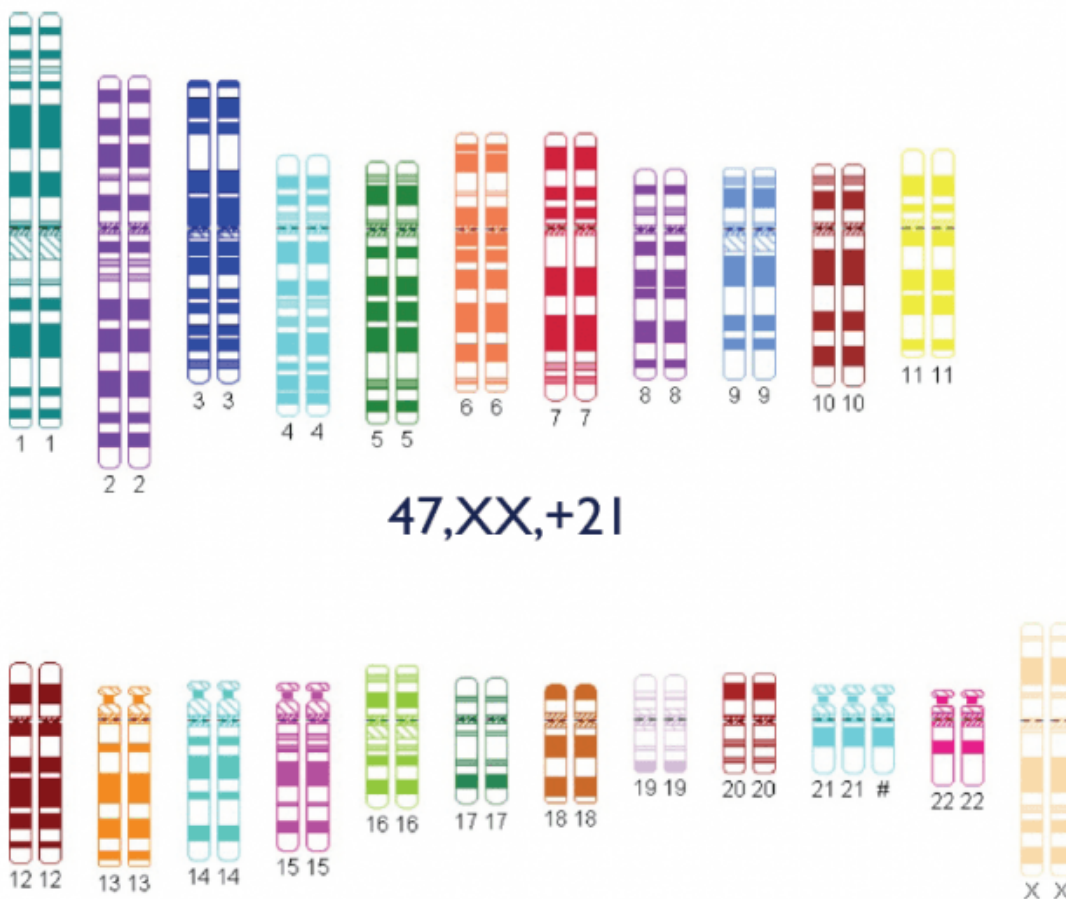


## Down Syndrome (Trisomy 21) — Causes, Symptoms and Diagnosis

[See online here](#)

**Down Syndrome, or trisomy 21, is not only the most common chromosomal aberration, but also the most frequent genetic cause of mental retardation. Nowadays, it is possible to assess the risk of having a child with Down syndrome via cytogenetic examination and to discuss the matter in detail with the respective families. Learn more about the epidemiology, clinical picture and diagnostics of Down syndrome and discover its most important treatment options.**



