Van Maldergem Syndrome — Comprehensive Disease Characteristics Report

Disease: Van Maldergem Syndrome (VMS) **Category:** Mendelian (rare autosomal recessive multisystem congenital disorder) **Suggested MONDO:** MONDO:0018852 (Van Maldergem syndrome). Subtypes: VMLDS1 (MONDO:0010875-class, *DCHS1*), VMLDS2 (*FAT4*).

> **Evidence source note:** VMS is an ultra-rare disorder. Essentially all knowledge is derived from *individual patient case reports and small case series* (aggregated disease-level resources such as OMIM/Orphanet compile these), supplemented by *model-organism* (mouse, zebrafish, Drosophila) and *in vitro* mechanistic studies. There are no EHR-scale cohorts, registries, clinical trials, GWAS, or population omics datasets for this disease. Frequencies below are therefore qualitative/small-denominator estimates, not population statistics.

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1. Disease Information

Overview. Van Maldergem syndrome is a rare autosomal recessive multiple-congenital-anomaly/intellectual-disability syndrome first described by Van Maldergem and colleagues in 1992. Its cardinal features are a distinctive craniofacial (blepharo-naso-facial) gestalt, intellectual disability, auditory (external/middle ear) malformations with conductive hearing loss, hand/digit anomalies and skeletal abnormalities, and — characteristically — periventricular and subcortical neuronal heterotopia on brain imaging (P 22473091). P 27739185).

It is caused by biallelic loss-of-function variants in one of two atypical cadherin genes, *DCHS1*

(type 1) or *FAT4* (type 2), which act as a receptor–ligand pair in Fat–Dachsous planar cell polarity (PCP)/Hippo signaling (24056717).

Key identifiers. - **OMIM:** #601390 — Van Maldergem syndrome 1 (VMLDS1; *DCHS1*); #615546 — Van Maldergem syndrome 2 (VMLDS2; *FAT4*). MIM#601390 explicitly cited in 25930014 and 40797481 . - **Orphanet:** ORPHA:314679 (Van Maldergem syndrome). - **ICD-10:** Q87.8 (other specified congenital malformation syndromes, not elsewhere classified); **ICD-11:** LD2F.1Y / LD2F.0Y class (multiple developmental anomalies). No VMS-specific ICD code. - **MeSH:** No dedicated MeSH heading; indexed under "Abnormalities, Multiple" / "Intellectual Disability" and gene terms *DCHS1*, *FAT4*. - **MONDO:** MONDO:0018852 (parent), with type-1/type-2 children.

Synonyms / alternative names. Van Maldergem syndrome 1 and 2 (VMLDS1/VMLDS2); "blepharo-naso-facial malformation with intellectual disability" (descriptive); historically overlapping with, and now recognized as allelic to, **Hennekam lymphangiectasia–lymphedema syndrome** when caused by *FAT4* (24913602 , 29681106).

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2. Etiology

Primary cause — genetic. VMS is monogenic and recessive. It is caused by **biallelic (homozygous or compound heterozygous) pathogenic variants** in: - ***DCHS1*** (Dachsous cadherin-related 1; HGNC:13681; NCBI Gene 8642; chromosome **11p15.4**; OMIM *603057)* → *VMLDS1*. - **FAT4** *(FAT atypical cadherin 4; HGNC:23109; NCBI Gene 79633; chromosome 4q28.1; OMIM* 612411) → VMLDS2.

> "Here we show that mutations in genes encoding the receptor-ligand cadherin pair DCHS1 and FAT4 lead to a recessive syndrome in humans that includes periventricular neuronal heterotopia."
> (P 24056717)

Risk factors. - *Genetic:* The two causal genes are the only established risk determinants. **Consanguinity** is a major risk amplifier — parental consanguinity was present in 3/5 families in the defining cohort, and homozygous variants predominate in consanguineous pedigrees (P 22473091). No susceptibility loci or GWAS signals exist (disease is monogenic). Potential modifier effects (e.g., *FAT4* vs *DCHS1* genotype, allelic *CCBE1/ADAMTS3* interactions in the lymphatic-overlap phenotype) are hypothesized but unproven. - *Environmental / lifestyle / infectious:* **None identified.** VMS is fully genetically determined; no toxin, teratogen, dietary, occupational, or infectious contributor is known or expected. (Not applicable.)

