Snyder-Robinson Syndrome
A 46 Year Odyssey

Arlington, VA
July 16, 2015
Recessive Sex-Linked Mental Retardation in the Absence of Other Recognizable Abnormalities

Report of a Family*

R. D. SNYDER, M.D., A. ROBINSON, M.D.
1969 - Snyder-Robinson publication
1989 - NIH funding to GGC-Miami for XLID research
<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene, Associated Protein(s)</th>
<th>OMIM Number</th>
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<tbody>
<tr>
<td>Ornithine transcarbamoylase deficiency</td>
<td>PRPS1</td>
<td>21.1</td>
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<tr>
<td>Arts, PRPP synthetase superactivity</td>
<td>PRPS1</td>
<td>21.2</td>
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<tr>
<td>Pyruvate dehydrogenase deficiency</td>
<td>PDK1</td>
<td>21.3</td>
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<td>Glycerol kinase deficiency</td>
<td>GCK</td>
<td>21.4</td>
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<tr>
<td>Duchenne muscular dystrophy</td>
<td>DMD</td>
<td>21.5</td>
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<tr>
<td>Ornithine transcarbamoylase deficiency</td>
<td>PRPS1</td>
<td>21.6</td>
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<tr>
<td>XIDE (Renin receptor; ATP6AP2)</td>
<td>STK9</td>
<td>22.1</td>
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<tr>
<td>X-linked lip/palate</td>
<td>PHF8</td>
<td>22.2</td>
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<tr>
<td>Microcephaly-stereotypies-seizures</td>
<td>Iqsec2</td>
<td>22.3</td>
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<tr>
<td>Allan-Herndon (SLC1A2, MCT8)</td>
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<tr>
<td>Cantagrel spastic paraplegia (KIAA2022)</td>
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<td>Menkes disease (ATP7A)</td>
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<td>Phosphoglycerate kinase deficiency</td>
<td>PGK1</td>
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<td>XLD-macrocephaly-long ears (BRWD3)</td>
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<td>XLD-hyperekplexia-seizures (ARHGEF9)</td>
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<td>Mohr-Tranebjerg (TIMM8A, DDP)</td>
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<td>Pelizaeus-Merzbacher (PLP)</td>
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<td>XLD-Rolandic seizures (SRPX2)</td>
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<td>Arts, PRPP synthetase superactivity</td>
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<td>Mitochondrial encephalopathy (NDUFA1)</td>
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<td>Danon cardiomyopathy (LAMP2)</td>
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<td>FG/Lujan phenotype (UPF3B)</td>
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<td>Chiyonobu XLD (GRIA3)</td>
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<td>Lowe (OCRL1)</td>
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<td>Simpson-Golabi-Behmel (GPC3)</td>
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<td>Christianson, Angelman-like (SLC9A6)</td>
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<td>Fragile XA (FMR1)</td>
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<td>Mucopolysaccharidosisis IA (ID)</td>
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<td>Myotubular myopathy (MTM1)</td>
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<td>Creatine transporter deficiency (SLC6A8)</td>
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<td>XLD-microcephaly-dystonia (BCAP31)</td>
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<td>Adrenoleukodystrophy (ABCD1)</td>
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<td>XLD-glycosylation defect (SSR4)</td>
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<tr>
<td>Hydrocephaly-MAFA spectrum (L1CAM)</td>
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<td>N-Alpha acetyltransferase deficiency (NAA10)</td>
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<td>Ret, PPM-X (MECP2)</td>
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<td>Autism (RPL10)</td>
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**Notes:**
- **XLID:** X-linked Intellectual Disability
- **VACTERL:** Vertebral defects, Anal atresia, Cardiac defects, Tracheoesophageal fistula, Esophageal atresia, Renal anomalies, Limb defects
- **Hydrocephaly:** enlargement of the cranium due to an abnormal accumulation of cerebrospinal fluid
- **Meiotic drive:** process in which one sex (usually female) is favored in the segregation of chromosomes during meiosis
- **MIDAS:** Microcephaly, Intellectual Disability, Angiofibromas, Seizures, Arthritis
- **Kabuki:** syndromes associated with developmental and facial features resembling Kabuki makeup
- **Duchenne muscular dystrophy:** a neuromuscular disorder characterized by muscle weakness and wasting
- **X-linked intellectual disability:** a genetic condition characterized by intellectual disability and other associated features
- **Fragile X:** a genetic disorder caused by a mutation in the FMR1 gene
- **Periventricular nodular heterotopia:** a condition characterized by the presence of abnormally located neurons in the white matter near the ventricles of the brain
- **Microcephaly:** a condition characterized by an abnormally small head circumference
- **Autism:** a developmental disorder characterized by impairments in social interaction, communication, and restricted, repetitive patterns of behavior
- **Wilson's disease:** a rare genetic disorder characterized by liver and brain damage
- **Dyskeratosis congenita:** a rare condition characterized by skin, nail, and mucosal changes, as well as bone marrow failure
- **Incontinentia pigmenti:** a rare genetic disorder characterized by skin lesions and developmental disabilities
- **Dyskeratosis congenita:** a rare condition characterized by skin, nail, and mucosal changes, as well as bone marrow failure
- **X-linked ichthyosis:** a genetic disorder characterized by dry, scaly skin
- **Polyunsaturated fatty acid:** a type of fatty acid that contains double bonds
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1991 - Visits with Gallagher/Leis/Marchetti Families

1991  Minnesota (MG, DG, CG, JG, MaG, TG, EG, JB, NS)
1991  Rochester (SL)
1992  Denver (JB)
2002  Minnesota (EG, TG, NL, SL, JG, MG, CPG, DG, MaG)
2002  Greenwood (SL, TG)
2009  Greenwood (DM)
1996  Mapping of gene - Xp22.11
    (Arena et al., AJMG 64:50, 1996)
2003  Identification of gene - SMS
2009  First treatment trial -
    (Spermine Supplements)
Snyder-Robinson Syndrome
Clinical Manifestations

Growth

Birth (usually normal)
Adult height-variable (<3rd >9th centiles)
Adult weight (usually low)
Adult head circumference (usually large)
Snyder-Robinson Syndrome
Clinical Manifestations

Development

Sit alone (delayed)
Walking alone (3 yr - never)
1st words (8 mo - never)
Phrases/sentences (3 yr - never)
Snyder-Robinson Syndrome
Clinical Manifestations

Craniofacial & Skeletal Manifestations

- Large head
- Facial asymmetry
- Mid-face flatness
- High palate*
- Prominent lower lip

- Narrow chest
- Pectus excavatum (sunken chest)
- Kyphosis/scoliosis*
- Long thin digits*
- Hyperextensible fingers
Snyder-Robinson Syndrome
Clinical Manifestations

Neurological Manifestations

- Hypotonia*
- Nasal speech*
- Unsteady gait
- Seizures (none - intractable)
- Intellectual disability (none-severe)*
Snyder-Robinson Syndrome
Clinical Manifestations

Brain Imaging
- Enlarged ventricles
- Small/thin corpus callosum
- White matter volume loss
Snyder-Robinson Syndrome
Clinical Manifestations

Possible Other Manifestations

Low/high blood sugar
Anemia
Thrombocytopenia
Heart defect (mild)
Fatty disposition in soft tissues
Osteoporosis*