CURE MED13L

MED13L

ICD-10 COORDINATION AND MAINTENANCE COMMITTEE

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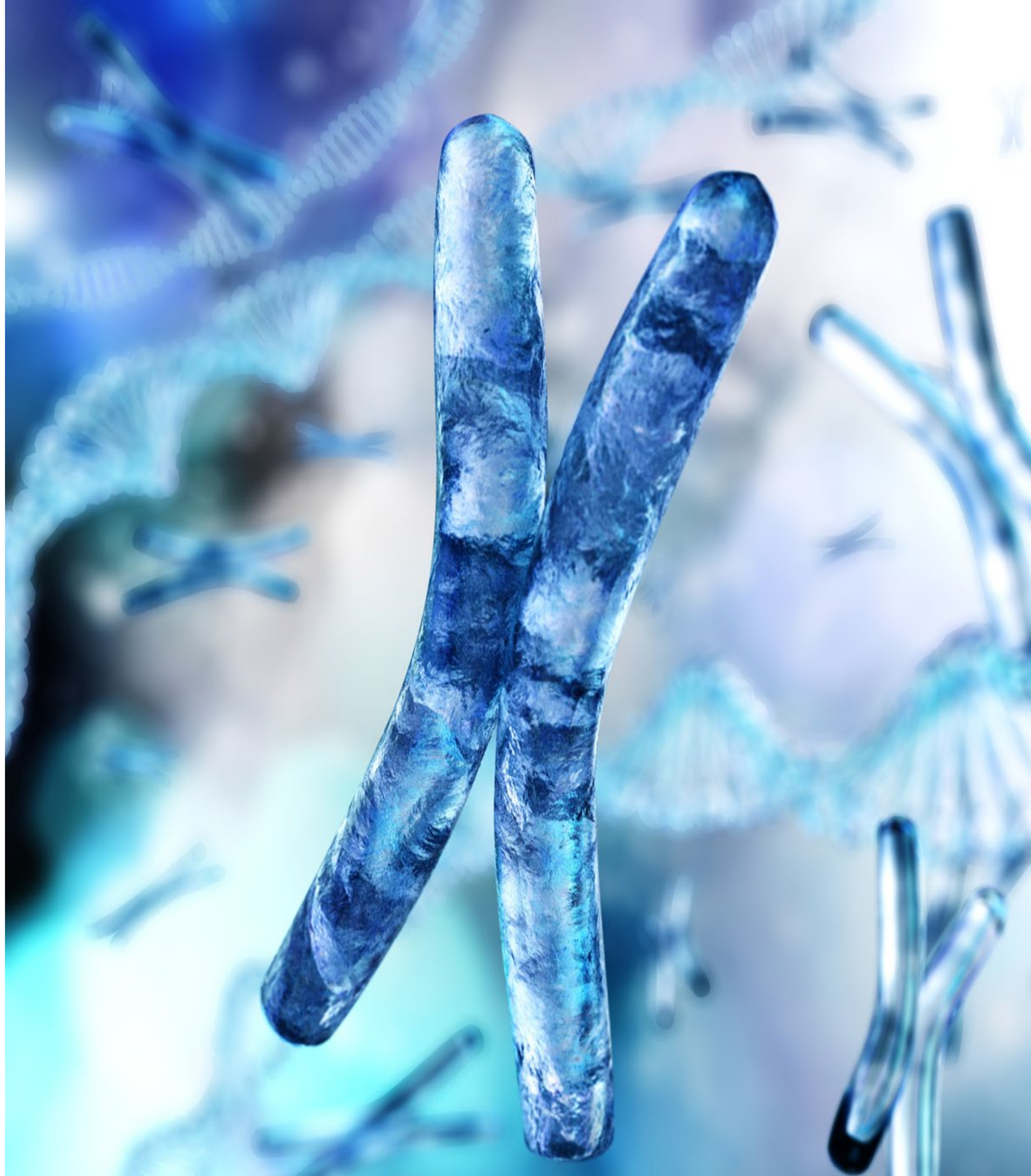
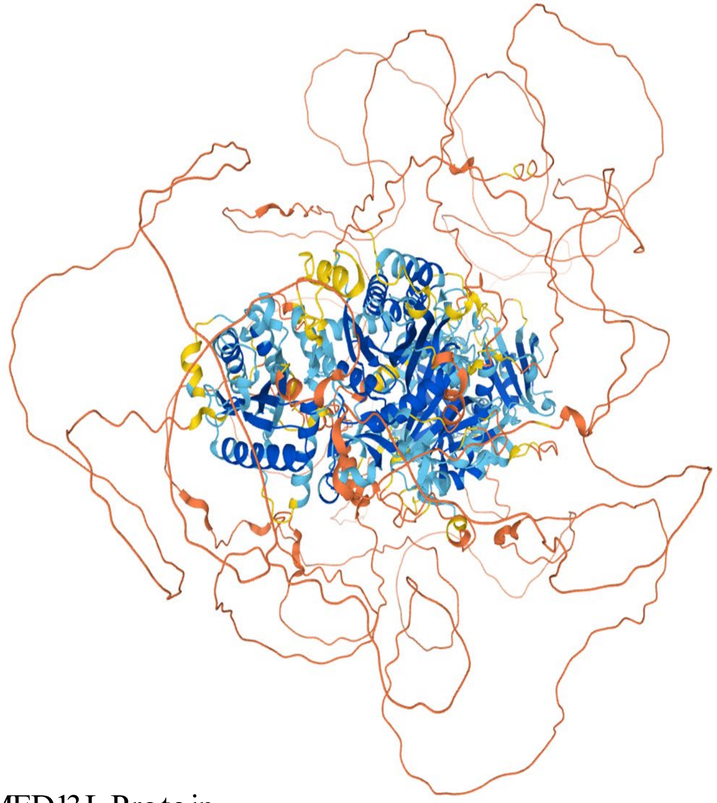


MED13L:

- MED13L syndrome is an autosomal dominant condition due to pathogenic variants in the MED13L gene which is located on chromosome 12. (12q.24.21).