Protective factors. None described. In principle, inheriting only one variant allele (heterozygous carrier) is "protective" in the Mendelian sense — carriers are unaffected — but no protective modifier alleles are known.

Gene–environment interactions. Not applicable/none reported; the phenotype is determined by biallelic genotype independent of environment.

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3. Phenotypes

VMS is a **congenital, multisystem, generally non-progressive** disorder; most features are present at birth or emerge in infancy, with intellectual disability apparent in childhood. Severity is **variable** (mild-to-moderate ID is typical). Frequencies are qualitative given the tiny reported population (~dozens of patients worldwide).

Craniofacial (physical manifestations — near-universal / "typical facial gestalt"): - Blepharophimosis (HP:0000581); telecanthus (HP:0000506); maxillary/midface hypoplasia (HP:0000327/HP:0011800); microtia (HP:0008551); atresia of external auditory canal

(HP:0000413); blepharo-naso-facial malformation. (PMID:22473091) (PMID:27739185)

Auditory (clinical sign — near-universal): - Conductive hearing impairment (HP:0000405), bilateral, from microtia + aural atresia ± middle-ear/ossicular and tympanic-cavity malformations. "Almost all nine described patients have been shown to be affected by conductive hearing impairment attributed to microtia, and atresia of the outer ear canal." (PMID:27739185)

Neurological / neurodevelopmental (near-universal): - Intellectual disability, mild-to-moderate (HP:0001249); neonatal hypotonia (HP:0001319); periventricular nodular heterotopia (HP:0032388) and subcortical/subependymal neuronal heterotopia (HP:0002518); altered functional cerebral asymmetry (PMID:25930014); poor coordination/clumsiness (HP:0002317). (PMID:22473091) (PMID:24056717)

Skeletal / limb (common): - Digital contractures/camptodactyly (HP:0100490/HP:0012385); brachydactyly / short 4th metacarpal (HP:0001156); scoliosis (HP:0002650); osteopenia (HP:0000938); general skeletal anomalies. (PMID:22473091) (PMID:28878612) (PMID:40797481) (PMID:29681106)

Neonatal / feeding / respiratory (common): - Feeding difficulties (HP:0011968); respiratory problems and **tracheal anomalies** (HP:0002778); failure to thrive (HP:0001508). (P 22473091) P 29681106

Endocrine (rare/variable): - Hypogonadotropic hypogonadism (HP:0000044); breast aplasia/hypoplasia/amazia with normal nipples (HP:0100783/HP:0003187) (P 29046692); central precocious puberty (HP:0000826) (P 40797481).

Genitourinary (rare/variable): - Unilateral renal agenesis (HP:0000122/HP:0000104); ureterovesical junction obstruction/urinary tract obstruction (HP:0000073); duplex/duplicated collecting system (HP:0000081). (P 28878612) P 30853441

Gastrointestinal / lymphatic (rare): - Intestinal lymphangiectasia (HP:0002593) — reported in VMS and blurring the boundary with Hennekam syndrome (P 31063239).

Quality-of-life impact. No formal EQ-5D/SF-36/PROMIS data exist. Inferred burden: lifelong intellectual disability and hearing loss impair communication, learning, and independence; feeding/respiratory issues and multiple surgeries burden infancy; craniofacial differences carry psychosocial impact. Hearing rehabilitation measurably improves social skills and language (P 26491591).

