NAGER SYNDROME

Otherwise known as?

Nager syndrome, also known as Nager acrofacial dysostosis, has a few alternative names, including:

1. Nager Acrofacial Dysostosis (NAFD) – The most common alternative name, emphasizing its classification as an acrofacial dysostosis syndrome (a condition affecting the face and limbs).
2. Acrofacial Dysostosis, Nager Type – Highlights that it is one type within the broader acrofacial dysostosis group.
3. Nager Syndrome of Acrofacial Dysostosis – Another variation that describes the condition's characteristics.

Despite these variations, Nager syndrome remains the most widely recognized and commonly used term.

Signs & Symptoms

Nager syndrome is a rare genetic condition that primarily affects the development of the face, jaw, and limbs. The severity of symptoms can vary, but the most common features involve craniofacial differences, limb anomalies, and potential breathing or feeding difficulties.

1. Craniofacial differences

The most noticeable characteristics of Nager syndrome affect the face and skull, including:

- Micrognathia (small lower jaw) - causes Pierre Robin sequence, leading to:
  - Airway obstruction (breathing difficulties).
  - Feeding difficulties in infancy.
  - Cleft palate (sometimes present).
- Malar Hypoplasia (underdeveloped cheekbones) - results in a sunken facial appearance.
- Downward-slanting Palpebral Fissures - the outer corners of the eyes slant downward.
- Absent or Underdeveloped Lower Eyelashes.
- External Ear anomalies - small, malformed, or absent ears (microtia), sometimes leading to hearing loss.

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- Hearing Loss - often due to middle ear differences rather than nerve-related issues.
- Cleft Lip and/or Cleft Palate (in some cases).

2. Limb anomalies

Nager syndrome is classified as an acrofacial dysostosis, meaning it affects both the face (cranio-) and limbs (-acro-). Common limb anomalies include:

- Thumb Hypoplasia (underdeveloped or absent thumbs).
- Radial Ray Defects - short or missing radius bone in the forearm, causing the wrist to curve inward (radial club hand).
- Syndactyly (fused fingers or toes).
- Shortened Forearms.
- Limited Elbow Movement due to differences in the bones and joints.
- Lower Limb Involvement (less common) - some individuals may have toe differences or mild leg differences.

3. Breathing and Feeding Difficulties

- Airway obstruction due to micrognathia (small lower jaw) may cause difficulty breathing, especially in newborns.
- Difficulty swallowing (Dysphagia) may require a feeding tube in infancy.
- Recurrent respiratory infections due to airway issues.

4. Other Possible Symptoms

- Intelligence is usually normal - most individuals have normal cognitive development.
- Speech Delays due to jaw differences and hearing loss.
- Growth Delay - some individuals may have a smaller overall stature.

Causes

Nager syndrome is a genetic condition that affects the development of the face, jaw, and limbs. It is primarily caused by mutations in the EIF4A3 gene, which plays a role in early embryonic development.

1. Genetic Cause

- EIF4A3 Gene Mutation:
  - The EIF4A3 gene is responsible for regulating RNA processing, which affects how proteins are made during early development.
  - Mutations in this gene disrupt craniofacial and limb formation, leading to the features of Nager syndrome.

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- Inheritance Pattern:
  - Most cases occur sporadically (de novo mutations) – meaning they happen randomly and are not inherited from parents.
  - However, some cases may follow an autosomal dominant inheritance pattern, where an affected parent can pass the mutation to their child.
  - There is also evidence suggesting autosomal recessive inheritance in rare cases, where both parents (who are carriers) pass on a faulty gene.

2. Effects of the Mutation

The EIF4A3 mutation affects the development of:

- Craniofacial structures - leading to micrognathia (small jaw), cheekbone underdevelopment, and ear anomalies.
- Limb formation - resulting in missing thumbs, short forearms, and fused fingers.

3. Other Possible Genetic Factors

- In some cases, no EIF4A3 mutation is found, suggesting other unknown genes may be involved.
- More research is needed to identify additional genetic causes of Nager syndrome.

Testing & Diagnosis

Diagnosing Nager syndrome involves a combination of clinical evaluation, imaging studies, and genetic testing to confirm the presence of a mutation in the EIF4A3 gene.

1. Clinical Evaluation

A doctor will assess the child's physical features, looking for:

- Facial differences - small jaw (micrognathia), underdeveloped cheekbones, downward-slanting eyes.
- Limb anomalies - missing or underdeveloped thumbs, shortened forearms, wrist curving (radial ray anomaly).
- Ear and hearing issues - small or absent ears (microtia), hearing loss.
- Breathing and feeding difficulties - due to airway obstruction from jaw differences.

