biopsy and relatively decreased mitochondrial enzyme activity. The singular case from family 2 (case 4), had a mildly myopathic muscle biopsy, but no overt myopathic symptoms. Our findings suggest that myopathic involvement should be considered in AAS.

KEYWORDS

Aarskog–Scott syndrome, adulthood, developmental disorder, *FGD1*, mitochondrial myopathy

1 | INTRODUCTION

Aarskog–Scott syndrome (AAS) is inherited by an X-linked trait (OMIM#305400) and is caused by hemizygous disease-causing variants in the FYVE, RhoGEF, and PH domain containing 1 (*FGD1*) gene

(OMIM#300546) (Orrico et al., 2004). AAS is characterized by short stature, dysmorphic features, genital malformation, and skeletal anomalies. In some cases, intellectual disability and behavioral difficulties have been reported (Orrico et al., 2004; Pasteris et al., 1994; Teebi et al., 1993; Zanetti Drumond et al., 2021). Female carriers have

Abbreviations: AAS, Aarskog–Scott syndrome; COX, cytochrome c oxidase; EMG, electromyography; ENG, electrical neurography; *FGD1*, faciogenital dysplasia protein; MRI, magnetic resonance imaging; MRC, Medical Research Council; mtDNA, mitochondrial DNA; PCR, polymerase chain reaction; SCR, succinate cytochrome c reductase; SDH, succinate dehydrogenase.

Allan Bayat and Bjørg Krett contributed equally to this study.

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milder features (Orrico et al., 2010; Teebi et al., 1993). Clinical features are easily confused with those of a number of other complex syndromes including Noonan syndrome and Robinow syndrome (Bae et al., 2020; Ge et al., 2017). Genetic testing should be performed in order to reach a definite diagnosis of AAS.

According to the Leiden Open Variation Database, 54 AAS cases with a genetic diagnosis have been reported (<https://databases.lovd.nl/shared/genes/FGD1>). Therefore, our knowledge about the phenotypic spectrum in AAS remains limited. Myopathic symptoms have only been described once (Al-Semari et al., 2013).

In this case series, we describe three adult AAS cases, with varying severity of disease, and one female carrier from two unrelated Danish families. We describe myopathic features and mitochondrial changes, which may be an additional phenotypic feature of AAS.

2 | METHODS

All cases were seen at our clinic and underwent clinical examinations. Clinical records were reviewed for congenital anomalies, developmental history, and signs of myopathy. Further medical information was collected by interviewing families.

All cases underwent muscle biopsy. We performed PCR of mitochondrial DNA (mtDNA) on biopsies and assessed them for mitochondrial complex I-IV and citrate synthase activities. Muscle biopsies were histologically examined and stained for cytochrome c oxidase (COX), succinate dehydrogenase (SDH), combined COX/SDH, hematoxylin and eosin (H&E), Gomori trichrome, Oil Red, Myosin heavy chain-slow and-fast.

Peripheral blood DNA was used for sequence analysis of the coding regions of the *FGD1* gene using standard Sanger sequencing according to routine diagnostic protocols. NM_004463.3 was used as reference sequence. Peripheral blood DNA from proband in family 1 was subsequently exom-sequenced to assess for potential additional genetic predispositions.

3 | CASE PRESENTATION

We identified four adults with pathogenic variants in the *FGD1* gene. Three male cases and one female carrier. The cases belonged to two unrelated Danish families with Aarskog-Scott syndrome. Figure S1, Supporting Information shows the pedigrees of the two affected families.

3.1 | Case 1: Proband, family 1

The proband of family 1, a 57-year-old man, was referred to our hospital due to muscular complaints. Two years before, he developed constant pain from muscles and joints, especially affecting proximal muscles in the lower extremities and hip and knee joints bilaterally. Symptoms were not responsive to mild analgesic drugs such as

paracetamol and ibuprofen and were triggered by everyday physical activity but were also noticeable at rest. He had left-sided tinnitus and intermittent left-sided headache. There was no history of seizures, stroke, or stroke-like episodes. He was on no medication. At birth he was diagnosed with bilateral ptosis. Orchiopexy for bilateral cryptorchidism was performed when he was 2 years old. His intellectual performance at school was reduced due to a learning disability including challenges with reading and writing. No data were available on developmental milestones nor on any formal cognitive assessments carried out during childhood. He attended a special needs class, finished primary school, and never received a formal education; subsequently, he has been employed as an unskilled worker.

