RETT SYNDROME
&
APPROACH TO GENETIC DISORDERS

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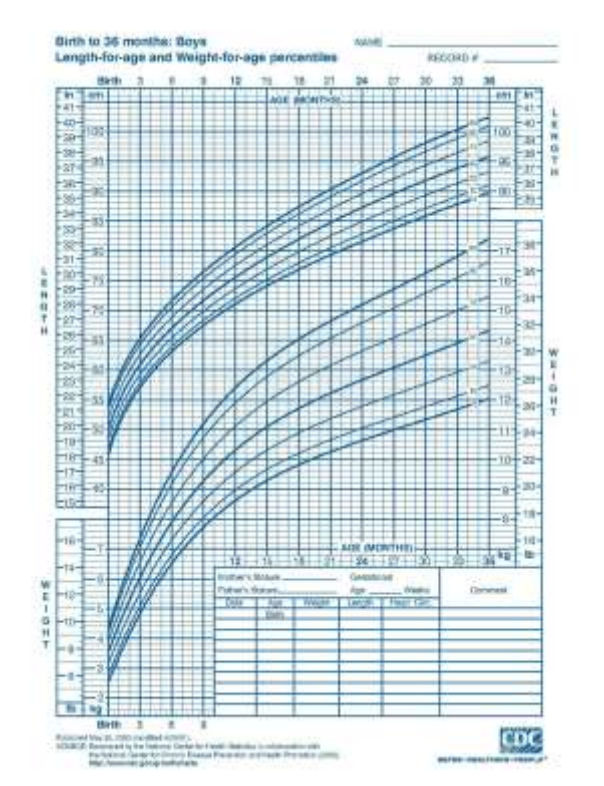
What is Rett Syndrome?

- Neurodevelopmental **arrest** caused by genetic aberration (mutation in *MECP2* gene of X-chromosome in majority of affected individuals)
  - MeCP2 (methyl-CpG binding protein 2) expressed in all tissues but most abundantly in brain
  - Most affected individuals are female due to X-linked inheritance pattern
  - De novo mutation of paternal origin
- Characterized by normal development in first 6-18 months followed by loss of spoken language, loss of purposeful hand use, stereotypic hand movements, and gait/motor abnormalities
  - Other manifestations include cardiac abnormalities, reduced bone density, growth failure (nutritional deficits, feeding difficulties), disorganized breathing pattern while awake, scoliosis, seizures, etc.

Diagnosis



- Clinical diagnosis through primarily history and developmental course
- Vigilant surveillance through well-child exams
  - Deceleration in head growth earliest clinical indicator
  - Milestones – did patient suddenly stop speaking? Attempting to communicate nonverbally? Not meeting motor milestones?
- Typical vs. atypical presentations
- DNA analysis to confirm diagnosis (*MECP2* is most common, but *CDKL5* or *FOXG1* can also lead to variant phenotypes)

Disease Course

Disease Course

- Stage I: developmental arrest between 6-18 months
  - Less eye contact, reduced play, decelerating head growth, motor delays
- Stage II: rapid deterioration/regression between 1-4 years of age (onset can be as rapid as 1 day)
  - Loss of purposeful hand movements and spoken language, hand stereotypies during wakefulness, autistic behavior

Disease Course, cont'd

- Stage III: plateau and behavioral improvement between 2-10 years of age
  - Motor dysfunction and seizures more prominent during this time
- Stage IV: late motor deterioration after 10 years of age
  - Increased rigidity, dystonia, bradykinesia, mobility issues (can become non-ambulatory)

Management

- Mostly consists of managing comorbidities:
  - Nutritional deficits: monitor somatic growth, g-tube placement if feeding difficulties, dietary counseling
  - Reduced bone density: DEXA scan, radiographs, eliminating risk factors for fractures, calcium/vitamin D supplementation
  - Seizures: EEG, standard antiepileptics
  - Cardiac abnormalities: baseline EKG, cardiologist referral, avoid QT-prolonging drugs
  - Motor dysfunction: referral to PT/OT and speech/language pathology

