MPS-like disease caused by *VPS16* -associated impairment of intracellular trafficking

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Introduction

Mucopolysaccharidoses (MPS) are monogenic disorders due to defects in lysosomal enzymes, transporters or membrane proteins usually presenting with multisystem involvement in childhood. The phenotype differs between the different forms of MPS but quite often includes neurological and skeletal abnormalities. Patients with MPS-like clinical symptoms but inconclusive findings at metabolic and genetic levels have recently been reported. Causative defects of intracellular trafficking – such as HOPS, CORVET, CHEVI tethering complexes (Fig. 1) – have been described. Recently, defects of different components of the vacuolar protein sorting (VPS) class C subunit, consisting of VPS11, VPS16, VPS18 and VPS33A, have been published. Clinically, patients carrying these variants present with neurological (e.g. VPS16: dystonia, VPS11: leukencephalopathy) or multisystemic symptoms with an MPS-like phenotype (VPS33A and VPS16). Recently, four patients with pathogenic variants in *VPS16* have been described that share an MPS-like phenotype with coarse facial features, skeletal abnormalities, bone-marrow involvement with anemia, neutropenia and thrombocytopenia, impaired psychomotor development and regression, myelination abnormalities and increased excretion of urine glycosaminoglycans.

We describe a further patient carrying a *VPS16* –variant which was initially classified as VUS but based on clinical symptoms in our patient and two other patients published by Yildiz et al., was reclassified as a likely pathogenic variant.

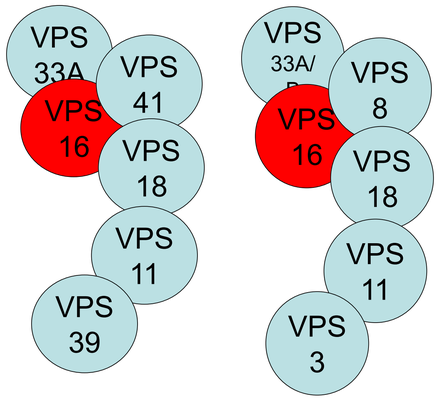

Figure 1: Composition of the HOPS (left) and CORVET (right) family of tethering complexes (7)

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Case report

The now 15 year old boy is the second child of healthy, consanguineous parents. During pregnancy, growth retardation and increased nuchal translucency were observed. After premature rupture of membranes the boy was born via C-section at 35 weeks of gestation (birth weight 1950g (P6), length 43cm (P4), head circumference 33cm (P48). Development in the first months of life was delayed and at the age of 8 months severe anemia (Hb 4.7g/dl) was noted requiring RBC transfusion. At this age MPS II was suspected but enzyme studies were normal. All developmental milestones were reached late with free walking at the age of 24 months and first words at the age of 4 years. With the exception of expressive language cognitive functions were evaluated as normal. Due to dysostosis and contractures multiple orthopedic surgeries were performed. Epileptic seizures manifesting with dystonic movements were suspected but could be excluded by video-EEG-monitoring. Multiple MRIs of the brain were reported normal At the age of 11 years, he lost the ability to walk and since the age of 9 years expressive language slowly deteriorated. During febrile infection neutropenia was noted (min. 100/µl) and bone marrow biopsy showed incomplete differentiation and signs of a storage disorder. GCSF treatment resulted in normalization of neutrophil counts and reduction of bacterial infections.

Trio whole exome analysis showed variants of unknown significance (VUS) in the *SETBP1* (Schinzel-Gideon-Syndrome), *PTCHD1*- (X-linked autism susceptibility) and *VPS16*- (dystonia) genes (homozygous). Both parents are heterozygote carriers of the *VPS16* variant.

The patient was referred to us for further workup. Due to the *VPS16* VUS (c.540G>T; p.Trp180Cys) and published association between variants in *VPS33A* and an atypical MPS an intracellular trafficking defect was suspected (Kondo et al., 2016). Clinical examination showed a 12 9/12 years old boy with coarse facial appearance, macroglossia, shortened long bones, scoliosis, splenomegaly and multiple contractures (Fig. 2). Further workup revealed features shown in the table similar to the four other patients published (Sofou et al., 2021 and Yildiz et al., 2021). Due to this publications, the *VPS16* VUS was reclassified as likely pathogenic. Functional analyses are underway.