4. Genetic / Molecular Information

Causal genes. | Gene | Locus | OMIM | Protein | Disease | |---|---|---|---|---| | *DCHS1* (HGNC:13681, Gene 8642) | 11p15.4 | *603057* | *Dachsous 1 (protocadherin, PCP ligand)* | *VMLDS1 (#601390)* | | | FAT4 *(HGNC:23109, Gene 79633)* | *4q28.1* | 612411 | FAT4 (protocadherin, PCP receptor) | VMLDS2 (#615546) |

DCHS1 and FAT4 form a **receptor–ligand pair**; FAT4 is a very large single-pass transmembrane protein with 34 extracellular cadherin repeats, EGF-like domains, and laminin-G–like domains; DCHS1 is its Dachsous-family cadherin ligand (P 28488382).

Pathogenic variants. - *Type/class:* predominantly **loss-of-function** — nonsense, frameshift, and canonical splice-site variants (e.g., *FAT4* NM_024582.6:c.7018+1G>A, loss of the intron-6 donor site, ACMG **pathogenic**; P 37551355), as well as missense variants. Compound heterozygous and homozygous configurations both occur (P 29046692). P 28878612

- *Classification:* Reported variants are curated as **pathogenic / likely pathogenic** by ACMG/AMP criteria; novel variants continue to be reported, some initially VUS pending segregation/functional data (P 31384091). P 40797481

- *Allele frequency:* Individually **rare/private**; consistent with a recessive ultra-rare disease, biallelic pathogenic genotypes are essentially absent from gnomAD, though single heterozygous LoF alleles exist at very low frequency. - *Origin:* **Germline**, biallelic. (Somatically, *FAT4* is a tumor-suppressor mutated in cancers, but that is unrelated to the germline VMS phenotype; P 28488382 notes FAT4's tumor-suppressor role.) - *Functional consequence:* **Loss of function** of the Dchs1–

Fat4 PCP/Hippo module. A 2026 study shows the **DCHS1 intracellular domain** is functionally critical — its loss expands neurogenic proliferation and generates VMS-like defects (P 41972678).

Modifier genes. None validated. Phenotype-modifying candidates include the specific gene affected (*FAT4* vs *DCHS1*) and, for the lymphatic-overlap phenotype, the allelic lymphangiogenesis genes *CCBE1* and *ADAMTS3* (which also cause Hennekam syndrome) (P 29681106).

Epigenetics. No DNA-methylation, histone-modification, or episignature data specific to VMS are available (not applicable at present).

Chromosomal abnormalities. VMS is a single-gene disorder; no recurrent aneuploidy, translocation, or copy-number syndrome. Chromosomal microarray is typically normal (useful mainly to exclude CNV mimics).

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5. Environmental Information

- **Environmental factors:** None. No toxin, radiation, pollutant, or occupational exposure is implicated.
- **Lifestyle factors:** None (congenital genetic disease).
- **Infectious agents:** None. VMS is not infectious or triggered by pathogens.

(All "Not applicable" — VMS is entirely genetically determined.)

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6. Mechanism / Pathophysiology

Core molecular pathway — Fat–Dachsous PCP and Hippo/YAP signaling. DCHS1 (Dachsous) and FAT4 are the vertebrate orthologs of the *Drosophila* Dachsous–Fat PCP system. They bind heterophilically across cell membranes and are expressed in **complementary gradients** that provide directional (planar polarity) information to tissues, feeding into the **Hippo kinase cascade** to restrain the transcriptional co-activator **YAP** (P 24056717)

). P 24998526

GO/pathway terms: planar cell polarity pathway (GO:0090175), Hippo signaling (GO:0035329), homophilic cell–cell adhesion via plasma-membrane adhesion molecules (GO:0007156), Reactome "Signaling by Hippo."

Causal chain (neurodevelopment — best-characterized): 1. **Trigger (upstream):** Biallelic LoF of *DCHS1* or *FAT4* → loss of Fat–Dachsous PCP signaling in the embryonic neuroepithelium. 2. **De-repression of YAP:** Hippo signaling is disrupted → YAP (Hippo effector) is inappropriately active.

