MECP2 duplication syndrome

MECP2 duplication syndrome is a condition that occurs almost exclusively in males and is characterized by moderate to severe intellectual disability. Most people with this condition also have weak muscle tone in infancy, feeding difficulties, poor or absent speech, or muscle stiffness (rigidity). Individuals with *MECP2* duplication syndrome have delayed development of motor skills such as sitting and walking. About half of individuals have seizures, often of the tonic-clonic type. This type of seizure involves a loss of consciousness, muscle rigidity, and convulsions and may not respond to medication. Some affected individuals experience the loss of previously acquired skills (developmental regression). Approximately half of individuals learn to walk, and about one-third of people with this condition require assistance when walking. Many individuals with *MECP2* duplication syndrome have recurrent respiratory tract infections. These respiratory infections are a major cause of death in affected individuals, with only half surviving past age 25.

Frequency

The prevalence of *MECP2* duplication syndrome is unknown; more than 200 affected individuals have been described in the scientific literature. It is estimated that this condition is responsible for 1 to 2 percent of all cases of intellectual disability caused by changes in the X chromosome.

Genetic Changes

MECP2 duplication syndrome is caused by a genetic change in which there is an extra copy of the *MECP2* gene in each cell. This extra copy of the *MECP2* gene is caused by a duplication of genetic material on the long (q) arm of the X chromosome. The size of the duplication varies from 100,000 to a few million DNA building blocks (base pairs). The *MECP2* gene is always included in this duplication, and other genes may also be involved, depending on the size of the duplicated segment. It is unclear whether extra copies of these other genes affect the severity of the condition.

The *MECP2* gene provides instructions for making a protein called MeCP2 that is critical for normal brain function. Researchers believe that this protein has several functions, including regulating other genes in the brain by controlling when they are able to participate in protein production. An extra copy of the *MECP2* gene leads to the production of excess MeCP2 protein and an increase in protein function. The resulting changes in gene regulation and protein production in the brain lead to abnormal nerve cell (neuronal) function. These neuronal changes disrupt normal brain activity, causing the signs and symptoms of *MECP2* duplication syndrome.

Inheritance Pattern

MECP2 duplication syndrome is inherited in an X-linked pattern. The gene associated with this condition is located on the X chromosome, which is one of the two sex chromosomes in each cell. In males (who have only one X chromosome), a duplication of the only copy of the *MECP2* gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a duplication of one of the two copies of the gene typically does not cause the disorder, but can be associated with behavioral and psychiatric symptoms such as depression, anxiety, and features of autism spectrum disorders that affect communication and social interaction.

Females with a *MECP2* gene duplication tend to be unaffected or less severely affected than males because the X chromosome that contains the duplication may be turned off (inactive) in many of their cells due to a process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell. Usually X-inactivation occurs randomly, such that each X chromosome is active in about half of the body's cells. Sometimes X-inactivation is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation.

Females with a *MECP2* gene duplication often have skewed X-inactivation, which results in the inactivation of the X chromosome containing the duplication in most cells of the body. Although this skewed X-inactivation ensures that the chromosome with the normal *MECP2* gene is active most often, some of these females develop behavioral and psychiatric symptoms thought to be related to the additional genetic material. It is unclear why these features develop in a small number of females with skewed X-inactivation. Researchers speculate that in these females some cells in the brain may have a different pattern of X-inactivation than the cells in the rest of the body so that the X chromosome with the duplicated *MECP2* gene is active, resulting in behavioral and psychiatric symptoms.

Other Names for This Condition

- Lubs X-linked mental retardation syndrome
- trisomy Xq28

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: MECP2 duplication syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1846058/

Other Diagnosis and Management Resources

- GeneReview: MECP2 Duplication Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1284
- RettSyndrome.org: Rett Syndrome, MECP2 Duplication, and Rett-related Disorders Natural History Study
  https://www.rettsyndrome.org/natural-history-study

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Hypotonia
  https://medlineplus.gov/ency/article/003297.htm
- Encyclopedia: Spasticity
  https://medlineplus.gov/ency/article/003297.htm
- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html

Genetic and Rare Diseases Information Center

- MECP2 duplication syndrome
  https://rarediseases.info.nih.gov/diseases/9781/mecp2-duplication-syndrome

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Seizures and Epilepsy
  https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Epilepsies-and-Seizures-Hope-Through
- National Institute of Neurological Disorders and Stroke: Spasticity Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Spasticity-Information-Page

Educational Resources

- Boston Children's Hospital: Respiratory Distress
  http://www.childrenshospital.org/conditions-and-treatments/conditions/r/respiratory-distress
- Boston Children's Hospital: Seizures
  http://www.childrenshospital.org/conditions-and-treatments/conditions/s/seizures
- Centers for Disease Control and Prevention: Intellectual Disability
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/IntellectualDisability.pdf
- Disease InfoSearch: MECP2 duplication syndrome
  http://www.diseaseinfosearch.org/MECP2+duplication+syndrome/4540
- March of Dimes: Chromosomal Conditions
  https://www.marchofdimes.org/baby/chromosomal-conditions.aspx
- Orphanet: Trisomy Xq28
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1762

Patient Support and Advocacy Resources

- Rare Diseases Clinical Research Network: Rett Consortium
  https://www.rarediseasesnetwork.org/cms/rett/Learn-More/Disorder-Definitions#MECP2
- RettSyndrome.org
  https://www.rettsyndrome.org/
- RettSyndrome.org: Rett Syndrome, MECP2 Duplication, and Rett-related Disorders Natural History Study
  https://www.rettsyndrome.org/natural-history-study
- The Arc
  https://www.thearc.org/

GeneReviews

- MECP2 Duplication Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1284

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22MECP2+duplication+syndrome%22+OR+%22Trisomy+Xq28%22+OR+%22RTT-related+conditions%22+OR+%22Rett-related+disorder%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28mecp2+duplication+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D

OMIM

- LUBS X-LINKED MENTAL RETARDATION SYNDROME
  http://omim.org/entry/300260

MedGen

- Trisomy Xq28 syndrome
  https://www.ncbi.nlm.nih.gov/medgen/930014

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