

Supplemental Table 1. Phenotypic comparison of *FAT4*-associated syndromes Van-Maldergem syndrome 2 (OMIM #615546) and Hennekam lymphangiectasia-lymphedema syndrome 2 (OMIM #616006). Phenotypic features were derived from the clinical synopsis section of the respective syndrome in OMIM (<https://www.omim.org/>). Features present in patient A4478-21 are highlighted in yellow. Please note the distinct overlap of phenotypic characteristics identified in patient A4478-21 with syndromes known to occur due to recessive mutations in *FAT4*.

Phenotype	Van-Maldergem Syndrome 2	Hennekam Syndrome 2
Molecular Basis	Mutations in <i>FAT4</i> or <i>DCHS1</i>	Mutations in <i>FAT4</i>
Inheritance	Autosomal Recessive	
Growth	Growth retardation	
Head&Neck		
-Head	Large anterior fontanels	-
-Face	Flat face	
	Bitemporal narrowing	Dysmorphic facies
	Micrognathia	-
	Maxillary hypoplasia	-
-Ears	Microtia	Small ears
	Atresia of the external auditory meatus	Thick helices
	Hearing loss (conductive and/or sensorineural)	Hearing loss (facultative)
-Eyes	Hypertelorism	
	Short palpebral fissures	Epicanthus
	Ptosis	Blepharophimosis
	Epicanthal folds	-
-Nose	Broad nasal bridge	Flat nasal bridge
	Thickening of the nasal alae	-
-Mouth	Tented upper lip	Small mouth
	Downturned mouth	-
	High-arched palate	-
	Thick gums	-
-Teeth	Irregular dentition	
	Dental malocclusion	-
Cardiovascular	-	Pericardial lymphangiectasia
Respiratory	Tracheomalacia	Pulmonary lymphangiectasia
Chest	Narrow thorax	-
	Short clavicles	-
Abdomen	Anteriorly positioned anus	Intestinal lymphangiectasia
	Poor feeding	-
Genitourinary	Hypospadias	Renal lymphangiectasia
	Bifid scrotum	-
	Micropenis	-
	Cryptorchidism	-
	Congenital anomalies of the kidneys and urinary tract (CAKUT)	-
Skeletal	Joint laxity	-
	Skeletal dysplasia	-
	Osteopenia	-
	Scoliosis	-
	Subluxation of radial heads	-
	Hand deformities	-
	Clinodactyly	Camptodactyly
	Flexion of PIP joints	-
	Webbing of the fingers	-
	Syndactyly (cutaneous)	-
	Foot deformities	-
Talipes equinovarus	-	
Short fourth metatarsals	-	
Muscle, Soft Tissues	Hypotonia	Lymphedema
	-	Lymphangiectasia
Skin, Nails & Hair	Sacral dimple	-
	Mental retardation	Impaired cognition
Neurologic	Intellectual disability	-
	Periventricular nodular heterotopia	-
	Subcortical band heterotopia	-
	Thin corpus callosum	-

(in toe)

(clino-, camptodactyly)

Supplementary Table 2. Search results (1-30) for individual A4478-21 using the Face2Gene tool. HS/VMS was not included in the list of 30 suggested syndromes. WES output of individual A4478-21 was analyzed for variants in genes for all respective syndromes, if applicable. Please note that no variants were identified in any of the genes listed.

Identifyer	Publication/ Figure	Molecular Diagnosis of Patient	Face2Gene Results						
			Total number suggested syndromes	Suggestion 1	Suggestion 2	Suggestion 3	Suggestion 4	Suggestion 5	Suggestion 6
A4478-21	this publication, Fig. 1b (+8 additional images, total of 9)	<i>FAT4</i>	30	Ocucerebro cutaneous Syndrome	Hyperphosp hataasia With Mental Retardation Syndrome	Prader-Willi Syndrome	Filippi Syndrome	Kaufmann Oculocerebr al Syndrome	Peters-Plus Syndrome
patient (single case report)	Van Maldergem et al., Fig. 1,2	ND	30	Palpebral Coloboma- Lipoma Syndrome	Blepharonas ofacial Malformatio n Syndrome	Mucopolidosis Type IV	Frontonasal Dysplasia	Branchioocul ofacial Syndrome	Schinzel- Giedion Midface Retraction Syndrome
D.N.A.R.	Zampino et al., Fig. 1a	ND	30	Acrofacial Dysostosis	3MC Syndrome	Nijmegen Breakage Syndrome	Otopalatodi gital Syndrome	Trisomy 18- Like Syndrome	Mandibulofaci al Dysostosis Syndrome
Patient 1	Mansour et al., Fig. 1a	ND	30	Hennekam Syndrome	Coffin-Lowry Syndrome	3MC Syndrome	Marshall- Smith Syndrome	Craniometap hyseal Dysplasia	Shprintzen- Goldberg Craniosynosi s Syndrome
Patient 2	Mansour et al., Fig. 1b	ND	0	-	-	-	-	-	-
Patient 3	Mansour et al., Fig. 1c	ND	30	Marshall Syndrome	Hennekam Syndrome	Robinow Syndrome	Kabuki Syndrome	Lenz- Majewski Hyperostotic Dwarfism	Frontonasal Dysplasia
Patient 4	Mansour et al., Fig. 1d	ND	10	Hennekam Syndrome	Dubowitz Syndrome	Smith-Lemli Opitz Syndrome	Palpebral Coloboma- Lipoma Syndrome	Microcephaly , Primary Autosomal Recessive	Cerebrocost omandibular Syndrome
Patient 5	Mansour et al., Fig. 1e	ND	30	Hennekam Syndrome	Acrocallosal Syndrome	Cerebrocost omandibular Syndrome	Lateral Meningocele Syndrome	Larsen Syndrome	Geleophysic Dysplasia
Patient 6	Mansour et al., Fig. 1f	ND	30	Mowat- Wilson Syndrome	Nablus Mask-Like facial Syndrome	Hennekam Syndrome	Marshall Syndrome	Marden- Walker Syndrome	Ectodermal Dysplasia 1
D3	Cappello et al., Fig. 1a	<i>DCHS1</i>	30	Hennekam Syndrome	NGLY1	Down Syndrome	Schilbach- Rott Syndrome	Craniometap hyseal Dysplasia	Weaver Syndrome
F1	Cappello et al., Fig. 1b	<i>FAT4</i>	30	Hennekam Syndrome	Schilbach- Rott Syndrome	Dubowitz Syndrome	Microcephaly, Primary Autosomal Recessive	Baraitser- Winter Syndrome	Craniometap hyseal Syndrome
patient (single case report)	Neuhann et al., Fig. 2b	ND	30	Ocucerebro cutaneous Syndrome	Hennekam Syndrome	Saethre- Chotzen Syndrome	NGLY1	Marden- Walker Syndrome	Nijmegen Breakage Syndrome