### Definition of Down Syndrome

Down syndrome as a mental and physical handicap

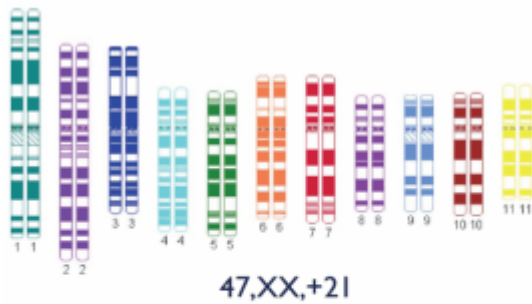


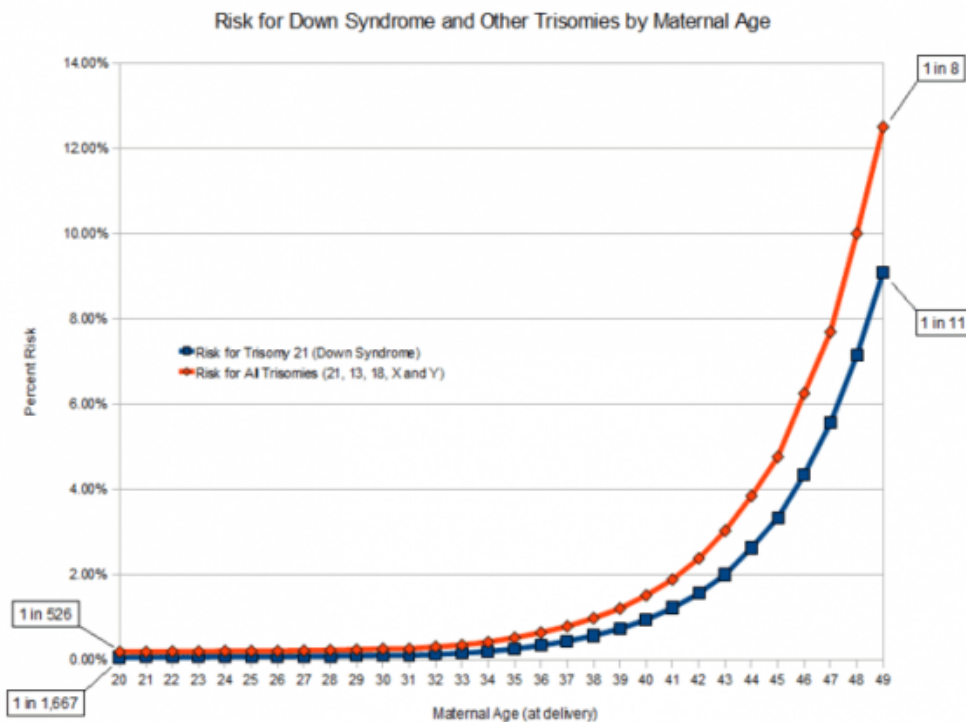
Image: "Trisomía" by UPO649 1112 mreycor1. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Trisomy 21, also known as Down syndrome, is a [chromosomal aberration](#) that leads to a triple presence of **chromosome 21**.

In consequence, patients show **mental and physical delayed or miscarried development**. The syndrome is named after the English physician **J. Langdon Down** who described the disease first in 1866.

## Epidemiology of Down Syndrome

### Down syndrome in the population



**SOURCES:**  
 Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. JAMA 1983;249(15):2034-38.  
 Newberger, D., *Down Syndrome: Prenatal Risk Assessment and Diagnosis*. American Family Physician. 2001.  
 Down syndrome births in the United States from 1989 to 2001. Egan JF - Am J Obstet Gynecol - 01-SEP-2004; 191(3): 1044-8.

**Image:** "A graph of data showing the risk (as a percentage of live births) of Down syndrome, along with other trisomies, by age of the mother (at delivery)." by Tdadamemd. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

A prevalence of **1:700** makes trisomy 21 the most common **autosomal chromosome** aberration. It is also the most frequent genetic cause of **mental retardation** in humans. **Life expectancy** is currently around 50 years and tends to increase due to improved therapeutic options.

The **older** the mother the higher is the risk of Down syndrome: If the mother is **below 30 years**, less than one child in 1000 is born with trisomy 21; in the group of **40- to 44-year-old** mothers, **10 to 20 of 1000** children are affected, and mothers **over 44 years** give birth to **20 to 40 of 1000** children with Down syndrome.

