Phelan-McDermid syndrome

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Overview of Phelan-McDermid Syndrome

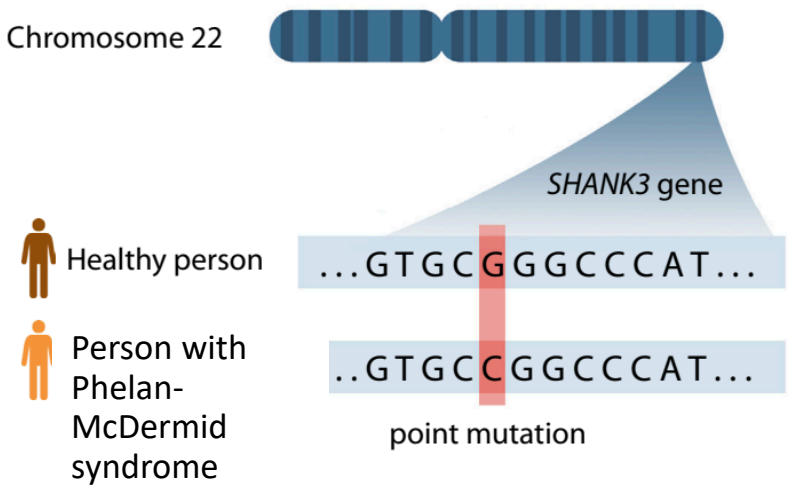
- Genetic neurodevelopmental disorder
- Diagnosed with genetic testing
- Estimated to impact ~1:10,000-1:15,000 people
- Core symptoms: intellectual disability, impaired speech, low muscle tone at birth (hypotonia), and developmental delay
- Can affect many major organ systems in the body, and commonly leads to frequent hospitalization
- Clinical trials are ongoing, but no treatments address the underlying cause of the disorder

Genetic Cause of Phelan-McDermid Syndrome

- The cause of Phelan-McDermid syndrome has been established to be genetic variations causing a loss or change to DNA in a specific portion of chromosome 22 (location q13.3)
- In **~80% of individuals**, the cause is a deletion of DNA that impacts region q13.3
- Genes in this region are known to be important for neurodevelopment
- Various genetic changes can cause a deletion of DNA at the end of part of chromosome 22 (all of which are considered Phelan-McDermid syndrome)

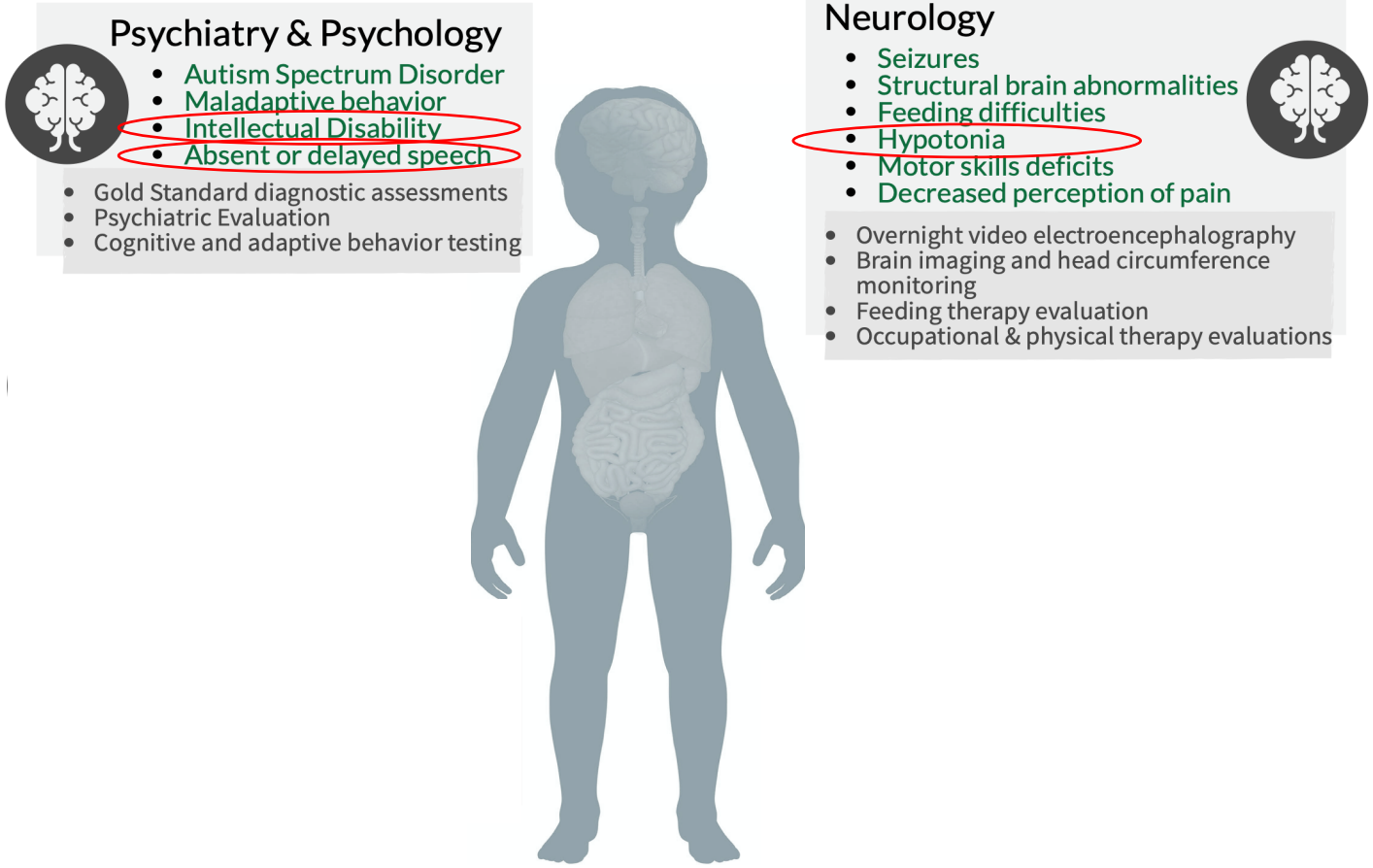
Genetic Cause of Phelan-McDermid Syndrome (*cont.*)