  - The vast majority of the MED13L variants are de novo & result in haploinsufficiency.

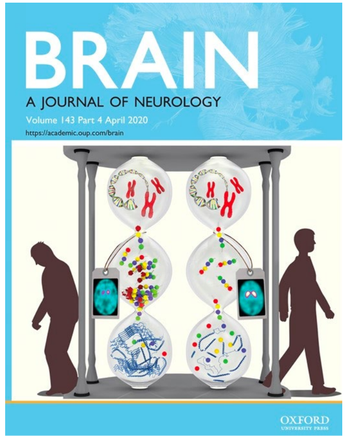


MED13L Protein

Incidence:

MED13L is a relatively high prevalence mutation among monogenic diseases, with an estimated incidence of approximately 6 per 100,000

gene	incidence
SYNGAP1	6.107454128
NSD1	6.041370616
MED13L	5.955180806
GRIN2B	5.910573574
KIF1A	5.216012949



A catalogue of new incidence estimates of monogenic neurodevelopmental disorders caused by *de novo* variants

Javier A López-Rivera, Eduardo Pérez-Palma, Joseph Symonds, Amanda S Lindy, Dianalee A McKnight, Costin Leu, Sameer Zuberi, Andreas Brunklaus, Rikke S Møller, Dennis Lal

Brain, Volume 143, Issue 4, April 2020, Pages 1099–1105, https://doi.org/10.1093/brain/awaa051

Clinical Presentation:

- Global developmental delay (milder motor delay, but often significant speech delay)
- Intellectual disability
- Hypotonia (~60% of patients)
- Autistic features (~30% of patients)
- Ataxia/coordination problems (~30% of patients)
- Epilepsy/abnormal EEG (~20% of patients)
- Abnormal brain MRI (~35% of patients, mainly white matter hyperintensity, dilatation of ventricles/CSF spaces, corpus callosum abnormality)
- Congenital cardiac anomalies (~30% of patients, mainly septal defects, secondly conotruncal anomalies such as TGA (Transposition of Great Arteries) and ToF (Tetralogy of Fallot) requiring surgery
- Vision and hearing abnormalities
- Abnormalities of extremities (variable from minor finger and toe anomalies to clubfoot and matatarsus adductus)
- Abnormal growth parameters
- Other anomalies (facial features, cleft palate, etc.)

https://rarediseases.info.nih.gov/diseases/12999/med13l-syndrome;
https://www.nature.com/articles/ejhg201519

Is MED13L-related intellectual disability a recognizable syndrome?
Author: Pernille Mathiesen Tørring,Martin Jakob Larsen,Charlotte Brasch-Andersen,Lotte Nylandsted Krogh,Maria Kibæk,Lone Laulund,Niels Illum,Ulrike Dunkhase-Heinl,Antje Wiesener,Bernt Popp,Giuseppe Marangi,Tina Duelund Hjortshøj,Jakob Ek,Ida Vogel et al.
Publication: European Journal of Medical Genetics
Publisher: Elsevier
Date: February 2019

Diagnostics & Need for Medical Management:

Genetic testing is required for diagnosis

Diagnosis should prompt further testing:

- EEG (electroencephalogram)
  - Around 20% of individuals develop seizures
    - Most respond well to therapy
  - Late onset seizures have been reported
    - Close monitoring of seizure activity is recommended
- Cardiac
  - Congenital cardiac anomalies: ASD (atrial septal defect) , PSD (atent ductus arteriosus), Pulmonary Stenosis, PDA, ToF, TGA, TAPVD (Total anomalous pulmonary venous drainage)
- Orthopedic
  - Talipes, Hip Dysplasia, Scoliosis
- Vision
  - Duane anomaly; hyperopic astigmatism; hypermetropia; and retinal dystrophy (progressive)
- Hearing
  - sensorineural as well as conductive

https://www.rarechromo.org/media/singlegeneinfo/Single%20Gene%20Disorder%20Guides/MED13L%20QFN.pdf

Medical Management:

- Early and frequent therapeutic management is imperative to increasing the quality of life
  - Physical therapy
    - Gross motor delays, ataxia
  - Occupational therapy
    - Sensory issues, fine motor delay, vestibular dysfunction
  - Vision therapy
    - Amblyopia impacts day to day life
  - Speech therapy
    - Early introduction of communication & language support:
      - Decrease likelihood of behavioral issues
      - Support future academic success
      - Improve social abilities
  - MED13L Foundation is currently working with partners to develop MED13L-specific medicines, including repurposed small therapeutics and gene-related approaches, including anti-sense oligonucleotides (RNA) and gene editing

Rationale for a New ICD-10 Code:

- Assist in access for **proper medical management**
- **Facilitate care** for patients seeking treatment when a targeted therapy is available
- Aid in **strengthening research & monitoring** of the disease and its progression
- Enable more **accurate quantification of the prevalence** of MED13L
- Prescription of **MED13L specific therapeutics**, including repurposed small molecule drugs (targeted availability 2023), with potential to dramatically improve healthcare economics

Specificity of diagnostic codes

Early idenitfication & management of comorbitities

Proper therapeutic support

Prevelance data for MED13L likely more accurate

MED13L is hypothesized to have an effect on mitochondrial function which may require additional intervention

CURE MED13L

MED13L FOUNDATION

Thank You!