Ataxia neuropathy spectrum

Ataxia neuropathy spectrum is part of a group of conditions called the *POLG*-related disorders. The conditions in this group feature a range of similar signs and symptoms involving muscle-, nerve-, and brain-related functions. Ataxia neuropathy spectrum now includes the conditions previously called mitochondrial recessive ataxia syndrome (MIRAS) and sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO).

As the name implies, people with ataxia neuropathy spectrum typically have problems with coordination and balance (ataxia) and disturbances in nerve function (neuropathy). The neuropathy can be classified as sensory, motor, or a combination of the two (mixed). Sensory neuropathy causes numbness, tingling, or pain in the arms and legs, and motor neuropathy refers to disturbance in the nerves used for muscle movement.

Most people with ataxia neuropathy spectrum also have severe brain dysfunction (encephalopathy) and seizures. Some affected individuals have weakness of the external muscles of the eye (ophthalmoplegia), which leads to drooping eyelids (ptosis). Other signs and symptoms can include involuntary muscle twitches (myoclonus), liver disease, depression, migraine headaches, or blindness.

Frequency

The prevalence of ataxia neuropathy spectrum is unknown.

Causes

Ataxia neuropathy spectrum is caused by mutations in the *POLG* gene or, rarely, the *TWNK* gene.

The *POLG* gene provides instructions for making one part, the alpha subunit, of a protein called polymerase gamma (pol γ). The *TWNK* gene provides instructions for making a protein called Twinkle. Pol γ and Twinkle function in mitochondria, which are structures within cells that use oxygen to convert the energy from food into a form cells can use. Mitochondria each contain a small amount of DNA, known as mitochondrial DNA (mtDNA), which is essential for the normal function of these structures. Pol γ and Twinkle are both integral to the process of DNA replication by which new copies of mtDNA are produced.

Mutated pol γ or mutated Twinkle reduce mtDNA replication. Although the mechanisms are unknown, mutations in the *POLG* gene often result in fewer copies of mtDNA (mtDNA depletion), and mutations in the *TWNK* gene often result in deletions of large regions of mtDNA (mtDNA deletion). MtDNA depletion or deletion occurs most commonly in muscle, brain, or liver cells. MtDNA depletion causes a decrease in

cellular energy, which could account for the signs and symptoms of ataxia neuropathy spectrum. It is unclear what role mtDNA deletions play in the signs and symptoms of the condition.

Inheritance Pattern

Ataxia neuropathy spectrum can have different inheritance patterns depending on the associated gene.

Mutations in the *POLG* gene cause a form of the condition that is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Mutations in the *TWNK* gene cause a form of the condition that is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Other Names for This Condition

- ANS
- MIRAS
- mitochondrial recessive ataxia syndrome
- SANDO
- sensory ataxia neuropathy dysarthria and ophthalmoplegia

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1843851/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22ataxia+neuropathy+spectrum%22+OR+%22Mitochondrial+Diseases%22

Other Diagnosis and Management Resources

- GeneReview: POLG-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK26471
- United Mitochondrial Disease Foundation: Getting a Diagnosis
  https://www.umdf.org/what-is-mitochondrial-disease/getting-a-diagnosis/

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Balance Problems
  https://medlineplus.gov/balanceproblems.html
- Health Topic: Degenerative Nerve Diseases
  https://medlineplus.gov/degenerativenervediseases.html
- Health Topic: Genetic Brain Disorders
  https://medlineplus.gov/geneticbraindisorders.html
- Health Topic: Movement Disorders
  https://medlineplus.gov/movementdisorders.html
- Health Topic: Seizures
  https://medlineplus.gov/seizures.html

Genetic and Rare Diseases Information Center

- Sensory ataxic neuropathy, dysarthria, and ophthalmoparesis
  https://rarediseases.info.nih.gov/diseases/9998/sensory-ataxic-neuropathy-dysarthria-and-ophthalmoparesis

