

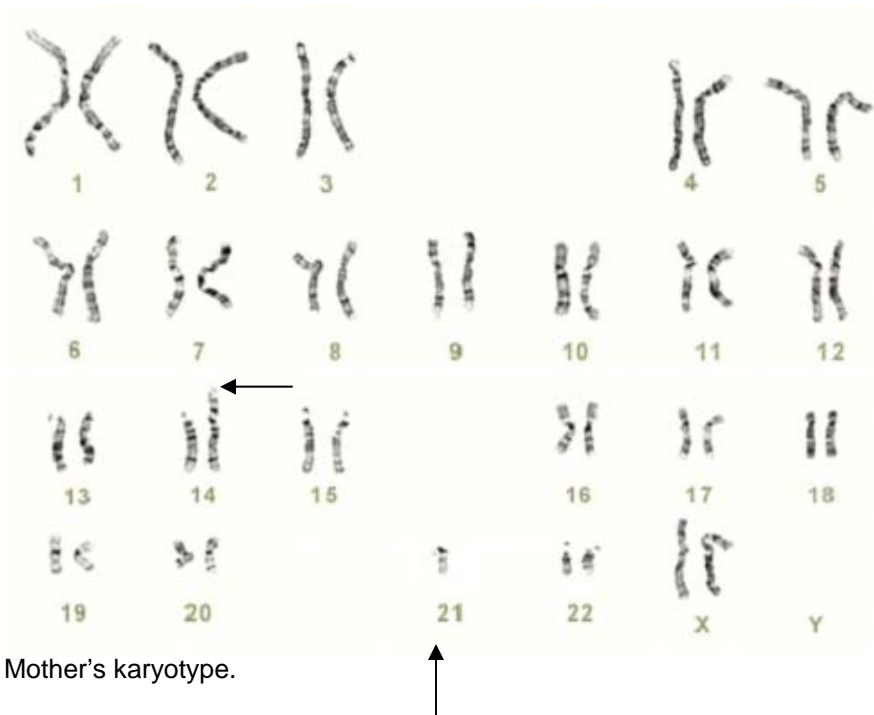
HOLY C.O.W.!

IT'S...

Clinical Question of the Week #17
 October 20th, 2008 through October 27th, 2008

Please e-mail your answers to Kuo, Tim, Wendy, and Kevin (klian@mednet.ucla.edu; tprovias@mednet.ucla.edu; wsimon@mednet.ucla.edu; kbreger@mednet.ucla.edu) by 0800 on Monday, October 27th, 2008. The resident or intern with the most correct answers at the end of each month will receive a prize!

Case: A 37-year-old woman presents for evaluation in family planning. She is healthy and does not drink, smoke, or use illicit drugs. She was adopted and her family history is unknown. She has been married to her husband for seven years and they have a three year old son. Her husband is healthy and has a family history notable for hypertension, but no other known disease. She notes that her son has progressed slowly in his development, with delayed onset of crawling and walking. He said his first word, "mommy" at eighteen months of age, but now has several words he uses to communicate. His height and weight are in the 30th percentile range. Physical examination of the mother reveals no abnormalities. Recent progress note from the son's pediatrician notes the developmental delay as described and also notes dysmorphic features on examination. A karyotype is obtained on the mother, which is shown below. Likewise, genetic analysis is performed also on the son.