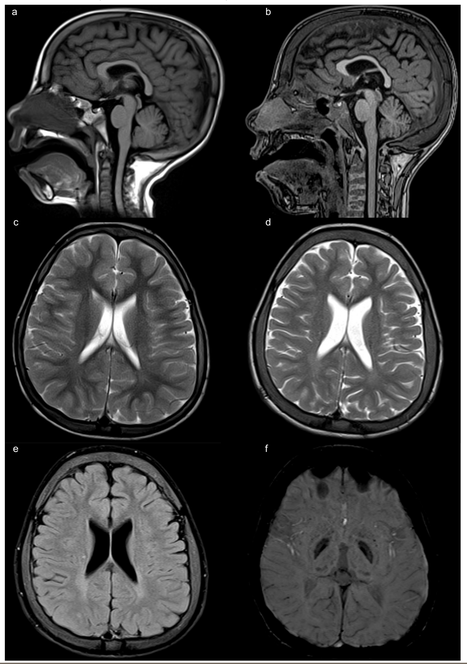

Figure 2:
MRI brain age 7 (a, c) and age 13 (b, d, e, f)
a-b) and c-d) progressive calvarial thickening. c-d) progressive atrophy – neurodegenerative. e) development of periventricular and deep white matter hyperintensities f) prominent, bilateral iron deposition also in the thalamus

	Our patient	Sofou et al., 2021 (2)	Yildiz et al., 2021 (1)
Genetic variant	c.540G>T	c.2272-18C>A	c.540G>T
Pregnancy			
ultrasound	SGA/IUGR, short bones	n/a	2/2 IUGR
Preterm birth	35 weeks of gestation	1 / 2	0 / 2
Neurology			
Motor development	Delayed since infancy, loss of skills after age 9-10	Impaired / delayed 2/2	2/2 Impaired / delayed
Language development	Mild delay, worsening after age 9, loss of active speech age 12	Impaired / delayed 2/2	2/2 Impaired / delayed
Pyramidal signs	None	2/2	n/a
Respiratory dysfunction	None	2/2	1/2
Seizures	None	0/2	1/2
EEG changes	pathologic slowing	1/2 encephalopathic., 1/2 normal	n/a
Peripheral neuropathy / NCS	Demyelinating sensomotor neuropathy	1/1	2/2
Ophthalmology	Vision impairment. Normal funduscopy	1/2 Optic nerve pallor	1/2 Optic nerve pallor 2/2 vision impairment
Hematology			
Anemia	Hb min 4,7mg/dl (age 4 months)	2/2	n/a
Neutropenia	min. 100/µl, normalized after GCSF	2/2	2/2
Granulated lymphocytes	none	1/1	0/2
Thrombocypenia	None	1/2	n/a
Bone marrow biopsy	No myeloid maturation arrest. Signs of storage disorder (non-specific)	1/2 densely stained granules in myelopoetic cells suggestive of LSD	2/2 no myeloid maturation arrest
Biochemical tests			
LSD enzymes	Normal	Normal 2/2	2/2Normal
Chitotriosidase	174 nmol(h/ml (normal)	Elevated 1/1	1/1 Elevated
Urine GAG	22,5mg/mmol Krea (elevated; Abnormal band pattern)	1/2 elevated GAG, abnormal pattern	1/2 Elevated
Urine oligosaccharides	Abnormal band pattern	1/2 abnormal band pattern	n/a
CSF	Amino acids on specific changes, normal lactate, protein and albumine	2/2 Elevated CSF protein	n/a
Sialic acid	Elevated	1/2 Elevated	n/a
Imaging			
MRI brain	Progressive calvarial thickening Progressive atrophy White matter abnormalities Iron deposition in thalamus bilat.	2/2 White matter abnormalities 2/2 progressive atrophy 1/1 NAA-peak 1/1 nerve root enhancement 2/2 thin corpus callosum	2/2 Normal
Abdominal ultrasound	Splenomegaly, Nephromegaly	1/2 hepatomegaly	2/2 Splenomegaly, liver abnormalities
Echocardiography	Normal	1/1 normal	1/2 Normal, 1/2 mitral insufficiency
Skeleton	Dysostosis multiplex	2/2 Dysostosis multiplex	2/2 Spondylar dysplasia

Conclusion

VPS16 pathogenic variants have been described in until now four patients with an MPS-like multisystem disorder and a common phenotype with coarse facial features, neuropathy, optic atrophy, retinopathy, dysostosis multiplex, severe neutropenia, elevated chitotriosidase-activity in blood and GAGs in urine. Our patient, aged 15 at last follow up, shares multiple features reported bei Yildiz et al. and Sofou et al. but generally seems to have a milder phenotype with no optic atrophy or retinopathy, only mild cognitive impairment (though loss of active speech occured at age 12) and no pyramidal signs. Brain iron accumulation and calvarial thickening have not been reported previously and might be the due to higher age of the patient. The variant *VPS16* VUS (c.540G>T; p.Trp180Cys) found in our patient can now be reclassified as likely pathogenic. Functional biochemical studies are pending. *VPS16*-variants should be included in the differential diagnosis of patients with a MPS-like phenotype.

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