Additional NIH Resources

- National Institutes of Health Rare Diseases Clinical Research Network: North American Mitochondrial Disease Consortium
  https://www.rarediseasesnetwork.org/cms/NAMDC

Educational Resources

- MalaCards: ataxia neuropathy spectrum
  https://www.malacards.org/card/ataxia_neuropathy_spectrum
- Mayo Clinic: North American Mitochondrial Disease Consortium Patient Registry and Biorepository (NAMDC)
  https://www.mayo.edu/research/clinical-trials/cls-20409244
- Orphanet: Sensory ataxic neuropathy-dysarthria-ophthalmoparesis syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=70595

Patient Support and Advocacy Resources

- MitoAction
  http://www.mitoaction.org/
- Muscular Dystrophy Association: Mitochondrial Myopathies
  https://www.mda.org/disease/mitochondrial-myopathies
- National Ataxia Foundation
  https://ataxia.org/
- United Mitochondrial Disease Foundation: What is Mitochondrial Disease?
  https://www.umdf.org/what-is-mitochondrial-disease/

Clinical Information from GeneReviews

- POLG-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK26471

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28miras%5BTIAB%5D%29+OR+%28sando%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- SENSORY ATAXIC NEUROPATHY, DYSARTHRIA, AND OPHTHALMOPARESIS
  http://omim.org/entry/607459

Sources for This Summary

- Chan SS, Longley MJ, Copeland WC. The common A467T mutation in the human mitochondrial DNA polymerase (POLG) compromises catalytic efficiency and interaction with the accessory subunit. J Biol Chem. 2005 Sep 9;280(36):31341-6. Epub 2005 Jul 16.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16024923
- Cohen BH, Chinnery PF, Copeland WC. POLG-Related Disorders. 2010 Mar 16 [updated 2014 Dec 18]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from http://www.ncbi.nlm.nih.gov/books/NBK26471/
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20301791
- Hudson G, Deschauer M, Busse K, Zierz S, Chinnery PF. Sensory ataxic neuropathy due to a novel C10Orf2 mutation with probable germline mosaicism. Neurology. 2005 Jan 25;64(2):371-3.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/15668446
- Milone M, Massie R. Polymerase gamma 1 mutations: clinical correlations. Neurologist. 2010 Mar; 16(2):84-91. doi: 10.1097/NRL.0b013e3181c78a89. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20220442

- Moraes CT, Shanske S, Tritschler HJ, Aprille JR, Andreetta F, Bonilla E, Schon EA, DiMauro S. mtDNA depletion with variable tissue expression: a novel genetic abnormality in mitochondrial diseases. Am J Hum Genet. 1991 Mar;48(3):492-501.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/1998336
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1682992/
- Rocher C, Taanman JW, Pierron D, Faustin B, Benard G, Rossignol R, Malgat M, Pedespan L, Letellier T. Influence of mitochondrial DNA level on cellular energy metabolism: implications for mitochondrial diseases. J Bioenerg Biomembr. 2008 Apr;40(2):59-67. doi: 10.1007/s10863-008-9130-5. Epub 2008 Apr 16.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18415670
- Stumpf JD, Copeland WC. Mitochondrial DNA replication and disease: insights from DNA polymerase γ mutations. Cell Mol Life Sci. 2011 Jan;68(2):219-33. doi: 10.1007/s00018-010-0530-4. Epub 2010 Oct 8. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20927567
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046768/
- Van Goethem G, Martin JJ, Dermaut B, Löfgren A, Wibail A, Ververken D, Tack P, Dehaene I, Van Zandijcke M, Moonen M, Ceuterick C, De Jonghe P, Van Broeckhoven C. Recessive POLG mutations presenting with sensory and ataxic neuropathy in compound heterozygote patients with progressive external ophthalmoplegia. Neuromuscul Disord. 2003 Feb;13(2):133-42.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/12565911

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