**Note:** The older the mother the higher the risk of trisomy 21!

## Etiology of Down Syndrome

### Causes of Down syndrome

As the name of the disease suggests, the underlying cause is a **trisomy**, thus a **triple set of chromosomes**. The chromosome number **21** is in surplus and exists thrice rather than twice. On a **cytogenetic** level the following possibilities are conceivable for the development of trisomy 21:

**Free trisomy 21:** In > 90% of all cases; the surplus chromosome 21 is free, caused by non-separation and usually of maternal origin (dependent on the age of the mother); chromosome number: 47

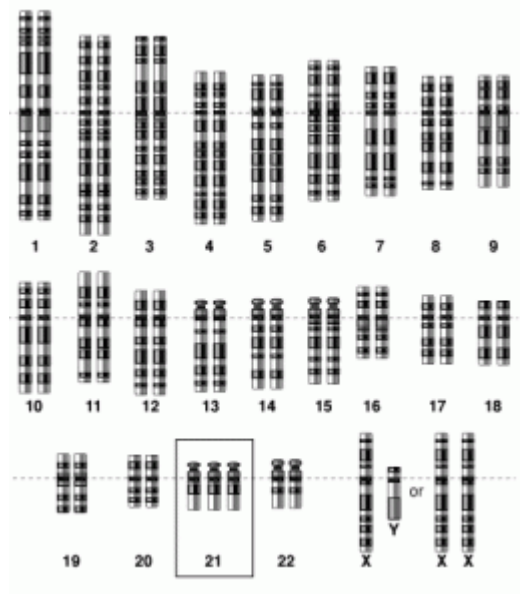


Image: "Scheme of a genetic mutation, in this case Trisomy 21" by National Human Genome Research Institute. License: Public Domain

**Trisomy 21 due to translocation:** In approx. 2 to 4% of all cases, the surplus chromosome 21 is attached to another acrocentric chromosome (often 14) (= **Robertsonian translocation**); the age of the mother does not have any influence here, chromosome number: 46

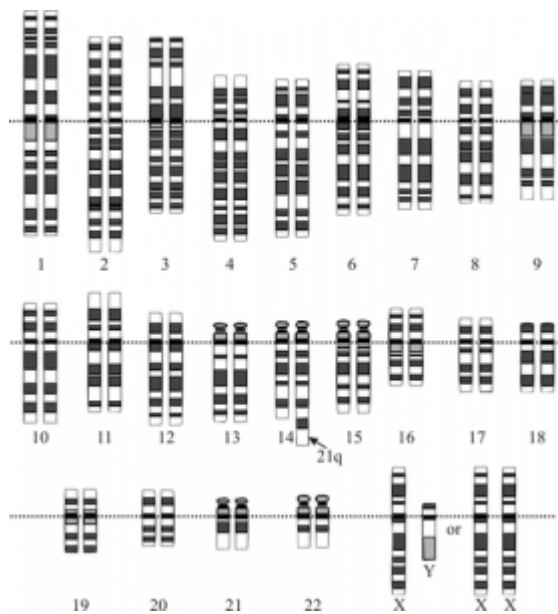


Image: "Down Syndrome translocation" by National Human Genome Research Institute. License: Public Domain

**Trisomy 21 in mosaic:** In 1 to 2 % of all cases, simultaneous existence of a normal cell line and another with trisomy; the phenotype depends on the distribution pattern in the brain.

**Partial trisomy 21:** Very rare, duplication of one segment of chromosome 21.

Trisomy 21 due to translocation occurs de novo (by **mutation**) or is **inherited**. Here it is possible that the parents are carriers of a **balanced translocation** with a well-balanced

genotype and without any clinical symptoms. If the father is carrier of the **translocation**, the **empirical risk of recurrence** (likelihood for an ill child) is approx. **1 to 2%**. If the mother carries it, the risk amounts raises to **10 to 15%**. With a translocation to chromosome 14 her **karyotype** would look like this: 46, XX, t(14;21).

If there is a **21/21 translocation**, the risk of trisomy 21 amounts to **100 %**.