On physical exam, his height was 167 cm (−2.2 SD) and his weight was 74 kg (0 SD). He had a broad nasal bridge, widely spaced eyes, prominent forehead, and a wide philtrum (Figure 2a–c). His hands were small and broad with brachydactyly and interdigital webbing (Figure 2d). Hyperextension of the proximal interphalangeal joint and flexion of the distal interphalangeal joint were observed. He had ulnar neuropathy on the left hand, following a complex arm fracture. Medical Research Council (MRC) muscle strength assessment was normal. There was no shawl scrotum. Ophthalmologic evaluation revealed external ophthalmoplegia and ptosis but no sign of pigmentary retinopathy, nystagmus, or renal vessel tortuosity. Magnetic resonance imaging (MRI) of the central nervous system was normal. MRI of lower extremities did not show fat replacement of muscles, atrophy, or edema. Electroneurography and electromyography, echocardiography, and creatine kinase levels were normal.

A novel hemizygous, likely pathogenic, truncating variant was detected in exon 15 of the *FGD1* gene (c.2266dup, p.Cys756Leufs*19, NM_04463.3). He also carried a rare heterozygous frameshift variant in the patatin-like phospholipase domain-containing protein 2 gene (*PNPLA2*); (NM_020376.4) c.798del, p.(Ala267Profs*53). This variant is not reported in ClinVar (Landrum & Kattman, 2018) and has an allele frequency of 0.000008692 (2/230108) in The Genome Aggregation Database (Karczewski et al., 2020). Biallelic pathogenic variants in *PNPLA2* are associated with neutral lipid storage disease (NLS), an autosomal recessive disorder characterized by severe accumulation of triglyceride cytoplasmic droplets in several tissues including muscles (Janssen et al., 2013). Muscle biopsy showed multiple COX-negative fibers and weakly stained fibers in SDH, indicating relative mitochondrial depletion (Figure 2a,b). No triglyceride droplets were seen in oil red stain. He was also found to have multiple mtDNA deletions at a higher load than expected for age (mtDNA from muscle tissue). In accordance with the apparent mitochondrial depletion on COX and SDH stains, mitochondrial complex activities for complexes I and IV were also decreased when compared to the citrate synthase activity (Table 1).

3.2 | Case 2: Family 1

A 74-year-old woman, sister to case 1 and mother to case 3, was a carrier of the familial *FDG1* variant. She had no comorbidities. Fifteen

TABLE 1 Mitochondrial complex I-IV and citrate synthase (CS) activities

	Reference	Case 1	Case 2	Case 3	Case 4	Unit
I/CS	0.19–0.54	0.14*	0.31	0.13*	0.39	mU/mU
II/CS	0.24–0.5	0.23*	0.38	0.26	0.38	mU/mU
SCR/CS	0.19–0.72	0.21	0.39	0.23	0.37	mU/mU
III/CS	0.72–2.14	0.67*	1.32	1.08	1.7	mU/mU
IV/CS	2.2–5	2.2	4.3	2.1*	3.6	mU/mU

Note: Asterisk (*) denotes results outside reference values.

Abbreviation: SCR, succinate cytochrome c reductase.

years earlier, she experienced symptoms indicative of acute inflammatory demyelinating polyradiculitis, but had full remission in the year after.

Clinical examination showed a widow's peak and downslanting palpebral fissures (Figure 2e–g). She had no other dysmorphic signs of AAS. Neurologic examination, muscle strength, muscle biopsy findings and mitochondrial complex and citrate synthase activities were all normal. She also carried the c.2266dup, p.Cys756Leufs*19 variant.

