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RESEARCH LETTER

Phenotypic expansion of *ARSK*-related mucopolysaccharidosis

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Mucopolysaccharidosis (MPS) are monogenic, multisystem disorders resulting from enzymatic defects in the degradation of glycosaminoglycans (GAGs). Although each of the 11 MPS subtypes is linked to a specific enzyme deficiency, phenotypic overlap is considerable. Recently, a 12th disorder, MPS type X, due to biallelic variants in the arylsulfatase K gene (*ARSK*) was reported (Verheyen et al., 2021). We describe herein two additional affected sibs and expand the phenotype.

The younger individual (Individual 1) was noted to have a waddling gate as a toddler. At presentation at age 7 years, he complained of stiffness and pain in his legs, and was diagnosed with Legg-Calvé-Perthes disease (LCPD). He experienced increasing pain in his hips, thighs, knees, legs, hands, and back. Radiographic changes in his hips were visible by age 7 years. Additional diagnostic suggestions at that time were multiple epiphyseal dysplasia or Meyers dysplasia. Assessment by a multispecialist skeletal dysplasia clinic at age 8 years 5 months concluded that he might have a MPS given his increasing symptoms as well as his similarly affected sibling. Radiological changes were not present in the hand of Individual 1 at age 2 years, but at age 8 years 5 months several carpal bones were either not ossified or small for his age. Lack of ossification of some carpal bones and osteonecrosis of the femoral heads were suggestive of a mild MPS (Figure 1).

The 2 years older sibling (Individual 2) complained of pain in her knees, thighs and hips from age 9 years. By age 10 years, she had developed pain in her legs, ankles, and back. Initial imaging showed slight anterior wedging of her vertebrae and lack of ossification of carpal bones, in keeping with a tentative diagnosis of MPS. Both individuals used paracetamol for pain.

On repeated analyzes, urinary GAG quantitation by dimethyl methylene blue (DMB) test was slightly increased in both children. Thin layer chromatography showed a normal glycosaminoglycan profile.

Morquio disease, MPS type IVA, was suspected, but both children had normal serum levels of galactose-6-sulfatase and beta-galactosidase. Whole exome sequencing for the sibs and their parents was initially performed assuming that the father was affected due to longstanding complaints of stiffness in his joints. When no molecular cause was detected, the variant data were re-interpreted with both parents considered unaffected. Both children were homozygous, and both parents heterozygous, for a predicted stop variant in *ARSK*, NM_198150.3:c.1251C > G p.(Tyr417*). The variant is located in the penultimate exon and is predicted to target ARSK-mRNA to nonsense-mediated decay. Urinary GAG excretion in both sibs assessed by HPLC-MS/MS (liquid chromatography–tandem mass spectrometry) analysis detected a threefold increase of dermatan sulfate (DS) while heparan sulfate (HS) was slightly above the upper reference range in Individual 2. The increased DS level is similar to that described in two of four individuals in the original report of MPS type X (Verheyen et al. 2021).

Clinical findings in the two children we describe and in the original report are summarized in Table 1. In contrast to the two