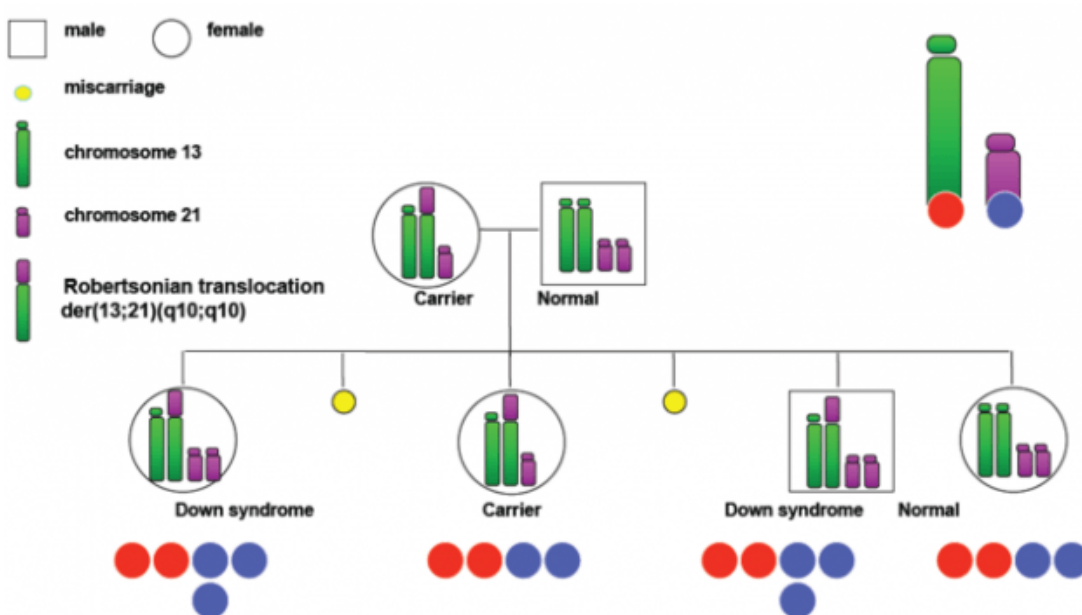


Image: "Robertsonian translocation of Down syndrome in families," by UPO649 1112 mreycor1. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

## Clinical Picture of Down Syndrome

### Symptoms of Down syndrome



Image: "A cropped photo of the eyes of a baby with Down Syndrome. Brushfield spots are visible between the inner and outer circle of the iris" by Szymon Tomczak. License: [CC0 1.0](https://creativecommons.org/licenses/by/1.0/)

While there is no difference between the symptoms of a free trisomy and those of a trisomy due to translocation, the degree of manifestation of a mosaic trisomy depends on the **amount of cells with trisomy**.

The affected show increased **susceptibility for infections** and a more frequent occurrence of **leukemia**.

### Phenotype of Down syndrome

Patients with Down syndrome have a characteristic outer appearance with the following **dysmorphic** features that can sometimes also be found in the normal population:

**Craniofacial:** brachycephalie, flattened and broad nasal bridge, oblique lid axis towards superior and lateral, epicanthus, small mouth and chin, macroglossia, furrows in lips and tongue, high roof of the mouth, abnormal teeth, abnormal auricles, Brushfield spots (whitish concentration of the iris), cataract, strabismus, nuchal fold, short neck.



**Image:** "Feet of a 10-year-old boy with Down Syndrome, with the typical large space between the large toe and second toe." by Loranchet. License: [CC BY 3.0](#)

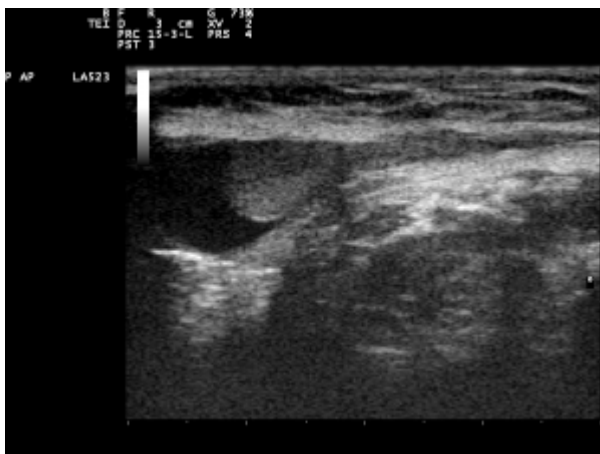
**Acral:** Shortened and broad hands and feet, clinodaktyly, brachydaktyly, single transverse palmar crease, separation of first and second toes (sandal gap).