3.3 | Case 3: Family 1

A 38-year-old man was nephew to the proband and the son of case 2. He was unemployed but had done physically strenuous work most of his life. He previously underwent surgery for a cleft lip and palate and for maldescent of testis. Despite not having a growth hormone deficiency, he was treated with such until 13 years of age due to his short stature. The treatment was stopped as it did not improve the growth velocity. He experienced a mild learning disability with spelling difficulties in school. He found it difficult to participate in physical activities during his youth. He is currently on no medication.

On physical exam, height was 1.62 cm (–3.0 SD), weight 59.7 kg (–1.7 SD) and he presented with widely spaced eyes, mild ptosis, downslant palpebral fissures, low set ears, short philtrum, high palate, and mild dysarthria (Figure 1i–k). Extremities showed brachydactyly and interdigital webbing. No scrotal shawl or inguinal hernia. Muscle bulk, MRC strength assessment, and general neurologic exam were normal. He also carried the c.2266dup, p.Cys756Leufs*19 variant. Muscle biopsy showed central nuclei and few COX-negative fibers (Figure 2c,d). Mitochondrial enzyme activities corrected for citrate synthase activity were moderately decreased for complexes I and IV (Table 1). There were no mtDNA deletions.

3.4 | Case 4: Family 2, proband

Case 4 was a 47-year-old man unrelated to family 1. He receives no medication and works at a protected institution, due to mild intellectual disability. He reported no issues doing physical activities and regularly runs 25–30 km. He underwent operation for maldescent of testes and multiple operations for inguinal hernia bilaterally.

On physical exam, his height was 159 cm (–3.4 SD) and he weighed 64 kg (–1.1 SD). Through childhood he had very short stature, and at 9 years of age his height was 4 SDs below normal. His features are characteristic of Aarskog–Scott syndrome with widely spaced eyes, flat nasal bridge, low set ears, broad hands and feet, single transverse palmar crease, and sandal gap bilaterally. He has a mild shawl scrotum and has been myopic since childhood (–5.5/–5.5) but otherwise with normal ophthalmological evaluation.

A truncating likely pathogenic variant was detected in *FGD1* (c.527dup, p.Leu177Thrfs*40). His muscle biopsy showed a higher prevalence of type 1 fibers and few COX-negative fibers (Figure 2e). Mitochondrial enzyme complexes and citrate synthase activities were normal.

4 | DISCUSSION

We present three adult men with AAS and a female carrier from two unrelated families, affected by two novel likely pathogenic *FGD1* variants and describe mitochondrial anomalies and myopathic features in the cases. All cases showed classic presentations of AAS with dysmorphic features and short stature.

Previous reports on cases with AAS have shown the majority of *FGD1* variants to be unique within families; no variant hotspots or common variants have yet been recorded for this disease (Orrico et al., 2004). Lists of disease-causing variants of the *FGD1* can be found at Leiden Open Variation Database (<https://databases.lovd.nl/shared/genes/FGD1>) and Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff (<http://www.hgmd.cf.ac.uk/ac/index.php>). According to ClinVar, 156 pathogenic and 14 likely pathogenic variants affecting the *FGD1* gene have been characterized (Landrum & Kattman, 2018). These comprise nine missense variants, 10 frameshift variants, 10 nonsense variants, four splice site variants, one in-frame deletion and 75 large-scale deletions. No definite genotype–phenotype correlation is apparent from comparison of cases with different variants (Orrico et al., 2004; Orrico et al., 2015).