- Less commonly, in **~20% of cases**, Phelan-McDermid syndrome is caused by pathogenic variants in only the *SHANK3* gene, which is located in the q13.3 region of chromosome 22
- *SHANK3* is a critical gene in neurodevelopment that allows neurons to communicate
- *SHANK3* defects are highly associated with autism and intellectual disability



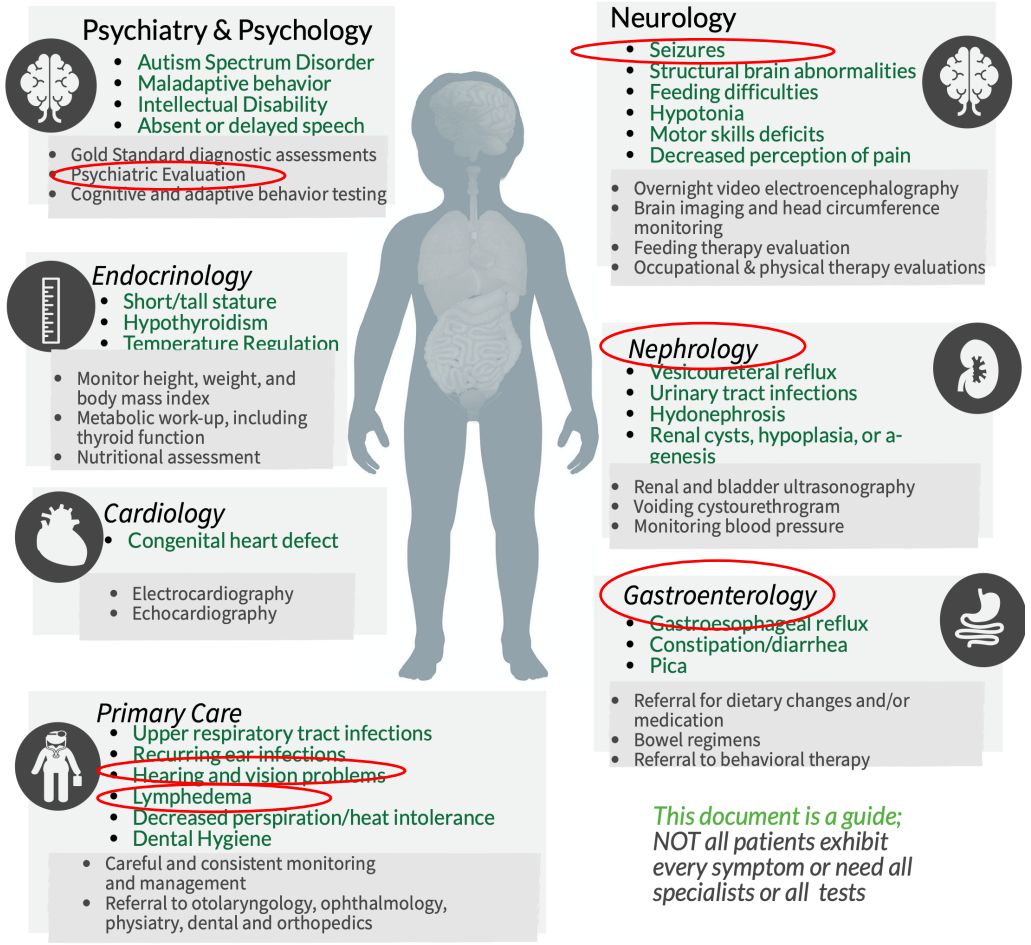
Most Common: >90%

- Neonatal hypotonia
- Intellectual disability
- Severely delayed or absent speech
- Global developmental delay



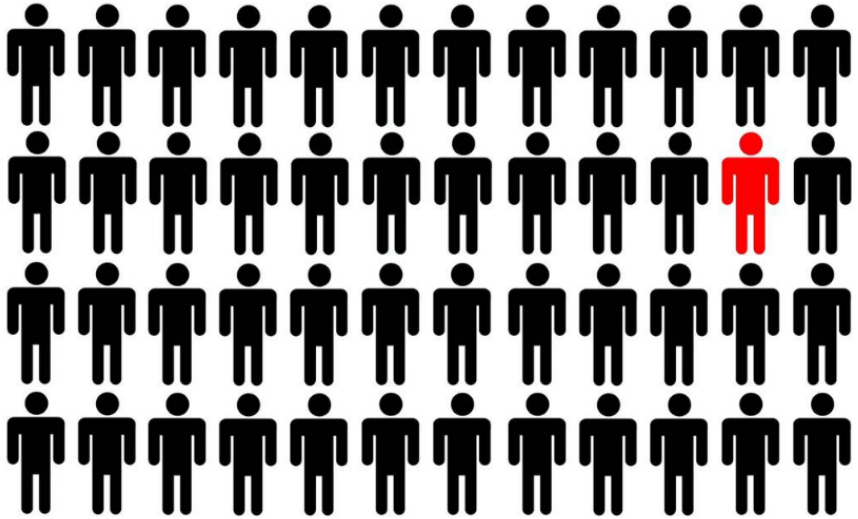
Additional Associated Features

- Seizures
- Gastrointestinal disorders
- Neuropsychiatric illness
- Kidney disorders
- Sleep disorders
- Autism Spectrum Disorders
- Lymphedema
- Abnormal pain responses
- Sleep disorders
- Vision difficulties



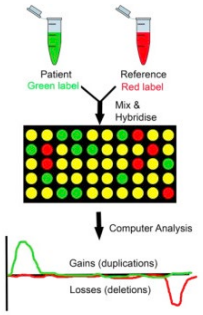
Prevalence of Phelan-McDermid Syndrome

- Phelan-McDermid syndrome has a strong link to autism
- Approximately 1% of autism diagnoses are estimated to be Phelan-McDermid syndrome
- Extrapolating based on autism, a worldwide estimate of the prevalence of Phelan-McDermid syndrome is ~1:10,000 people