Supplementary Table 3. List of previously reported cases of Van Maldergem Syndrome (VMS) and respective search results in the Face2Gene tool. Images, if available, were extracted from the literature and uploaded onto the Face2Gene website (<https://app.face2gene.com>). The first 6 results were listed. The majority of previously reported patients (8/10) yielded results including Hennekam syndrome (HS) within the first 3 suggestions. HS has a large phenotypic overlap with VMS and is also caused by recessive mutations in the *FAT4* gene. A suggestion of HS was therefore interpreted as successful match. Please note that pictures of our patient (total of 9 images) did not result in the suggestion of VMS/HS. Patients reported by Van Maldergem et al. (1992), and Zampino et al. (1994) also did not yield a suggestion of VMS/HS. This might be caused by lower quality of published images. The image of patient 2 by Mansour et al. was not recognized by the software and therefore did not result in suggestions. ND: no data.

Name Syndrome	OMIM #	Related Gene	Mode of Inheritance
Ocucerebrocutaneous Syndrome/ Delleman Syndrome	164180	-	uncertain
Hyperphosphatasia With Mental Retardation Syndrome	-	-	-
Prader-Willi Syndrome	176270	<i>SNRPN</i> , <i>NDN</i>	Microdeletion, Disomy
Filippi Syndrome	272440	<i>CKAP2L</i>	AR
Kaufmann Oculocerebral Syndrome	244450	<i>UBE3B</i>	AR
Peters-Plus Syndrome	261540	-	AR
Microphthalmia with Limb Anomalies	206920	<i>SMOC1</i>	AR
Peho syndrome	260565	-	AR
Warburg Micro Syndrome	600118	<i>RAB3GAP1</i>	AR
Mental Retardation, autosomal dominant 22 (MRD22)	612337	<i>ZBTB18</i>	AD
Laurin-Sandrom Syndrome	135750	<i>LMBR1</i>	AD
Omodysplasia	258315	<i>GPC6</i>	AR
Trisomy 18-like Syndrome	-	-	-
Arthrogryposis, Distal, Type 5	108145	<i>PIEZO2</i>	AD
Dubowitz Syndrome	223370	<i>LIG4</i>	AR
Mandibulofacial Dysostosis, Guion- Almeida Type	610536	<i>EFTUD2</i>	Uncertain, Sporadic
Cold-Induced Sweating Syndrome	-	-	-
Charge Syndrome	214800	<i>SEMA3E</i> , <i>CHD7</i>	Microdeletion
Cardiofacialcutaneous Syndrome	-	-	-
Baraitser-Winter Syndrome	243310	<i>ACTB</i> , <i>ACTG1</i>	AD, microdeletion
Frontofacionasal Dysplasia	229400	-	AR
TAF1 Mutation (Mental Retardation, X- linked, syndromic 33)	300966	-	X-linked recessive
Frontonasal Dysplasia	136760	<i>ALX3</i>	uncertain
Hypotonia, Infantile, with Psychomotor Retardation And Characteristic Facies 2	-	-	-
Mucopolipidosis II Alpha/Beta	252500	<i>GNPTAB</i>	AR
Cockayne Syndrome	216400	<i>ERCC8</i>	AR
Simpson-Golabi-Behmel Syndrome, Type 1	312870	<i>GPC3</i>	X-linked recessive
Mental Retardation, Autosomal Dominant 17 (MRD17)	-	-	-
1q24q25 Deletion	-	-	-
Epiphyseal Dysplasia, Multiple	-	-	-