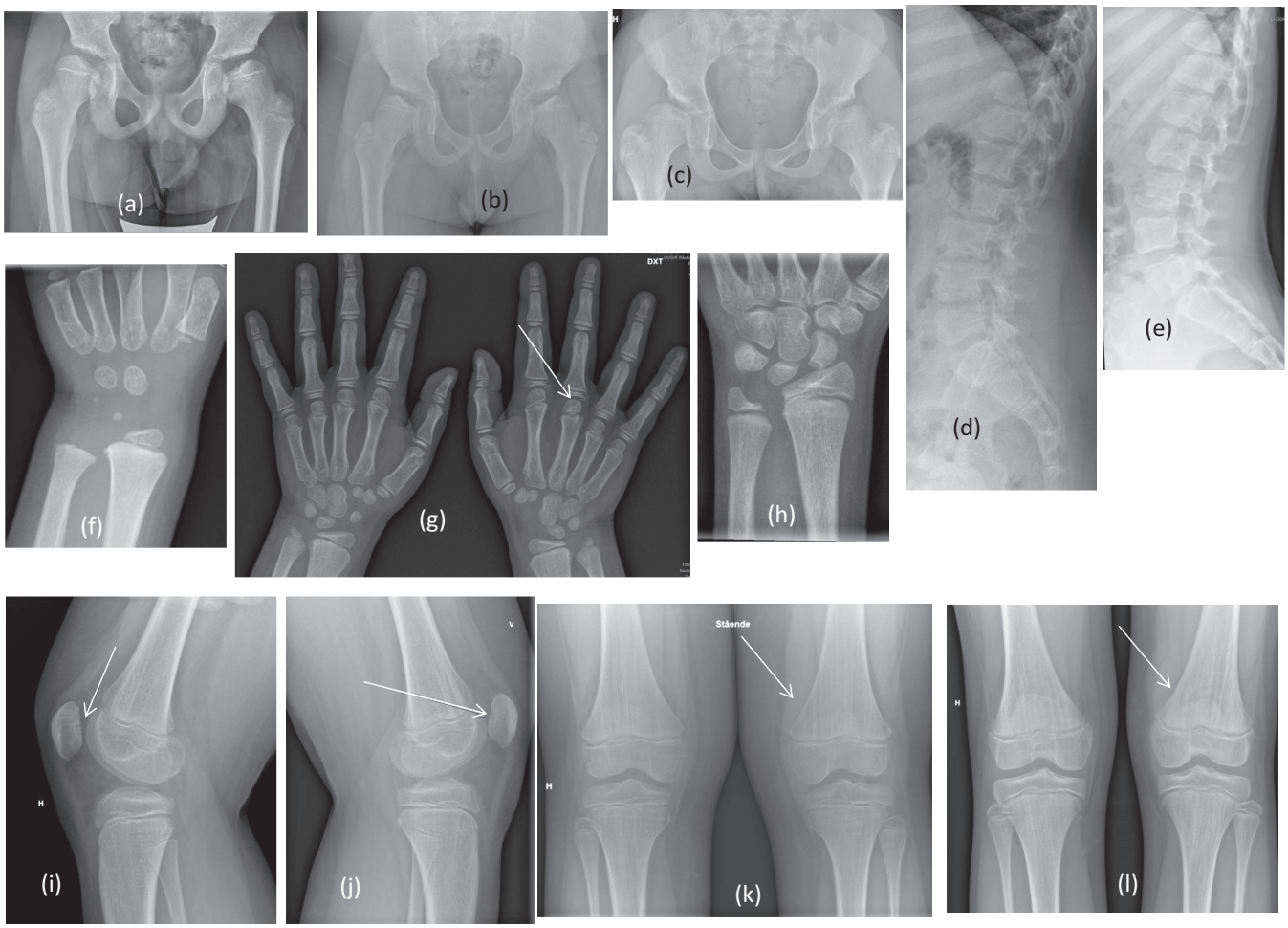

FIGURE 1 Sector-shaped osteonecrosis of femoral heads are seen in Individual 1 at age 7 years (a), 9 years (b), and in Individual 2 at age 10 years (c). Slight anterior wedging of vertebrae in Individual 1 at age 9 years (d) and in Individual 2 at age 10 years (e). Normal wrist in Individual 1 at age 2 years (f), defective ossification of carpals in Individual 1 at age 9 years (g), and at age 11 years in Individual 2 (h). In Individual 1, osteochondral lesions of metacarpal heads are visible (g). Osteochondral lesions of both patellae at age 9 years in Individual 1 (i, j). Vertical striae in the metaphyses in Individual 1 at age 9 years (k) and in Individual 2 at age 10 years (l)

individuals described by Verheyen et al. for whom data are available, the sibs we report were normocephalic at birth, and did not have recurrent ear infections or sleep apnea as young children. Furthermore, at age 9 years 5 months and at 11 years, respectively, they did not have coarse facial features or short stature, and were not disproportionate. The individuals we report are younger than those reported previously (ages 14–18), which might explain the absence of short stature, a disproportionally short trunk, and coarse facies.

Both children have slightly hypomineralized enamel on their permanent teeth. The older sibling had several teeth extracted due to enamel defects and has hypoplasia of a permanent incisor (an enamel pit). Defective enamel might be a feature of MPS type X, analogous to what is seen in MPS type IV (Barker & Welbury, 2000; Ribeiro et al., 2015).

Both children had hypermobile interphalangeal finger joints, which is also a feature of MPS type IV (Raff & Byers, 1996).

Both individuals have vertical striae in the metaphyses similar to those described by Verheyen et al., but noted at an earlier age (Figure 1). Osteochondral lesions were present in the dorsal aspect of the patellae in Individual 1 and in some metacarpal heads. Similar lesions were seen in the metatarsals of Individual 2 (not shown), this may be a distinguishing feature of MPS type X.