> "These effects were countered by concurrent knockdown of Yap, a transcriptional effector of the Hippo signaling pathway. These findings implicate Dchs1 and Fat4 upstream of Yap as key regulators of mammalian neurogenesis." (P 24056717)
>
> 3. **Cellular consequence: Expanded neural progenitor proliferation** with **reduced neuronal differentiation** → excess progenitors. Confirmed by DCHS1-intracellular-domain loss expanding neurogenic proliferation (P 41972678).
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> 4. **Migration failure:** Loss of Dchs1/Fat4 expression gradients disrupts collective tangential neuronal migration and planar polarity (P 24998526).
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> 5. **Clinical manifestation (downstream):** Neurons fail to reach the cortical plate → **periventricular/subcortical neuronal heterotopia**, intellectual disability, and altered functional cerebral asymmetry (P 24056717). P 25930014

Parallel causal chains in other organs (same module, tissue-specific outputs): - **Bone/craniofacial:** Dchs1–Fat4 regulates **osteoblast differentiation**; its disruption produces the craniofacial abnormalities of VMS (P 31358536).

→ maxillary hypoplasia, skeletal anomalies, osteopenia. - **Kidney:** FAT4 fine-tunes kidney development by **regulating RET receptor-tyrosine-kinase signaling**; Fat4 deletion causes duplex-kidney phenotypes ( ). P 30853441 → renal agenesis/duplex kidney/urinary obstruction. - **Cytoskeleton (early embryo):** Dchs1 influences **actin and microtubule** organization, partly independent of Fat, via its intracellular domain (zebrafish;). P 26160902 - **Neuronal maintenance:** *Drosophila* fat loss in neurons impairs neuromuscular-junction structure and axonal targeting ( ). P 28488382

Cellular processes: cell proliferation/cell-cycle control (GO:0008283), neuron differentiation (GO:0030182), neuron migration (GO:0001764), osteoblast differentiation (GO:0001649), establishment of planar polarity (GO:0001736). **Cell types (CL):** radial glial/neural progenitor cells (CL:0000047 / CL:0000031), migrating neurons (CL:0000540), osteoblasts (CL:0000062), ureteric-bud/renal epithelial cells (CL:1000454). **Subcellular (GO CC):** plasma membrane (GO:0005886), cell–cell junction (GO:0005911), actin cytoskeleton (GO:0015629), microtubule (GO:0005874); YAP acts in the nucleus (GO:0005634).

Protein dysfunction: loss of function of large transmembrane protocadherins (adhesion/signaling), not misfolding/aggregation. **Metabolic changes:** none characteristic. **Immune involvement:** none (not an immune disease). **Tissue-damage mechanism:** developmental **malformation/dysplasia** (failed morphogenesis) rather than degeneration, ischemia, or fibrosis. **Molecular profiling (transcriptomics/proteomics/metabolomics/lipidomics):** no patient-derived omics datasets available. **Functional genomics:** mechanistic knockdown/knockout screens in mouse/zebrafish/fly and YAP-epistasis (above) constitute the functional evidence.

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7. Anatomical Structures Affected

Organ / system level (primary): - **Nervous system** (UBERON:0001016): cerebral cortex (UBERON:0000956), periventricular white matter/lateral ventricle margins (UBERON:0002289) — heterotopia; brainstem branchiomotor nuclei (migration). Body system: **nervous**. - **Ear**

(UBERON:0001690): external ear/auricle (UBERON:0001757) — microtia; external auditory canal (UBERON:0001352) — atresia; **middle ear / ossicles / tympanic cavity** (UBERON:0001756) — malformation (P 27739185).

Body system: **special sensory/auditory**. - **Craniofacial skeleton & face** (UBERON:0001456 face; UBERON:0001684 mandible/maxilla UBERON:0002397): midface/maxillary hypoplasia. - **Skeleton / limbs** (UBERON:0002091): hands/digits (UBERON:0002389), vertebral column (UBERON:0002415) — contractures, brachydactyly, scoliosis, osteopenia.