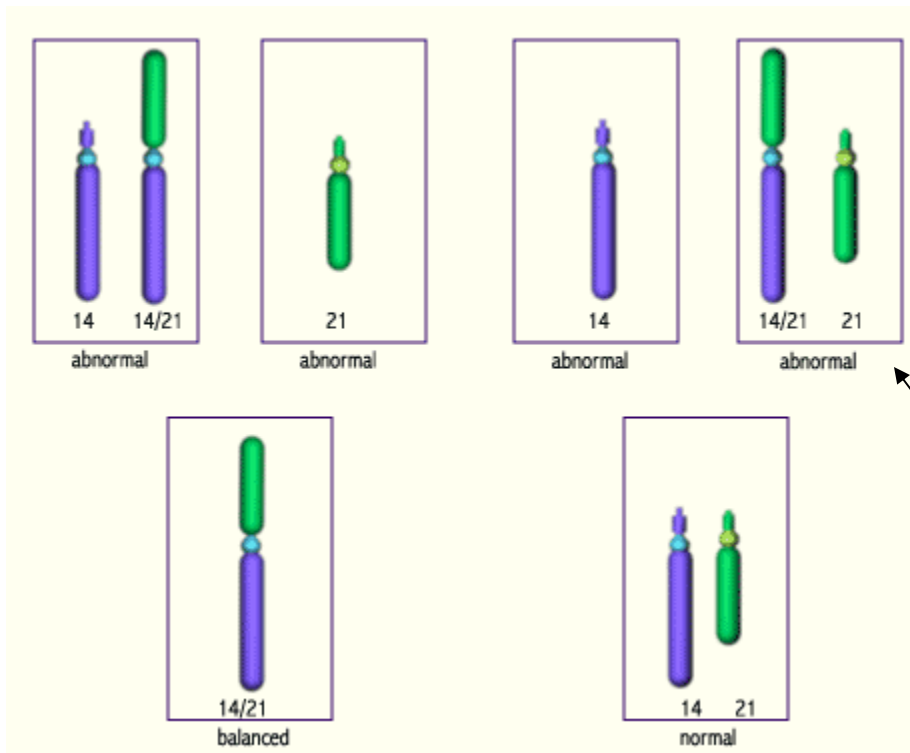


Diagram of a subset of chromosomes inherited by the son with Down's syndrome from the mother (arrow). Other gamete possibilities are listed.

Questions:

1. Name the condition that the child has.

Down syndrome (trisomy 21), characterized by dysmorphic features including upslanting palpebral fissures, epicanthic folds, flat nasal bridge, dysplastic/folded ears, protruding tongue, short neck with excess skin, short broad hands with transverse palmar crease, etc. It is the most common chromosomal abnormality among liveborn infants, and is the most frequent form of mental retardation resultant from a chromosomal abnormality.

Most individuals with Down syndrome have mild to moderate mental retardation, manifesting in infants/toddlers as delayed developmental milestones. One half of individuals have heart disease, including defects such as VSD, AVSD, and Tetralogy of Fallot (see Holy C.O.W.! Clinical Question of the Week #11). Other features include GI and endocrine disorders, stunted growth, vision and hearing problems, immune deficiency, hematologic disorders, impaired reproduction, sleep apnea, skin disorders, and atlantoaxial instability.

While Morbus Langdon Down described the syndrome in detail in 1866, which later was named for him "The face is flat and destitute of prominence. Cheeks are roundish and extended laterally. The eyes are obliquely placed and the internal canthi more than normally distant from one another. The palpebral fissure is very narrow. The lips are large and thick with transverse fissures. The tongue is long, thick and much roughened. The nose is small." However, others preceded him in actuality, including Edouard Sequin (1884) and Jean Etienne Dominique Esquirol (1838). The chromosome aberration was described in 1959 by Jerome Jean Louis Marie Lejeune. (0.5)

2. What is the genetic defect, and how does it occur?

The genetic defect is trisomy 21, which in this case is due to a Robertsonian translocation, which accounts for approximately 3-4 percent of Down syndrome cases.

The Robertsonian translocation occurs when two acral chromosomes undergo a rearrangement that results in one long chromosome and a small fragment containing one centromere and minimal genetic material, which is usually lost. This usually occurs with chromosomes 13-15 and 21-22. In our case, the mother had a Robertsonian translocation resulting in one portion of chromosome 21 being attached to the acral portion of chromosome 14, or 45,XX, t(14;21q). She then passed along her translocated 14/21 chromosome as well as her normal chromosome 21, which when combined with the father's chromosome 21 resulted in trisomy. (1)

3. Name two other causes of the child's genetic defect.

The most frequent cause of Down syndrome is trisomy 21 (47, +21) in which an extra chromosome 21 is inherited, accounting for 94% of cases. Another genetic variant in Down syndrome is mosaicism (47, +21/46), which occurs in 2-3 percent of cases, and results from two populations of cell lines – one with 46 chromosomes and one with the extra chromosome 21. (0.5)

4. If the mother has another child, what are her chances of having a normal baby? A miscarriage?

The six possible gamete combinations from the mother are diagrammed above. Three are fatal – monosomy 14, monosomy 21, and trisomy 14 (top row) – or 1/2 chance of having a miscarriage. One gamete leads to Down syndrome (arrow) as in our case. Finally, two gametes result in phenotypically normal children – one with normal chromosomes 14 and 21, and one with the sole Robertsonian translocated 14/21, resulting in a 2/6 chance of having a normal baby (1/2 of which will be truly genetically normal). (1)