XLID98 (X-Linked Intellectual Disability Type 98) aka NEXMIF-Related Neurodevelopmental Disorder

A quick reference for clinicians

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Gene: NEXMIF (formerly *KIAA2022* / *KIDLIA*; older clinical term MRX98) · **OMIM:** #300912 (disorder), *300524 (gene) · **Inheritance:** X-linked · **Prevalence:** ultra-rare (a few hundred identified worldwide; likely under-recognized)

Prepared by the XLID98 Foundation for clinicians who may be caring for a patient with this rare condition. Most clinicians will not have encountered it before. This sheet is a brief orientation to aid recognition and day-to-day management — not a standard of care; the evidence base is small and evolving.

What it is

An X-linked neurodevelopmental disorder caused by loss-of-function variants in *NEXMIF*, a gene highly expressed in the developing brain that governs neuronal growth, migration, and connectivity. The core phenotype is a triad of **intellectual disability / developmental delay, epilepsy, and autism-spectrum features**, across a very wide range of severity.

When to suspect & how to confirm

- Consider in any patient with **unexplained developmental delay / intellectual disability and epilepsy**, with or without autism features.
- **Most pathogenic variants are sequence-level** (truncating, splice, or missense) and are found by **whole-exome / whole-genome sequencing or a multigene epilepsy/ID panel** — not by chromosomal microarray, which detects only the minority of cases caused by larger deletions / duplications. **A normal microarray does not exclude the diagnosis; pursue sequencing if suspicion persists.**
- Confirm with **CLIA-certified clinical sequencing**; refer to **clinical genetics** for confirmation, parental testing (*de novo* vs inherited), and counseling.
- Presentation overlaps with other neurodevelopmental / epilepsy syndromes (e.g., **Angelman, CDKL5, Dravet, atypical absence / Jeavons**), which may be considered first. Reconsider a prior diagnosis that does not fully fit.

Inheritance — females are affected, not only carriers

- **X-linked.** Most females are mild to severely affected depending on the X-inactivation pattern; most males are severely affected.

- **Do not assume heterozygous females are unaffected carriers.** They are commonly symptomatic — epilepsy is often prominent — because **X-inactivation** creates a mosaic of cells expressing the normal vs variant allele. Female phenotype ranges from severe to (with skewed X-inactivation) asymptomatic.
- **Males** have a single X; they are generally more uniformly and severely affected (development, speech).
- Most reported cases are *de novo*; some are inherited from an often minimally affected carrier mother. For an apparently *de novo* variant, recurrence risk is low but not zero (germline mosaicism; the general counseling estimate is ~1%). Once the variant is known, family testing and PGT / prenatal options are available — refer to genetics for recurrence counseling.

Clinical features at a glance

> In the largest cohort to date — 87 individuals (63 female, 24 male; Stamberger et al, 2021) — **developmental delay / ID was present in ~99%** and **epilepsy in ~83%**. Severity is highly variable: "if you've met one patient, you've met one patient."

- **Cognition / speech:** DD/ID mild → severe; speech most affected (many nonverbal or limited; some verbal).
- **Epilepsy (~83%):** multiple seizure types; onset usually childhood but can be later (incl. adolescence/adulthood).
- **Behavior:** autism features common; self-injurious behavior in some.
- **Tone / motor:** hypotonia, motor delay, dyspraxia, gait abnormality.
- **Growth / craniofacial:** variable poor growth and/or relative microcephaly; nonspecific dysmorphism in some.
- **GI / feeding:** dysphagia / aspiration risk, constipation, feeding difficulty.
- **Eyes:** strabismus, nystagmus, cerebral visual impairment.
- **Other:** sleep disturbance, mild scoliosis, early puberty in some.

Management priorities by system

Epilepsy. No single first-line agent. Reported seizure types include myoclonic, tonic, tonic-clonic, absence, atonic / drop, and eyelid myoclonia, frequently sleep-related; overlapping syndromic labels (Lennox-Gastaut, Jeavons, Dravet-like) occur. Co-manage with neurology / epileptology, and note:

- **Cannabidiol (Epidiolex) + valproate sharply raises the risk of hepatic transaminase elevation** — ALT >3× ULN in ~21% on valproate vs ~3% on neither (≈30% if clobazam is also present). Monitor LFTs, especially in the first 1–3 months. (FDA Epidiolex label.)
- **Nonconvulsive status epilepticus (NCSE)** is reported in NEXMIF (including recurrent nonconvulsive status in females) and may present only as altered behavior or alertness — have a **low threshold for EEG**.
- Caregivers have reported seizure worsening with hormonal changes in girls (e.g., around menarche) — a catamenial-type pattern worth asking about *(caregiver-reported)*.
- Ensure a written **rescue / seizure action plan**.

Feeding & GI. Screen for dysphagia / aspiration and constipation; some need texture modification or gastrostomy. SLP/OT feeding evaluation; treat constipation proactively (it can affect medication absorption and seizure threshold).

Growth, metabolic & hepatic. Monitor growth and weight — several antiseizure, antipsychotic, and ADHD agents predispose to weight gain. A **preliminary, not-yet-established** signal (early human observation plus mild hepatic steatosis in the mouse model) links *NEXMIF* to metabolic / hepatic features; this is not guideline-based, but some clinicians consider baseline liver enzymes reasonable.

Behavior, development & psych. In largely nonverbal patients, behavior is frequently communicative. Engage developmental-behavioral pediatrics, psychology, and AAC / speech, OT (sensory), PT, and ABA as appropriate. **Caution:** activation / agitation on SSRIs has been reported by families *(caregiver-reported)*, consistent with the recognized activation risk in young / neurodevelopmentally affected patients — start low and monitor.

Vision, orthopedic & sleep. Ophthalmology (strabismus, CVI); orthopedic monitoring (scoliosis); sleep assessment (melatonin used by some families).

Suggested surveillance & referrals

- **Clinical genetics** — confirmation, counseling, family testing.
- **Neurology / epileptology** — seizures, EEG.
- **Developmental-behavioral pediatrics** & psychology.
- **GI / nutrition** & feeding (SLP/OT).
- **Ophthalmology**; **orthopedics** as needed.

- **PT / OT / SLP**; AAC for nonverbal patients.
- Baseline **liver enzymes**; monitor growth & weight.
- Written seizure / rescue plan on file.

Resources & patient registry

- **XLID98 Foundation** — family support and clinician connection: xlid98.org
- **XLID98 Foundation Facebook group** — connect with other families and the foundation for peer support and shared experience; a good first step for a newly diagnosed family: facebook.com/groups/1737543686499443
- **NORD (National Organization for Rare Disorders)** — rare-disease information, patient & family support resources, and patient-assistance programs: rarediseases.org
- **Gene-targeted therapies are in active preclinical development.** The XLID98 Foundation's patient registry is being established; family participation builds the natural-history data that future trials will require.

Selected references

- Stamberger H, et al. NEXMIF encephalopathy: an X-linked disorder with male and female phenotypic patterns. *Genet Med.* 2021;23(2):363-373. PMID 33144681.
- de Lange IM, et al. *De novo* mutations of *KIAA2022* in females cause intellectual disability and intractable epilepsy. *J Med Genet.* 2016;53(12):850-858. PMID 27358180.
- OMIM #300912 (XLID98): omim.org/entry/300912

Prepared by the XLID98 Foundation · July 2026 · Summarizes current, evolving knowledge of a rare condition for general clinical orientation; published sources are listed above, and items marked "caregiver-reported" reflect family observation rather than published study. Not a substitute for specialist consultation or individual clinical judgment. Learn more at xlid98.org.