Secondary / variable organ involvement: - **Kidney/urinary tract** (UBERON:0002113 kidney; UBERON:0000056 ureter): agenesis, duplex kidney, ureterovesical obstruction (P 28878612). P 30853441

- **Endocrine/reproductive** (UBERON:0000990 reproductive system; hypothalamic–pituitary–gonadal axis): hypogonadotropic hypogonadism, precocious puberty; **breast** (UBERON:0000310) aplasia (P 29046692). P 40797481

- **Respiratory tract / trachea** (UBERON:0003126): tracheal anomalies, respiratory problems (P 29681106).

- **Gastrointestinal/lymphatic** (UBERON:0002108 small intestine; lymphatic vessels UBERON:0001473): intestinal lymphangiectasia (P 31063239).

Tissue level: neuroepithelium/neural tissue, connective/skeletal tissue (bone), epithelial tissues (renal, otic). **Cell level (CL):** neural progenitors/radial glia, migrating neurons, osteoblasts, renal epithelial cells (see §6). **Subcellular (GO CC):** plasma membrane, cell–cell junctions, cytoskeleton; nuclear YAP.

Localization / lateralization: brain heterotopia typically **bilateral**; ear/hearing involvement **bilateral**; renal malformations may be **unilateral** (e.g., unilateral renal agenesis,). P 28878612

Notably, functional cerebral asymmetry is *increased* ( ). P 25930014

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8. Temporal Development

- **Onset: Congenital / prenatal–neonatal.** Craniofacial, ear, and brain malformations are established in utero; neonatal hypotonia, feeding, and respiratory problems present at birth ( ). P 22473091
  Intellectual disability manifests through infancy/childhood. Endocrine features (precocious or hypogonadotropic puberty) emerge in childhood/adolescence (P 40797481). P 29046692
- **Onset pattern: Chronic/static (congenital malformation)** rather than acute.
- **Progression:** Generally **non-progressive/stable** — the structural malformations are fixed; neurodevelopmental deficits remain stable rather than degenerating. In the 2025 case, "the neurodevelopmental deficits remained stable without progression" over 2-year follow-up ( ). P 40797481
  No defined disease "stages."
- **Progression rate / course:** Static congenital course; lifelong (chronic). Not episodic or relapsing–remitting.
- **Remission:** Not applicable (structural congenital disorder; no spontaneous remission). Specific manifestations are **treatment-modifiable** (e.g., precocious puberty controlled with GnRH analog; hearing improved with implants).
- **Critical periods:** Embryonic corticogenesis and organogenesis are the windows during which the pathology is set; there is no post-natal window to reverse the heterotopia.

Intervention windows exist for *managing* sequelae (early hearing amplification for language development; timely endocrine therapy).

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9. Inheritance and Population

Epidemiology. Ultra-rare. Orphanet prevalence class **<1/1,000,000**; fewer than ~50 patients reported worldwide since 1992 (only ~9 described by 2016–2017; P 27739185).
Incidence not quantifiable. No registry/GBD data.

Inheritance & genetics. - **Pattern: Autosomal recessive** for both *DCHS1* and *FAT4* forms (P 22473091). P 24056717
- **Penetrance:** Essentially **complete** in biallelic individuals (all reported biallelic patients are affected), though **expressivity is variable** (organ involvement and severity differ between patients, even within the same gene). - **Anticipation:** None (not a repeat-expansion disorder). - **Germline mosaicism:** Not specifically reported. - **Consanguinity: Important risk factor** — parental consanguinity in 3/5 defining families; homozygous variants common in consanguineous unions (P 22473091).
- **Founder effects:** None established; variants are largely private. - **Carrier frequency:** Not formally estimated; expected very low. Heterozygous carriers are asymptomatic.

Population demographics. - **Affected populations:** Reported across diverse ancestries (European, Middle Eastern, Chinese, Macedonian, etc.; PMIDs 22473091, 40797481, 28878612) — no ethnic predilection beyond enrichment where consanguinity is common. - **Geographic distribution:** Worldwide, non-endemic. - **Sex ratio:** No clear sex bias; both sexes affected (autosomal). Some sex-specific manifestations reported (breast aplasia/hypogonadism in a female, P 29046692).
- **Age distribution:** Diagnosed from newborn period

(P 29505454) through adulthood (retrospective WES at age 37, P 29046692).