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2. Imaging Tests

a. X-rays & CT Scans are used to examine:
- Skull structure (craniofacial differences).
- Forearm and hand bones (for radial ray anomalies).

b. MRI (Magnetic Resonance Imaging) may be used to assess airway structure or brain development if needed.

3. Hearing and Developmental Tests

a. Hearing Tests (Audiometry) - since hearing loss is common, newborn hearing screening and follow-up audiology tests are important.
b. Developmental Assessments - if speech or motor delays are suspected, early intervention can be planned.

4. Genetic Testing (Definitive Diagnosis)

A blood or saliva sample is taken for DNA sequencing to check for mutations in the EIF4A3 gene.

a. Targeted Gene Testing - if Nager syndrome is strongly suspected, doctors test specifically for EIF4A3 mutations.
b. Whole Exome Sequencing (WES) - if the diagnosis is unclear, WES can help identify other possible genetic causes.

Treatment

There is no cure for Nager syndrome, but treatment focuses on managing symptoms and improving breathing, feeding, hearing, and mobility. A multidisciplinary team of specialists, including craniofacial surgeons, ENT specialists, audiologists, speech therapists, and orthopaedic surgeons, is involved in care.

1. Airway and Breathing Support

Because micrognathia (small jaw) can cause airway obstruction, treatment may include:

a. Positioning techniques - keeping the baby on their stomach or side to help with breathing.
b. Nasopharyngeal airway (NPA) - a tube placed in the nose to help keep the airway open.
c. Tracheostomy (if severe) - a breathing tube inserted into the neck if other methods do not work.
d. Mandibular distraction osteogenesis (MDO) – in severe cases, surgery can gradually enlarge the lower jaw and improve airway function.

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2. Feeding and Nutrition Support

Feeding difficulties due to cleft palate and jaw differences may require:
a. Specialized feeding bottles – to help babies with weak suction.
b. Nasogastric (NG) tube or Gastrostomy (G-tube) - if the baby cannot swallow properly, a feeding tube provides nutrition.
c. Cleft palate repair surgery - if a cleft palate is present, it can be addressed surgically.

3. Hearing Management

Since hearing loss is common, early intervention is key:
a. Hearing aids - to improve hearing if middle ear problems cause hearing loss.
b. Cochlear implants - for severe cases of hearing loss.
c. Speech therapy - to support language development.

4. Facial and Jaw Surgery

a. Mandibular Distraction Osteogenesis (MDO) – in severe cases, surgery can gradually lengthen the jaw and improve breathing, feeding, and facial symmetry.
b. Orthodontic treatment - braces or other dental work to align teeth properly.
c. Cheekbone reconstruction - if needed for facial structure support.

5. Limb and Hand Surgery or Therapy

a. Thumb reconstruction - if a thumb is missing, a finger (usually the index finger) may be surgically repositioned to function as a thumb.
b. Wrist and forearm surgery - to improve movement in cases where the radius bone is missing.
c. Physical and occupational therapy – to help with fine motor skills and daily activities.

6. Developmental and Educational Support

a. Early intervention programs - to help with speech, motor skills, and cognitive development.
b. Speech therapy - supports children with speech delays due to hearing loss or jaw problems.
c. Specialized learning support - if developmental delays are present.

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7. Psychological and Social Support

a. Counselling for families - helps parents and caregivers navigate challenges.
b. Support groups - connecting with other families affected by Nager syndrome can provide emotional support.

8. Regular Follow-Ups and Monitoring

a. Ongoing medical check-ups - to monitor jaw growth, hearing, and limb function.
b. Craniofacial team evaluations - ensures long-term treatment planning.

Did you know?

Nager syndrome affects males and females in equal numbers. The exact incidence and prevalence in the general population is unknown. Many cases go misdiagnosed or undiagnosed, making it difficult to determine the true frequency in the general population. More than 100 cases have been reported in the medical literature.*

Nager syndrome primarily affects facial and limb development. Despite having challenges with speech and eating due to jaw problems, many individuals with Nager syndrome develop creative ways to communicate and thrive in school and professional settings.

References:

*https://rarediseases.org/rare-diseases/nager-syndrome Accessed 7th March 2025

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How we can support you:

- Care packs
- Financial assistance
- Family support coordinator
- Connection to other families