

## The Baby with Down Syndrome

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Down syndrome, also known as Trisomy 21, is the single most common genetic pattern of malformation in man. Most text books quote the incidence of Down syndrome to be between one in 700 to 800 live births. The actual gene or genes on chromosome 21 that are responsible for Down syndrome are now being identified in a critical region of 20-40 genes.<sup>6</sup>

### Background

In 1866, John Langdon Haydon Down described the physical features and associated medical problems that have come to be known as Down syndrome. In 1959, Lejeune and Jacobs et al independently determined that Down syndrome is caused by trisomy 21. Down syndrome is by far the most common and best known chromosome disorder in humans. Mental retardation, dysmorphic facial features, and other distinctive phenotypic traits characterize the syndrome.<sup>6</sup>

### Incidence and Types of Down Syndrome

Type	%	Mechanism
<b>Nondisjunction</b>	94	Nondisjunction during meiotic division of the primary oocyte.
<b>Translocation</b>	3.5	Robertsonian translocation in which all or part of an extra chromosome 21 is fused with another chromosome (14 or 15.,21,22).
<b>Mosaicism (A mixture of normal diploid and trisomy 21 cells)</b>	2.5	Nondisjunction during mitotic division of a cell line during early embryogenesis.

- For the common nondisjunction type of trisomy 21, the rate varies markedly with the age of the mother when conception occurs. This is not the case for the rare translocational

form. Women who are 20 years old apparently have the lowest chance (1 in 2000) of having a Down syndrome child of the former type. Women do not reach the average risk rate of 1 in 800 until they are about 30. Older mothers have a far higher frequency as indicated in table 2. As a result, amniocentesis is regularly recommended for women 35 and over. It is not routinely recommended for younger women because the diagnostic benefits do not

Table 2. Frequency of Down syndrome according to maternal age.<sup>6</sup>

Age of Mother	Frequency of Down Syndrome
30	1 in 800
35	1 in 384
36	1 in 307
37	1 in 242
38	1 in 189
39	1 in 146
40	1 in 112
45	1 in 32

outweigh the risk of miscarriage.

- 75% of these unbalanced translocations are de novo, and approximately 25% result from familial translocation.

### Pathophysiology

The presence of an extra copy of the proximal part of 21q22.3 appears to result in the typical physical phenotype: mental retardation, characteristic facial features, hand anomalies, and congenital heart defects. Molecular analysis reveals that the 21q22.1-q22.3 region appears to contain the gene(s) responsible for the congenital heart disease observed in Down syndrome. The new gene (*DSCR1*), identified from region 21q22.1-q22.2, is highly expressed in the brain and the heart and is a candidate for involvement in the pathogenesis of Down syndrome, in particular, the mental retardation and/or cardiac defects.

Abnormal physiological functioning affects thyroid metabolism and intestinal malabsorption. Frequent infections are presumably due to impaired immune responses, and incidence of autoimmunity, including hypothyroidism and rare Hashimoto thyroiditis, is increased.

Down syndrome patients exhibit decreased buffering of physiological reactions, resulting in

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hypersensitivity to pilocarpine and abnormal responses on sensory-evoked electroencephalographic tracings. Leukemic Down syndrome children also demonstrate hyperreactivity to methotrexate. Decreased buffering of metabolic processes results in predisposition to hyperuricemia and increased insulin resistance. Diabetes mellitus develops in many affected patients. Premature senescence causes cataracts and Alzheimer disease. Bone marrow dysfunction is indicated by leukemoid reactions of infancy and an increased risk of acute leukemia.

### Recurrence Risk and Family History

- If a patient has had a trisomy 21 pregnancy in the past, the risk of recurrence in a subsequent pregnancy increases to approximately 1 percent above the baseline risk determined by maternal age.
- Diagnosis of a chromosome-21 translocation in the fetus or newborn is an indication for karyotype analysis of both parents. If both parents have normal karyotypes, the recurrence risk is 2 to 3 percent. If one parent carries a balanced translocation, the recurrence risk depends on the sex of the carrier parent and the specific chromosomes that are fused.
- *Race*: No known racial predilection exists.
- *Sex*: The male-to-female ratio is increased (approximately 1.15:1) in newborns with Down syndrome. This effect is restricted to free trisomy 21.