- The PMSF currently has 3,000 members and is growing at a rate of ~one new family per day
- Numbers have rapidly increased with more frequent use of DNA sequencing in genetic testing

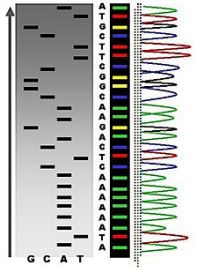


Diagnosis

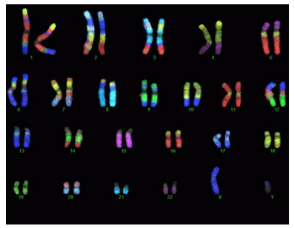
- Phelan-McDermid syndrome is definitively diagnosed with genetic testing
- Common genetic tests are used
- The majority of cases can be diagnosed by any trained geneticist without specific expertise in the syndrome
- Follow-up tests can determine added risks & possible inheritance



Chromosomal microarray: can detect deletions



Sequencing: Resolution of individual DNA bases, can catch small changes in SHANK3 alone



Cytogenetic tests: visualization of chromosomes, can detect rearrangements, deletions

Current Treatments

- Current treatments aim to manage symptoms
  - e.g., extensive monitoring by specialists, behavioral therapy, occupational therapy, seizure medications, psychiatric medications
- No treatments exist to address the underlying genetic cause of the disorder
- There are currently 3 ongoing and 6 completed clinical trials in the U.S.

Thank you!

Clinical Questions?