The *FGD1* gene encodes the FGD1 protein, a guanine nucleotide exchange factor that activates the Rho GTPase Cdc42 (3,10) and may also affect growth control and nuclear signaling (Whitehead et al., 1998). *FGD1* and *CDC42* together, influence cell growth, cell cycle progression and transcription (Whitehead et al., 1998). Hence, a deficient *FGD1* with such extensive cellular functions may



FIGURE 1 Clinical presentation of cases 1–4: Case 1 (a–d) shows a broad nasal bridge, widely spaced eyes, prominent forehead, and low set ears. His hands were small and broad, with brachydactyly and interdigital webbing; case 2 (e–h) notice widow's peak; case 3 (i–l); case 4 (m–p) shows a broad nasal bridge, widely spaced eyes and low set ears. He had a sandal gap. His hands were small and broad with bilateral single transverse palmar creases

theoretically cause oxidative stress, which has been shown to cause secondary mitochondrial dysfunction or destabilization of other cellular functions leading to mitochondrial dysfunction (Schwartz et al., 2000).

Among our AAS cases, all cases had some mild myopathic symptoms or histological abnormalities. Thus, case 1 had the most severe myopathic phenotype with prominent muscular fatigue and exercise intolerance. In addition, he had multiple deletions in mtDNA and low

respiratory chain activity. His younger nephew, case 3, had difficulties doing sports in his youth and had a mildly abnormal muscle biopsy and relatively decreased mitochondrial enzyme activity. The singular case from family 2 (case 4), had a possibly myopathic muscle biopsy, but no overt myopathic symptoms. Hence, the AAS cases seen at our center displayed varying degrees of myopathic pathology.

Biallelic variants in *PNPLA2* lead to NLSD while carriers commonly have no organ involvement; a few carriers have been reported to have