**Table 3. Frequency of Dymorphic Signs in Neonates with Trisomy 21<sup>(23 &24)</sup>**

Dymorphic Sign	Frequency (%)
Flat facial profile	90
Poor Moro reflex	85
Hypotonia	80
Hyperflexibility of large joints	80
Loose skin on back of neck	80
Slanted palpebral fissures	80
Dymorphic pelvis on radiographs	70
Small round ears	60
Hypoplasia of small finger, middle phalanx	60
Single palmar crease	45

### Clinical Manifestations

Down syndrome is usually identified soon after birth by a characteristic pattern of dysmorphic features. The diagnosis is confirmed by karyotype analysis.

#### Clinical Features

1. *Skull*: Brachycephaly, microcephaly, sloping forehead, flat occiput, large fontanels with late closure, patent metopic suture, absent frontal and sphenoid sinuses, and hypoplasia of the maxillary sinuses occur.
2. *Eyes*: Up-slanting palpebral fissures, bilateral epicanthal folds, Brushfield spots (speckled iris), refractive errors (50%), strabismus (44%), nystagmus (20%), blepharitis (33%), conjunctivitis, tearing from stenotic nasolacrimal ducts, congenital cataracts (3%), pseudopapilledema, spasm nutans, acquired lens opacity (30-60%), and keratoconus in adults are observed. Frequently, their eyes have an East Asian-like appearance due to an epicanthic fold. This is a fold of skin over the inner corner of each eyelid, which makes the eyes appear to slant upward. Because of this eye characteristic, Down syndrome was referred to as Mongoloidism when it was first described in 1866 by the English physician John Langdon Down. However, this term was misleading because Down syndrome can occur in any human group, not just Asians. As a result, Mongoloidism has been rejected as a synonym for Down syndrome.
3. Hypoplastic nasal bone and flat nasal bridge
4. An open mouth with a tendency of tongue protrusion, a fissured and furrowed tongue, mouth breathing with drooling, a chapped lower lip, angular cheilitis, partial anodontia (50%), tooth agenesis, malformed teeth, delayed tooth eruption, microdontia (35-50%) in both the primary and secondary dentition, hypoplastic and hypocalcified teeth, malocclusion, taurodontism (0.54-5.6%), and increased periodontal destruction are noted.
5. Ears are small with an over-folded helix. Chronic otitis media and hearing loss are common. From 66-89% of children have a hearing loss of greater than 15-20 dB in at least one ear by auditory brainstem response (ABR).
6. Atlantoaxial instability (14%) can result from laxity of transverse ligaments that ordinarily hold the odontoid process close to the anterior arch of the atlas. Laxity can cause backward displacement of the odontoid process, leading to spinal cord compression.
7. Internipple distance is decreased.

8. Short stature and obesity occurs during adolescence.
9. Moderate-to-severe mental retardation occurs, with an IQ range of 20-85 (mean IQ is approximately 50). Hypotonia improves with age. Articulatory problems are present. Sleep apnea occurs when inspiratory airflow from the upper airway to the lungs is impeded for 10 seconds or more; it often results in hypoxemia or hypercarbia.
10. *Behavior:* Natural spontaneity, genuine warmth, cheerful, gentleness, patience, and tolerance are characteristics. A few patients exhibit anxiety and stubbornness.
11. *Psychiatric disorders:* Prevalence of psychiatric disorders among children is 17.6% and among adults is 27.1%. Children and adolescents are at a higher risk for autism, attention deficit hyperactivity disorder, and conduct disorder. Obsessive-compulsive disorder, Tourette syndrome, and depressive disorder may occur during the transition from adolescence to adulthood.
12. *Seizure disorder (5-10%):* Infantile spasms are the most common type of seizures observed in infancy, while tonic-clonic seizures are most commonly observed in older patients.
13. Premature aging.
14. Congenital heart defects are common (40-50%). The most frequent congenital heart defects are endocardial cushion defect (43%), ventricular septal defect (32%), secundum atrial septal defect (10%), tetralogy of Fallot (6%), and isolated patent ductus arteriosus (4%). Thirty percent of patients have multiple cardiac defects. The most common associated lesions are patent ductus arteriosus (16%) and pulmonic stenosis (9%). About 70% of all endocardial cushion defects are associated with Down syndrome.
15. Diastasis recti and umbilical hernia occur.
16. Duodenal atresia or stenosis, Hirschsprung disease (less than 1%), TE fistula, Meckel diverticulum, imperforate anus, and omphalocele are observed.
17. Renal malformations, hypospadias, micropenis, and cryptorchidism occur.
18. Short and broad hands, clinodactyly of the fifth fingers with a single flexion crease (20%), hyperextensible finger joints, increased space between the great toe and the second toe, and acquired hip dislocation (6%) are typical presentations.
19. Hypothyroidism (16-20% of young patients), diabetes, and decreased fertility occur.
20. Children have a 10- to 15-fold increased risk of developing leukemia. Approximately 1 in 150 patients develops leukemia.