10. Diagnostics

Genetic testing (definitive). - **Approach:** Molecular confirmation of **biallelic pathogenic variants in *DCHS1 or FAT4***. **Whole-exome sequencing (WES)** is the principal diagnostic modality and has repeatedly established the diagnosis, including via **reverse phenotyping** and **expanded carrier screening** of parents (P 37551355 P 29046692 P 28878612). P 31384091 **WGS** is an alternative that also detects deep-intronic/structural variants. **Multigene panels** for intellectual disability / periventricular heterotopia / malformation syndromes should include *DCHS1*, *FAT4*, and — given phenotypic overlap — *CCBE1* and *ADAMTS3* (Hennekam). **Single-gene testing** is reasonable when the gestalt is classic. **Chromosomal microarray/karyotype/FISH** are typically normal and serve to exclude CNV/aneuploidy mimics. Mitochondrial and repeat-expansion testing are not indicated.

Imaging & clinical tests. - **Brain MRI:** periventricular nodular and subcortical heterotopia — a **recognizable pattern** that, in the right clinical context, should prompt targeted testing (P 39462795). P 24056717 - **Temporal-bone high-resolution CT:** external/middle-ear and tympanic-cavity malformations (P 27739185).

- **Audiology:** confirms conductive hearing loss; **EEG** documented altered functional cerebral asymmetry in a research setting (P 25930014).
- **Renal ultrasound/urography:** for renal agenesis/duplex kidney/obstruction (P 28878612).
- **Endocrine labs:** gonadotropins/sex steroids for hypogonadotropic hypogonadism or precocious puberty (P 29046692; P 40797481).

Biomarkers / omics diagnostics: No specific biochemical biomarker; **DNA sequence variants are the diagnostic marker.** No validated RNA/proteomic/metabolomic/epigenomic test; no liquid biopsy role.

Clinical criteria & differential diagnosis. No formal consensus criteria; diagnosis rests on the **characteristic facial gestalt** + **hearing loss** + **intellectual disability** + **neuronal heterotopia**, confirmed genetically. **Differential diagnoses:** Hennekam syndrome (allelic *FAT4*; distinguished classically by lymphedema — though intestinal lymphangiectasia can overlap; P 31063239; P 29681106); other periventricular-heterotopia disorders (*FLNA*-related; ARFGEF2-related; EML1-associated) (P 39462795); blepharophimosis-ptosis-epicanthus-inversus syndrome (BPES, *FOXL2*); other multiple-congenital-anomaly/ID syndromes.

Screening. Not part of newborn screening. **Cascade/carrier screening** of relatives once the familial variants are known; **expanded carrier screening** can identify at-risk couples (P 37551355). Prenatal/preimplantation testing feasible for known familial variants.

11. Outcome / Prognosis

- **Survival/mortality:** No formal survival statistics. Prognosis ranges from **early death in severely affected infants** (two siblings died undiagnosed with multiple congenital anomalies;
  P 37551355
) to **survival into adulthood** with stable disability (diagnosis at age 37;
  P 29046692
). Mortality is driven by severe neonatal respiratory/feeding complications and major malformations rather than by a degenerative process.
- **Morbidity/function:** Chief long-term morbidities are **intellectual disability** and **conductive hearing loss**, with variable skeletal, renal, endocrine, and respiratory contributions. Disability is lifelong but **non-progressive**.
- **Quality-of-life measures:** No EQ-5D/SF-36/PROMIS data; hearing rehabilitation improves communication/social outcomes
  (P 26491591
).
- **Complications:** recurrent respiratory issues (tracheal anomalies), feeding failure/failure-to-thrive, hearing-loss–related language delay, urinary-tract obstruction/renal impairment, endocrine dysfunction; psychosocial impact of craniofacial differences.
- **Recovery potential:** Structural malformations do not resolve, but sequelae are **manageable** (hearing devices, hormone therapy, surgery). Neurodevelopmental deficits are stable.
- **Prognostic factors:** severity/extent of neonatal respiratory and feeding compromise and of CNS involvement predict early outcome; no molecular prognostic biomarker validated (possible gene-specific/genotype effects unproven).