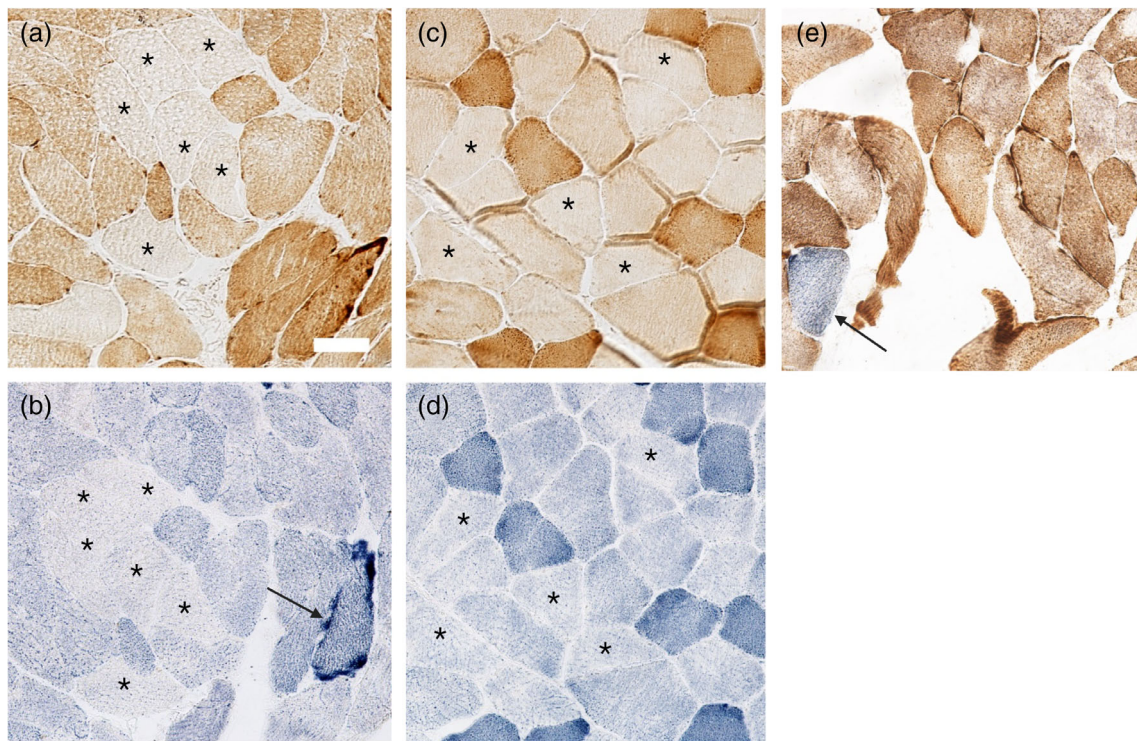


FIGURE 2 (a, b) Muscle biopsy from case 1 where the cytochrome oxidase (COX) stain shows high prevalence of type 1 fiber, multiple COX-negative fibers (asterisks) and a few ragged blue fibers (arrow), which is in accordance with the succinate dehydrogenase (SDH) stain also showing weak staining (asterisks), indicative of relative mitochondrial depletion. (c, d) Muscle biopsy from case 3, COX stain shows normal staining of type 1 fiber and faint staining of type 2 fiber, which is also seen in the SDH stain (asterisks), indicating a relative mitochondrial depletion. H&E stain (not shown here) showed central nuclei. (e) COX/SDH stain from case 4, showing a COX-negative fiber that turns blue (arrow)

muscle weakness, episodes of muscle pain and significant neutral lipid storage in muscle (Janssen et al., 2013). Case 1 was a carrier but had no lipid accumulation in his muscle biopsy. Although we cannot rule out that the heterozygous *PNPLA2* could contribute to his phenotype, this variant is less likely to explain the mitochondrial dysfunction.

Myopathic laboratory findings have previously been reported in one AAS family published in 2013 with a nonsense variant in exon 6 (Al-Semari et al., 2013). In that report, two children had muscle biopsies showing increased subsarcolemmal staining of mitochondria and the authors argued that while the findings were not diagnostic, they were suggestive of a mitochondrial myopathy. They did not find any respiratory chain defects and did not report any myopathic symptoms.

Myopathic symptoms in AAS may be somewhat age dependent. Many AAS cases have ptosis, but few report other signs of myopathy. The prominent myopathic symptoms of case 1, started at age 55 years. The other two male AAS cases, aged 38 and 47, have somewhat abnormal histology and mitochondrial enzyme activity, but they did not report significant myopathic symptoms. Previously published reports of AAS have mainly included children and very few adults older than 30 years (Al-Semari et al., 2013; Altincik et al., 2013; Aten et al., 2013; Bedoyan et al., 2009; Bottani et al., 2007; Lebel et al., 2002; Orrico et al., 2004; Orrico et al., 2007; Pilozi-Edmonds et al., 2011; Ronce et al., 2012; Schwartz et al., 2000; Verhoeven et al., 2012). Myopathic symptoms, which emerge in older AAS cases,

may be caused by a secondary mitochondrial dysfunction, because of increased cumulative mtDNA damage. This may possibly explain the lack of reported myopathy among AAS cases, as reported cases have been relatively young and not yet cumulated sufficient mtDNA damage to reach a symptomatic threshold. It is also likely that since few cases undergo muscle biopsy, cases of asymptomatic myopathic histology in younger AAS cases, may not have been recognized. Lastly, myopathic symptoms may be unspecific and easily overlooked in older cases. There is already one previously published AAS family with reported myopathy and we found myopathic pathology in two unrelated families. Therefore, it is possible that the reported mitochondrial pathology is associated with AAS.

5 | CONCLUSION

Based on our findings, we suggest that mitochondrial dysfunction could be responsible for some of the symptoms in AAS. None of our cases fulfill the criteria for a definite diagnosis of a respiratory chain disorder (Bernier et al., 2002). However, we report unspecific mitochondrial and myopathic symptoms that are backed by histological, enzymological and molecular pathologic findings, which seem to suggest that myopathy and mitochondrial dysfunction may be considered in AAS, especially in older cases.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

John Vissing and Allan Bayat contributed to the initialization of the study. John Vissing, Pernille Mathiesen Tørring, Morten Dunø, and Allan Bayat performed clinical examination and laboratory investigations. The article was drafted by Bjørg Krett. All authors have approved the final article.

DATA AVAILABILITY STATEMENT

Data concerning the published participants are available upon request.

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SUPPORTING INFORMATION

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