21. *Immunodeficiency:* Patients have about a 12-fold increased risk of developing infectious diseases, especially pneumonia, secondary to impaired cellular immunity.
22. *Skin:* Xerosis, localized hyperkeratotic lesions, elastosis serpigginosa, alopecia areata (up to 10%), vitiligo, folliculitis, abscess formation, and recurrent skin infections are observed.
23. *Dermatoglyphics:* Distal axial triradius in the palms, transverse palmar creases, a single flexion crease in the fifth finger, ulnar loops (often 10), a pattern in hypothenar, and interdigital III regions are observed.

**Table 4. Incidence of Some Associated Medical Complications in Down Syndrome**

Disorder	Incidence (%)
Mental retardation	>95
Growth retardation	>95
Early Alzheimer's disease	Affects 75% by age 60
Congenital heart defects (atrioventricular canal defect, ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot)	40
Hearing loss (related to otitis media with effusion or sensorineural)	40 to 75
Ophthalmic disorders (congenital cataracts, glaucoma, strabismus)	60
Epilepsy	5 to 10
Gastrointestinal malformations (duodenal atresia, Hirschsprung disease)	5
Hypothyroidism	5
Leukemia	1
Atlantoaxial subluxation with cord compression	<1
Increased susceptibility to infection (pneumonia, otitis media, sinusitis, pharyngitis, periodontal disease)	Unknown
Infertility	>99% in men; anovulation in 30% of women

**Mortality and Morbidity**

- Approximately 75% of conception with trisomy 21 die in embryonic or fetal life. Approximately 85% of infants survive to 1 year and 50% can be expected to live longer

than 50 years. The presence of congenital heart disease is the most significant factor that determines survival. In addition, esophageal atresia with or without transesophageal (TE) fistula, Hirschsprung disease, duodenal atresia, and leukemia contribute to mortality.

- Increased infections due to impaired immune response.
- Upper airway obstruction by large tonsils and adenoids, lingual tonsils, choanal stenosis, or glossoptosis. Airway obstruction can cause serous otitis media, alveolar hypoventilation, arterial hypoxemia, cerebral hypoxia, and development of pulmonary artery hypertension with resulting cor pulmonale and heart failure.
- A delay in recognizing atlantoaxial and atlantooccipital instability may result in irreversible spinal cord damage.
- Visual and hearing impairments in addition to the presence of mental retardation may further limit the child's overall functioning.