12. Treatment

No disease-modifying or curative therapy exists. Management is **multidisciplinary, supportive, and symptom-directed** (NCIT: Supportive Care, C15277).

- **Pharmacotherapy (symptom-specific):**

- **GnRH analog (leuprorelin/leuprolide acetate, e.g., Enantone®)** for central precocious puberty — successfully controlled pubertal progression over 2 years (P 40797481).
  NCIT: Leuprolide (C1300); ATC L02AE02.
- Endocrine replacement/management for hypogonadotropic hypogonadism as clinically indicated (P 29046692).
- No pharmacogenomic considerations specific to VMS.
- **Surgical / interventional:**
- **Hearing rehabilitation:** bone-conduction hearing device (bone-anchored), or, when tympanic-cavity hypoplasia precludes ossiculoplasty, an **active middle-ear implant (Vibrant Soundbridge)** — improved hearing, social skills, and language (P 27739185; P 26491591).
  NCIT: Cochlear/Middle Ear Implant; Hearing Aid.
- Orthopedic/craniofacial and urological surgery as needed (e.g., for obstruction, scoliosis).
- **Supportive & rehabilitative:** nutritional support/feeding management for infantile feeding difficulties; respiratory care for tracheal anomalies; **physical, occupational, and speech therapy**; special education for intellectual disability. (NCIT: Physical Therapy C15327; Occupational Therapy; Speech Therapy.)
- **Advanced therapeutics (gene/cell/RNA/targeted/immunotherapy): None** developed or in trials; not applicable.
- **Experimental treatments / clinical trials: None registered** for VMS (no NCT identifiers).
- **Treatment strategy:** individualized, organ-system–based (audiology, neurodevelopment, endocrinology, nephrology, orthopedics, genetics). No standardized algorithm exists; "Neurodevelopmental deficits were managed with regular follow-ups due to the lack of established therapeutic protocols" (P 40797481).

13. Prevention

- **Primary prevention:** Not preventable at the individual level (congenital genetic disease). **Genetic counseling** is the cornerstone: for consanguineous couples and families with an affected child, recurrence risk is **25%** per pregnancy (autosomal recessive).
- **Secondary prevention (early detection):** early brain MRI/audiology/renal imaging in suspected cases; early hearing amplification to protect language development; endocrine surveillance.
- **Tertiary prevention:** manage complications (hearing devices, hormone therapy, respiratory/feeding support, surgery) to limit disability.
- **Genetic/reproductive prevention: carrier/cascade screening**, **expanded carrier screening** for at-risk couples
  (P 37551355),
  and **prenatal or preimplantation genetic diagnosis** for known familial *DCHS1*/*FAT4* variants.
- **Immunization / behavioral / public-health / environmental / prophylaxis:** Not applicable (no infectious or environmental component).

14. Other Species / Natural Disease

- **Taxonomy of orthologs studied:** *Mus musculus* (NCBI Taxon 10090), *Danio rerio* (7955), *Drosophila melanogaster* (7227).
- **Orthologous genes:** mouse **Dchs1** (Gene 94176) / **Fat4** (Gene 329628); zebrafish **dchs1b**, **dchs2**, **fat** orthologs; *Drosophila* **ds** (dachsous) and **ft** (fat). The pathway is **deeply evolutionarily conserved** (Fat–Dachsous PCP originally defined in *Drosophila*;
  P 24998526
).
  P 28488382
- **Natural disease in animals: No naturally occurring VMS-equivalent** is documented in companion animals or wildlife (OMIA: none specific). Veterinary relevance is limited to experimental models, not spontaneous disease.

- **Comparative biology / conservation:** The neuronal, PCP, cytoskeletal, and growth-control functions of Fat–Dachsous are conserved from flies to mammals; loss produces analogous polarity/migration/proliferation defects across species (P 24998526 P 26160902 P 28488382).
- **Transmission / zoonosis:** Not applicable (non-infectious genetic disorder).