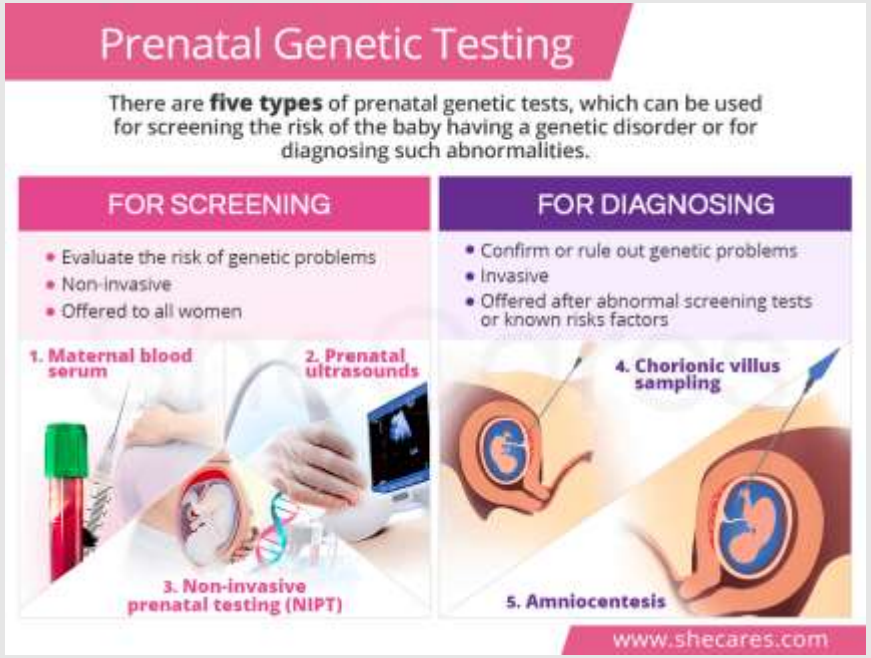
- Possibility of gene therapy?
  - AVXS-201 (AAV9 virus carries healthy *MECP2* gene into central nervous system past blood-brain barrier) – idea scrapped by Novartis in 2021, preclinical data incompatible with continuing onward with human clinical trials

Approach to Genetic Diseases in General

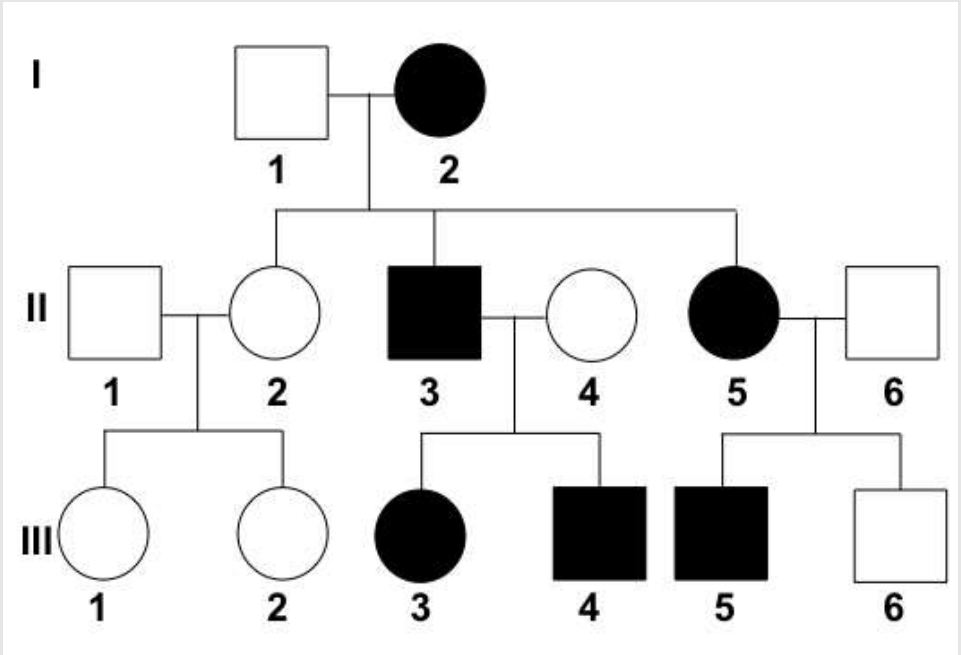
- All 46 chromosomes are in every cell of the body → chromosomal abnormalities result in a wide variety of signs/symptoms (problems are never isolated to a single body system) → thorough work-up is imperative
- There is no "cure" for genetic disorders: treatment is mostly interdisciplinary management of medical comorbidities and behavioral/psychological disturbances
  - Prader-Willi (loss of function of 15q11-13 region of chromosome 15): management of type II diabetes, correct hormonal deficiencies, behavioral intervention to prevent overeating
  - Osteogenesis Imperfecta (variety of inheritance patterns): DEXA scan, PT/OT to work around skeletal limitations
  - Spinal Muscular Atrophy (autosomal recessive): respiratory/feeding support, assistive devices for mobility
  - Angelman Syndrome (deletion of 15q11-13 region of maternal chromosome 15): anticonvulsants for seizures, improving non-verbal communication
  - Down's Syndrome (trisomy 21): hearing aids, speech therapy, transthoracic echocardiography
  - Turner's Syndrome (missing X chromosome in females): estrogen replacement, growth hormone