**Musculoskeletal system:** hypotension of the muscles, hypermobility of joints, umbilical/inguinal hernia, diastasis recti, surplus ribs, abnormal vertebral bodies, levelled angle of the acetabulum and ilium, stunted growth.

**Skin:** rough, dry, mottled.

**Note:** The mentioned abnormalities can also be found in the normal population and are hence not specific for Down syndrome!

## Organic malformations in Down syndrome



**Image:** "Cryptorchidism, undescended testis" by Nevit Dilmen. License: [CC BY-SA 3.0](#)

Not only the outer appearance of the patients is different, **organs** can be malformed, too. Patients with Down syndrome can, for example, suffer from **hypothyroidism**. Furthermore, male patients are, contrarily to the female ones, mostly **infertile** and exhibit **cryptorchidism**.

The most common (up to 50%) malformations are, however, represented by **congenital**

**heart diseases.** They include, above all, an **atrioventricular septal defect** but also other heart diseases like a **ventricular septal defect**, a **patent ductus arteriosus Botalli** or isolated **atrial septal defects**.

Concerning the **intestinal tract**, you can often find a **duodenal atresia** or **Hirschsprung's disease**. You may also possibly find **atresia of the esophagus** or **anus** as well as **malformation** of the **bile duct** and the **pancreas**.

## Mental retardation in Down syndrome

The **IQ** of patients with trisomy 21 lies between 20 and 50. The mental retardation can however vary considerably in its severity. Usually, it is possible to learn how to read and write so that in some cases the possibility of an autonomous life exists.

## Diagnosis of Down Syndrome

### Postnatal diagnosis of Down syndrome

The diagnosis of trisomy 21 can often be suspected **postnatally** on the basis of the **clinical picture**. Since many symptoms of Down syndrome can also be found in the normal population, Jackson et al. (1976) created an **index** to contribute to the visual diagnosis. The index lists the following 25 symptoms of Down syndrome:

1. Brachycephaly
2. Oblique lid axis towards superior and lateral
3. Nystagmus
4. Flattened nasal bridge
5. Narrow roof of the mouth
6. Clynodaktyly V
7. Hypotension of the muscles
8. Sandal's gap
9. Folded auricle
10. Short neck
11. Epicanthus
12. Blepharitis, conjunctivitis
13. Brushfield spots
14. Constantly open mouth
15. Abnormal teeth
16. Protruding tongue
17. Scrotal tongue
18. High roof of the mouth
19. Nuchal fold
20. Shortened and broad hands
21. Brachydaktyly V
22. Single transverse palmar crease
23. Congenital heart diseases
24. Cardiac murmur
25. Hyperflexible ligaments

If **at least 13** of these symptoms can be noticed in a child, the child suffers from trisomy 21 with a probability of **100%**. **12 to 10** characteristics mean a probability of **85%**; **9 to 7** one of **75%** and **6 to 5** a likelihood of **23%**. If **less than 5** characteristics can be found,

the probability is **0%**.

It is, however, necessary to confirm the diagnosis via **cytogenetic examinations (analysis of the karyotype)** in order to diagnose or rule out Down syndrome. It is, moreover, important to determine the underlying type of trisomy 21 in order to be, among other things, able to assess the risk of recurrence (see above).

## Prenatal diagnosis of Down syndrome

### Triple test

The **triple test** is used between the 16<sup>th</sup> and the 20<sup>th</sup> week of pregnancy. It measures the **blood serum levels** of the mother and compares them to **reference values** of other pregnant women in the same week of pregnancy. The test includes  **$\beta$ -hCG,  $\alpha$ -fetoprotein** and **estriol**. If those values differ from the standard ( $\beta$ -hCG high,  $\alpha$ -fetoprotein and estriol low), a trisomy 21 can be the reason. This test is, however, **not specific** for Down syndrome and susceptible to faults. It is also necessary to calculate the exact gestational age in order to be able to draw a conclusive comparison.