## References

1. American College of Medical Genetics Clinical Practice Committee. ACMG position statement on multiple marker screening in women 35 and older. *American College of Medical Genetics College Newsletter*. 1994; 2.
2. American Academy of Pediatric Committee on Genetics: Health supervision for children with Down syndrome. *Pediatrics*. 1994; **93**(5): 855-9.
3. American Academy of Pediatrics Committee on Sports Medicine and Fitness. Atlantoaxial instability in Down syndrome. Subject review. *Pediatrics*. 1995; **96**: 151-4.
4. Chitty L. Antenatal screening for aneuploidy. *Curr Opin Obstet Gynecol*. 1998; **10**: 91-6.
5. Cuckle H, Wald N, Thompson S. Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol*. 1987; **94**: 387-402.
6. Epstein C. Down syndrome (Trisomy 21). In: Scriver C, Beaudet A, Sly W, et al (eds). *The metabolic and molecular bases of inherited disease*. New York: McGraw-Hill. 1995; 749-94.
7. Ferencz C, Neill C, Boughman J. Congenital cardiovascular malformations associated with chromosome abnormalities, an epidemiologic study. *J Pediatr*. 1989; **114**(1): 79-86.
8. Fuentes J, Pritchard M, Planas A. A new human gene from the Down syndrome critical region encodes a proline-rich protein highly expressed in fetal brain and heart. *Hum Mol Genet*. 1995; **4**(10): 1935-44.
9. Gross S, Bombard A. Screening for the aneuploid fetus. *Obstet Gynecol Clin North Am*. 1998; **25**: 573-95.
10. Haddow J, Palomaki G, Knight G, et al. Prenatal screening for Down's syndrome with use of maternal serum markers. *N Engl J Med*. 1992; **327**: 588-93.
11. Haddow J, Palomaki G, Knight G, et al. Reducing the need for amniocentesis in women 35 years of age or older with serum markers for screening. *N Engl J Med*. 1994; **330**: 1114-8.
12. Huether C, Martin R, Stoppelman S. Sex ratios in fetuses and liveborn infants with autosomal aneuploidy. *Am J Med Genet*. 1996; **63**(3): 492-500.
13. Kuller J, Laifer S. Contemporary approaches to prenatal diagnosis. *Am Fam Physician*. 1995; **52**: 2277-83, 2285-6. Krantz D, Larsen J, Buchanan P. First-trimester down syndrome screening, free beta-human chorionic gonadotropin and pregnancy-associated plasma protein A. *Am J Obstet Gynecol*. 1996; **174**(2): 612-6.
14. Marino B. Congenital heart disease in patients with Down's syndrome, anatomic and genetic aspects. *Biomed Pharmacother*. 1993; **47**(5): 197-200.
15. NEWBERGER D. Down Syndrome, Prenatal Risk Assessment and Diagnosis. *American Family Phys.J. Vol. 62/No. 4 (2000)*: 19
16. Opitz J, Gilbert-Barness E. Reflections on the pathogenesis of Down syndrome. *Am J Med Genet Suppl*. 1990; **7**: 38-51.
17. Palomaki G, Knight G, Mc Carthy J, et al. Maternal serum screening for Down syndrome in the United States, a 1995 survey. *Am J Obstet Gynecol*. 1997; **176**: 1046-51.
18. Pueschel S. Clinical aspects of Down syndrome from infancy to adulthood. *Am J Med Genet Suppl*. 1990; **7**: 52-6.
19. Reynolds T, Nix A, Dunstan F, et al. Age-specific detection and false-positive rates: an aid to counseling in Down syndrome risk screening. *Obstet Gynecol*. 1993; **81**: 447-50.
20. Roizen N. Down syndrome and associated medical disorders. *Mental Retardation and Developmental Disabilities Research Reviews*. 1996; **2**: 85-9.
21. Rose N. Pregnancy screening and prenatal diagnosis of fetal Down syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*. 1996; **2**: 80-4.
22. Saller D, Canick J. Maternal serum screening for Down syndrome, clinical aspects. *Clin Obstet Gynecol*. 1996; **39**: 783-92.
23. Smith D, Jones K. Smith's Recognizable patterns of human malformation. 4th ed. Philadelphia: Saunders, 1988; 10-5.
24. Tolmie J. Down syndrome and other autosomal trisomies. In: Rimoin D, Connor J, Pyeritz R (eds). *Emery and Rimoin's Principles and practice of medical genetics*. 3rd ed. New York, Churchill Livingstone. 1996; 925-71.
25. Vintzileos A, Campbell W, Rodis J, et al. The use of second-trimester genetic sonogram in guiding clinical management of patients at increased risk for fetal trisomy 21. *Obstet Gynecol*. 1996; **87**: 948-52.
26. Wald N, Cuckle H, Densem J, et al. Maternal serum screening for Down's syndrome in early pregnancy. *BMJ*. 1988; **297**: 883-7 [Published erratum appears in *BMJ*. 1988; **297**: 1029].
27. Wells G, Barker S, Finley S. Congenital heart disease in infants with Down's syndrome. *South Med J*. 1994; **87**(7): 724-7
28. Zigman W, Silverman W, Wisniewski H. Aging and Alzheimer's disease in Down syndrome, Clinical and pathological changes. *Mental Retardation and Developmental Disabilities Research Reviews*. 1996; **2**: 73-9.