In conclusion, the two individuals described herein illustrate that short stature, a short trunk and coarse facies are not necessarily present in young children with MPS type X. A waddling gait and joint pain, accompanied by skeletal radiological changes resembling mild MPS warrants examination for *ARSK*-related MPS. Normal urinary GAG quantitation does not rule out the diagnosis (Verheyen et al., 2021). As in the four previously published individuals, MPS was suspected, though one of the children we report was originally thought to have LCPD. Bilateral LCPD should result in considering the possibility of MPS type X as well as other MPS subtypes (Mendelsohn et al., 2013). The diagnosis of MPS type X allows for tailored cardiac, ophthalmologic and audiological surveillance, and can inform genetic counseling.

TABLE 1 Phenotype and genetic variants of individuals with *ARSK* deficiency

Individuals described in Verheyen et al.					Individuals described in this research letter	
Genetic variants and phenotype of individuals with *ARSK* deficiency, table adapted from Verheyen et al. 2021						
Variant in *ARSK*	Subject 1	Subject 2	Subject 3	Subject 4	Individual 1	Individual 2
	c.250C > T, p.(Arg84Cys), homozygous NM_198150.2	c.250C > T, p.(Arg84Cys), homozygous NM_198150.2	c.560 T > A, p.(Leu187Ter), homozygous NM_198150.2	c.560 T > A, p.(Leu187Ter), homozygous NM_198150.2	c.1251C > G, p.(Tyr417*) homozygous NM_198150.3	c.1251C > G, p.(Tyr417*) homozygous NM_198150.3
Ethnicity	Turkish	Turkish	Indian	Indian	Norwegian	Norwegian
Age, gender	16 years, female	14 years, male	18 years, male	17 years, male	9 years 5 months, male	11 years, female
Birth weight	NA	NA	NA	NA	2610 g, <1st centile	3014 g, 9th centile
Birth length	50th percentile	50th percentile	NA	NA	46 cm, 1st centile	50 cm, 42nd centile
Birth head circumference	Macrocephaly	Macrocephaly	NA	NA	34 cm, 18th centile	34 cm, 17th centile
Suspected diagnoses	MPS, spondyloepiphyseal dysplasia, Turner syndrome	MPS, spondyloepiphyseal dysplasia	Brachyolmia, MPS, spondyloepiphyseal dysplasia	Brachyolmia, MPS, spondyloepiphyseal dysplasia	LCPD, MED, Meyers dysplasia MPS IV	MPS IV
Height	146,5 cm, −3.25 SD	150 cm, −1.94 SD	157 cm, −3.22 SD	145 cm, −4.53 SD	149,5 cm at age 9 years 5 months, SDS 1,93Predicted adult height based on midparental height: 178,5 +/−10 cm	149,5 cm at age 11 years, SDS 0,40Predicted adult height based on midparental height: 165,5 +/−10 cm
Weight	68 kg	49 kg	NA	32.48 kg	64 kg, 17 kg above 97,5th centile (weight for age)	37,1 kg, 50th percentile (weight for age)
Occiptofrontal head circumference	59 cm, 2.52 SD	58.5 cm, 1.95 SD	53 cm, −2.21 SD	52.5 cm, −2.41 SD	55 cm, SDS 1,17	54 cm, SDS 0,64 at age 10 years 9 months
Arm span	150,5 cm	155 cm	164 cm	147 cm	151 cm	148 cm
Facial phenotype	Coarse facial features	Coarse facial features	Coarse facial features	Coarse facial features	Not coarse facial features	Malar hypoplasia, not coarse facial features
Visual concern	Mild myopia since 14th year of life, mild lens and vitreous opacity, mild retinal pigmentation temporal of the fovea	Mild lens and vitreous opacity, mild retinal pigmentation temporal of the fovea	Normal	Normal, no corneal opacity	Normal	Slight myopia at age 11 years 4 months
Auditory system	Normal audiogram and tympanogram	Normal audiogram and tympanogram	Normal	Normal	Normal audiogram	Normal audiogram
Jaw and teeth	Open bite, wide spaced teeth, diastemata, canine-like appearance of lateral incisors	Open bite, wide spaced teeth, canine-like appearance of lateral incisors	Normal	Normal	Slightly hypomineralized enamel	Slightly hypomineralized enamel
Hands/wrists	Normal	Normal, intermittent paresthesias	Normal	Brachydactyly, arthropathy of right wrist	Hypermobile distal interphalangeal joints and	Hypermobile distal interphalangeal joints and