Overall, early identification of disorder and early intervention leads to better prognosis and improved quality of life! Important to be aware of hallmark features of more common genetic abnormalities

Determining Risk



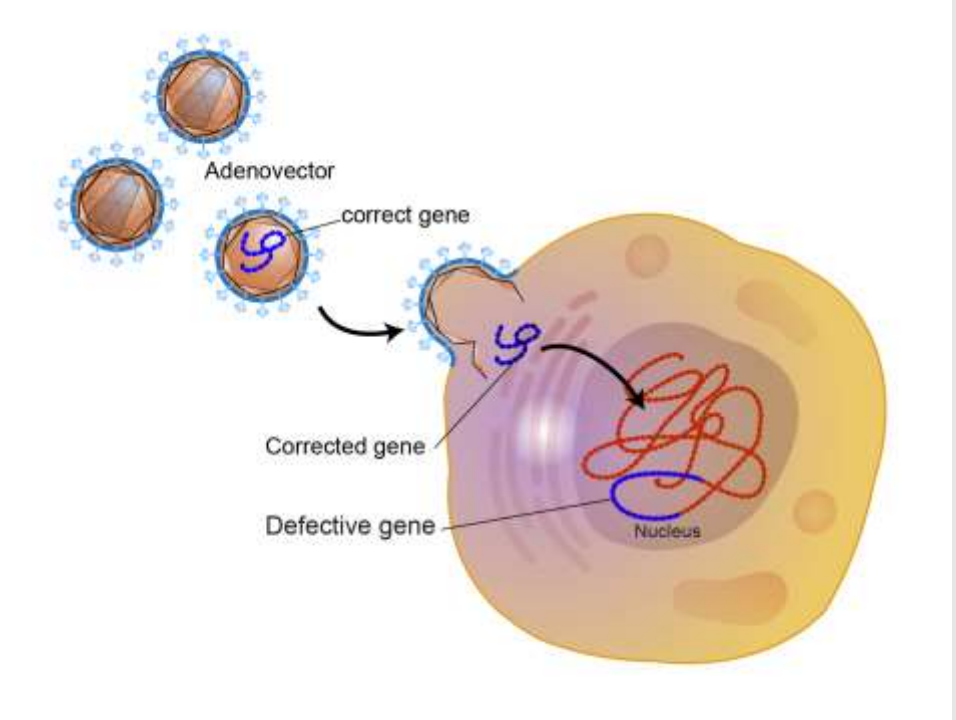
- Prenatal genetic testing can detect trisomy 21/18/13 as well as sex chromosome aneuploidies



- If there is genetic disorder in family history with known inheritance pattern, can create pedigree with genetic counselor

Gene Therapy?

- No cure for genetic disorders but gene therapy is being researched heavily as an option to ameliorate symptoms more effectively than conventional interventions
- Gene transfer/addition: introducing a new gene into cells or using a healthy copy of a gene to counteract abnormalities caused by faulty genes
- Genome editing: changes existing DNA in the cell (turn genes off/on, removing faulty genes, etc.)
- Gene therapy already being used to treat some diseases (e.g. spinal muscular atrophy, Leber congenital amaurosis)



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