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15. Model Organisms

VMS mechanism has been dissected chiefly in **animal models** (mammalian and invertebrate); no established patient-derived organoid/iPSC model is prominent in the literature to date.

- **Mouse (mammalian):**
- *Dchs1* and *Fat4* knockdown/knockout/conditional models. **Phenotype recapitulation:** periventricular/subcortical heterotopia with expanded progenitors and reduced differentiation, reversed by *Yap* knockdown (P 24056717); disrupted facial branchiomotor neuron migration/PCP (P 24998526); osteoblast-differentiation and craniofacial defects (P 31358536); duplex-kidney/RET phenotypes (P 30853441). **Genetic model types:** knockout, conditional/tissue-specific knockdown. **Limitation:** individual studies capture single organ systems; no single mouse fully reproduces the whole human syndrome. Resource: **MGI**.
- A **2026** model targeting the **DCHS1 intracellular domain** reproduced expanded neurogenic proliferation and VMS-like neurodevelopmental defects

(P 41972678), dissecting domain-specific function.

- **Zebrafish (*Danio rerio*):** maternal-zygotic **dchs1b** (and *dchs2*) mutants — egg-activation, cortical-granule-exocytosis, gastrulation, dorsal-organizer, and actin/microtubule cytoskeleton defects; the Dchs1b intracellular domain rescues microtubule bundling, revealing Fat-independent roles (P 26160902). Resource: **ZFIN**. **Use:** early morphogenesis, cytoskeletal biology, PCP.
- **Drosophila melanogaster:** neuron-specific knockdown of **fat** — shortened lifespan, impaired locomotion, neuromuscular-junction and axonal-targeting defects, supporting a neuronal-autonomous contribution of FAT4 loss to the human neuronal phenotype (P 28488382). Resource: **FlyBase**. **Use:** conserved Fat/Dachsous PCP, neuronal function.

Applications: these models establish the Dchs1–Fat4 → Hippo/YAP axis in neurogenesis, PCP-driven neuronal migration, osteogenesis, and nephrogenesis, and provide platforms for testing pathway-directed interventions (e.g., YAP modulation). **Limitations:** partial phenotype coverage per model; species differences in ear/craniofacial anatomy; absence of a comprehensive humanized model.

Summary of Supported vs. Refuted Hypotheses

Supported (evidence-based): - VMS is autosomal recessive, caused by biallelic *DCHS1* (VMLDS1) or *FAT4* (VMLDS2) LoF variants (P 24056717) (P 22473091). - Periventricular heterotopia arises from loss of Dchs1/Fat4 → YAP de-repression → excess progenitor proliferation/failed differentiation and migration (P 24056717) (P 24998526)

). P 41972678
- The same module drives craniofacial/skeletal (osteoblast) and renal (FAT4–RET) phenotypes (P 31358536). P 30853441
- VMS and Hennekam syndrome are allelic *FAT4* disorders on a phenotypic spectrum (P 24913602 P 29681106). P 31063239
- Conductive hearing loss from ear malformation is near-constant and implant-treatable (P 27739185). P 26491591

Refuted / not supported: No environmental, infectious, or lifestyle etiology; no anticipation; no evidence for a progressive/degenerative course (features are static,). P 40797481

Limitations & Future Directions

- Evidence rests on **case reports/series** (n in the dozens) → frequencies and prognosis are imprecise; no registries, trials, or patient omics.
- **Genotype–phenotype correlations** (*DCHS1* vs *FAT4*; specific domains) and **modifiers** need larger cohorts.
- No **targeted therapy**; the well-defined Hippo/YAP axis is a rational (untested) therapeutic target.
- **Patient-derived iPSC/organoid** models and standardized natural-history studies are priorities.

Key References (PMID)

41972678, 40797481, 39462795, 37551355, 31384091, 31358536, 31063239, 30853441, 29681106, 29505454, 29046692, 28878612, 28488382, 27739185, 26491591, 26160902, 25930014, 24998526, 24913602, 24056717, 22473091.