### Sonography



**Image:** "Atrioventricular septal defect. Four-chamber view shows the absent crux (arrow). RA - right atrium, LA - left atrium, RV - right ventricle, LV - left ventricle" by openi. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Sonography represents an option to possibly detect **malformations** like a flat face, macroglossia, shortened femur, lacking ossification of the nasal bone, shortened fingers, dilated renal pelvis or heart defects. These malformations increase the risk of trisomy 21, but they can not always be interpreted as manifestation of a disease. Sonography can thus yield **false positive** or **false negative** results.

A sonography of the **fetal nuchal translucency** (subcutaneous tissue between neck and cervical spine) in the 11<sup>th</sup> to 14<sup>th</sup> week of pregnancy can also lead to the suspicion of increased risk of Down syndrome. Still, this examination is also **not specific** for trisomy 21.



**Image:** "Ultrasound image of measurements of fetal nuchal translucency, and absent nasal bone at 11 weeks of pregnancy."



## Amniocentesis and chorionic villus sampling

If non-invasive examinations like sonography or the triple test show noticeable findings, invasive examinations like **amniocentesis** and **chorionic villus sampling** need to be considered. For this procedure, the **fetal** or **placental** cellular material is extracted and a **chromosomal analysis** is performed with it. Both methods can diagnose a trisomy 21 with a high degree of certainty; they are, however, known to be associated with an increased risk of **miscarriage**.

## Treatment of Down Syndrome

Organic malformations have to be treated symptomatically. For example, **hypothyroidism** can be treated by substituting **thyroxine**; **congenital heart diseases** can be operated in order to considerably increase the quality of life. A **physiotherapy** (as early as possible) can mitigate the extent of muscular hypotension.

It is, furthermore, essential to **encourage** the affected children and to treat them with all the **care** they need. Hence, they need a loving environment as well as **medical** and **psychosocial** care. Caring for a child with Down syndrome often presents a special challenge for the parents, so it can be helpful for them to join **self-help groups**. The accessibility of a **sociopediatric center** is useful, too.

**Medical check-ups** are also quite important for patients with trisomy 21. It is indispensable to watch out for abnormalities of the **gastrointestinal tract** and of the **heart** in **newborn** babies or later in **infants**. It is also necessary to detect eye diseases like **cataract** and **strabismus** as early as possible in order to prevent additional handicaps due to visual impairment.

## Review Questions

You can find the correct answers beneath the list of references.

**1. A woman at the age of 35 gives birth to a child with Down syndrome. Which symptom is the child least likely to exhibit?**

- A. Brushfield spots
- B. Abnormalities of the auricle
- C. Single transverse palmar crease
- D. Cleft palate
- E. Macroglossia

**2. A couple comes to you in your human genetic consultation. They have one child with trisomy 21 and want to know the risk of recurrence for their second child. The cytogenetic examination of the father shows that he is a carrier of a balanced translocation (46, XY, t(14;21)). How likely is it for the couple to give birth to another child with Down syndrome?**

- A. 1 %
- B. 5 %
- C. 10 %
- D. 15 %
- E. 20 %

### 3. Which diagnostic method delivers the safest diagnosis of trisomy 21?

- A. Triple test
- B. Sonography
- C. Chorionic villus sampling
- D. Double test
- E. Auscultation

## References

Apgar, V., & New York Academy of Sciences. (1971). *Down's syndrome (mongolism)*. New York: New York Academy of Sciences.

Eckdahl, T. T. (2018). *Down syndrome: The amazing cookie*.

Evans, R. (1994). Phonological awareness in children with Down syndrome. *Down Syndrome Research and Practice*, 2(3), 102-105. doi:10.3104/reports.38

Pueschel, S. M., & Down Syndrome State-of-the-Art Conference. (1987). *New perspectives on Down syndrome*. Baltimore: P.H. Brookes Pub. Co.

**Correct answers:** 1D, 2A, 3C

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Notes