(Continues)

TABLE 1 (Continued)

Individuals described in Verheyen et al.					Individuals described in this research letter	
					first metacarpophalangeal joint	first metacarpophalangeal joint
Skeletal features	Disproportionate short-trunk short stature, genu valgus, mild scoliosis	Disproportionate short-trunk short stature, mild genu valgus	Disproportionate short-trunk short stature, genu valgus	Disproportionate short-trunk short stature, genu valgus, mild scoliosis	ProportionateOsteochondral lesions	ProportionateOsteochondral lesions
Liver, spleen	Normal in size and structure (ultrasound examination)	Normal in size and structure (ultrasound examination)	Normal on clinical examination	Normal on clinical examination	Slightly hyperechogenic liver, otherwise normal (ultrasound)	Normal (ultrasound)
Kidneys	Normal (ultrasound)	Normal (ultrasound)	Not available	Renal calculus at 6 years	Normal (ultrasound)	Normal (ultrasound)
Heart	Systolic murmur, mild aortic valve stenosis and regurgitation, thickened ends of aortic cusps, mild left ventricular hyperthrophy	Systolic and diastolic murmur, mild aortic valve stenosis and regurgitation, thickened ends of aortic cusps	Normal on clinical examination	Normal on clinical examination	Normal ECG. Possible slight diastolic dysfunction, otherwise normal echocardiogram	Normal ECG and echocardiogram
Neurological examination, cognition	Normal	Normal	Normal	Normal	Normal. Possible Tourette syndrome	Normal
Urinary GAG (DMB test)	Normal at 11 and 16 years	Borderline at 14 years	Not available	Not available	At age 8 yearsU-GAG 13 mg/mmol creatinine (age adjusted reference range 5–11)At age 9 yearsU-GAG 14 mg/mmol creatinine (age-adjusted reference range 5–11)	At age 10 yearsU-GAG 14 mg/mmol creatinine (age-adjusted reference range 4–11)U-GAG 15 mg/mmol creatinine on repeat analysis (age-adjusted reference range 4–11)
LC–MS/MS[a]Metabolic diseases	DS 165 μg/mmol (expected 0–53 μg/mmol creatinine) at age 17 years	DS 234 μg/mmol (expected 0–53 μg/mmol creatinine) at age 15 years	Not available	Not available	Increased DS 338 μg/mmol creatinine (reference value 0–109) at 9 years 5 months	Increased DS 358μg/mmol creatinine, (reference value 0–53).HS 365 μg/mmol creatinine(reference values 0–323). At age 10 years 11 months

Abbreviations: LCPD, Legg-Calvè-Perthes disease; MED, multiple epiphyseal dysplasia; MPS, mucopolysaccharidosis.
[a]Analysis performed at Amsterdam Universitair Medische Centra, Academic Medical Center, Lab Genetic Metabolic diseases.

AUTHOR CONTRIBUTIONS

Conception and design: Cecilie F. Rustad, Trine E. Prescott, Else Merckoll, Erle Kristensen, Cathrin L. Salvador, Hilde Nordgarden, and Kristian Tveten. *Data collection*: Cecilie F. Rustad, Trine E. Prescott, Else Merckoll, Erle Kristensen, Cathrin L. Salvador, Hilde Nordgarden, and Kristian Tveten. *Data analysis and interpretation*: Cecilie F. Rustad, Trine E. Prescott, Else Merckoll, Erle Kristensen, Cathrin L. Salvador, Hilde Nordgarden, and Kristian Tveten. *Drafting the article*: Cecilie F. Rustad, Trine E. Prescott, Else Merckoll, Erle Kristensen, Cathrin L. Salvador, Hilde Nordgarden, and Kristian Tveten. *Critical revision of the article*: Cecilie F. Rustad, Trine E. Prescott, Else Merckoll, Erle Kristensen, Cathrin L. Salvador, Hilde Nordgarden, and Kristian Tveten. *Final approval*: Cecilie F. Rustad, Trine E. Prescott, Else Merckoll, Erle Kristensen, Cathrin L. Salvador, Hilde Nordgarden, and Kristian Tveten.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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