

GENETICS

GENETIC BACKGROUND:

Humans have a genetic makeup of 46 chromosomes divided into 23 pairs. Chromosomes carry genes, which determine the characteristics of each person (color of eyes, hair, etc.). They are divided into one sexual pair XX or XY (which determines the sex of the unborn child) and 22 autosomal pairs (non-sexual).

In reproductive cells (eggs and sperm) there are only 23 chromosomes: 22 autosomes and one sexual (X or Y). The child, resulting from the fusion of the two cells, therefore receives a complete genetic complement of 46 chromosomes, half from one parent and half from the other. Since reproductive cells consist of only one set of chromosomes and not two, their production requires a random choice of genes. This randomness is visible in siblings, who, although have the same parents, differ from each other.

Genetic conditions are caused by mutations/variation in genes that produce the expression of traits which are quite unique and/or differing in function. If either parent has a gene that carries a mutation/variation, they can pass it on to their child. In the event of pregnancy, these people may benefit from prenatal diagnosis to know if their child is affected (refer to point 7 of this fact sheet).

DOMINANT TRANSMISSION:

On each chromosome, there are hundreds of genes. The gene on the chromosome from one parent matches an identical gene on the chromosome from the other parent. Genes can cause diagnoses such as dwarfism. For a condition to be expressed, it may require the presence of only one mutated gene or both.

Several genetic sequences that cause dwarfism are transmitted dominantly, including achondroplasia, spondyloepiphyseal dysplasia or Kniest syndrome. In this case, it will only take one copy of the mutated gene for the child to inherit the condition.

Table 1. Dominant transmission (i.e.: achondroplasia)

Parent's situation	Percentage of affected children	Percentage of non-affected children	Risk of a lethal form (not compatible with life)
1 affected parent	50 %	50 %	X
2 affected parents	50 %	25 %	25 %



DE NOVO DOMINANT MUTATION:

The majority of children with short stature are born to parents of average height. In this case, the parents do not carry a gene expressing dwarfism. The diagnosis was therefore transmitted by mutation, either by changes that occur spontaneously, in the chromosomes of an egg or sperm, or during the embryonic stage. The causes of these mutations are most often unknown, although it is known that the mutations increase with the age of the parents. However, it is important to mention that every human being, whether they have a genetic condition or not, is born, on average, with ten *de novo* mutations, one of which affects a gene! Mutations are therefore a very common occurrence, although they rarely give rise to a significant or diagnosable genetic condition.

With a *de novo* mutation, there is a low risk of recurrence (between 1 and 2%). Indeed, it may happen that one of the two parents is the carrier of several mutated reproductive cells (this phenomenon is called "germinal mosaicism"). In this case, the parent can therefore transmit the mutation to another child, via the mutated cell. If these parents wish to expand their family, they can be offered a prenatal diagnosis (refer to point 7 of this fact sheet).

RECESSIVE TRANSMISSION:

A trait or condition that is transmitted recessively means that both copies of the gene, from each parent, must carry a genetic mutation for it to be expressed in their child. In this case, the parents are most often carriers (without knowing it) of the diagnosis and do not have any signs or symptoms of it. Parents who are carriers of the condition each have one healthy and one mutated copy of the gene.

Some diagnoses that cause dwarfism are transmitted through a recessive fashion, such as Morquio syndrome, diastrophic dysplasia or Seckel syndrome. For a child to be affected by the condition, they must receive the gene expressing the condition from each of their two parents.

Table 2. Recessive transmission (i.e.: Morquio syndrome)

Parent's situation	Percentage of affected children	Percentage of carrier children	Percentage of non-carrier children
1 parent is a carrier of the condition	0 %	50 %	50 %
2 parents are carriers of the condition	25 %	50 %	25 %



DELETION OR DUPLICATION OF CHROMOSOMAL MATERIAL:

Some conditions are caused by deletion or duplication. In practical terms, this means that there may be a loss or an addition of a section of a chromosome, or even an entire chromosome. This creates haploinsufficiency (a lack): the affected gene does not produce enough protein for the body to function properly. People with any of these chromosomal abnormalities can have multiple visible characteristics of a condition.

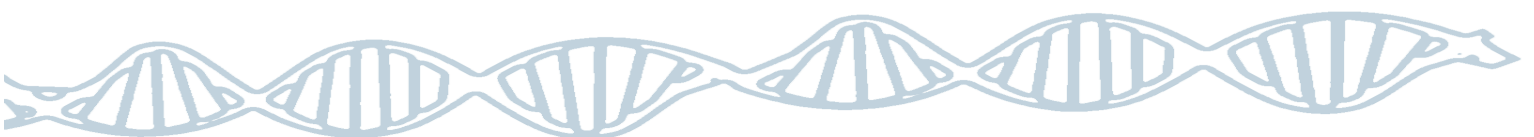
As such, Turner syndrome, which affects women exclusively, is an example of a diagnosis caused by deletion of chromosomal material. Most affected women have 45 chromosomes instead of 46. They have 22 pairs of normal autosomal chromosomes and a single X chromosome instead of one pair of sex chromosomes XX. Women with this condition cannot pass it on because they are infertile. Thus, they will have to resort to adoption or egg donation if they wish to have children. Another example of a deletion causing a type of dwarfism is dyschondrosteosis. Here, it is the deletion of the SHOX gene (located on the X and Y sex chromosomes) that causes haploinsufficiency.

Duplication can result in either an increase in the expression of one or more genes (because there are three copies rather than two), or a loss of expression if one of the breakpoints of the duplication touches a gene. This is, for example, the case with trisomy 21 (presence of an extra chromosome on the 21st pair) or any other condition where only one gene is affected.

EPIGENETIC MODIFICATIONS:

Other diagnoses made are caused by epigenetic changes. To understand what this is about, you have to know that, while genetics is the science related to the study of genes, epigenetics is concerned with a layer of complementary information that defines how genes are used (or not) by the cells of the body (heart, liver, skin, neurons, etc.). Epigenetics is therefore the study of changes in gene activity, not the modification of the chromosomes themselves. In this way, if we compare the chromosome to the magnetic tape of a cassette: each gene of the chromosome represents a track recorded on the tape, while the epigenetic modifications correspond to repositionable adhesive tape, which will mask or unmask certain tracks to make them readable or unreadable.

Thus, the cells of the body are constantly receiving all kinds of aimed at regulating their activity. These signals can lead to changes in the expression of our genes, without affecting the essence of the chromosomes. However, some epigenetic changes can become long-lasting when the signal inducing them disappears. In addition, certain hereditary syndromes can result from mutations in the genes encoding the epigenetic phenomenon. In this case, the epigenetic mechanism no longer works properly, which creates dysfunctions and pathologies in the body. Epigenetic changes, for example, are the source of Silver-Russell syndrome, a diagnosis belonging to the family of "primordial dwarfism".



PRENATAL DIAGNOSIS:

If one or both parents are carriers or have a genetic condition, they can pass it on to their child. For these reasons, parents will often be offered a prenatal diagnosis to see if their future child is affected.

Two techniques are used to perform prenatal diagnosis. Chorionic biopsy can be performed as early as the 11th week of pregnancy. This technique, which involves collecting and examining small pieces of the placenta, allows molecular, biochemical and chromosomal analysis of the unborn baby.

Amniocentesis, the second technique for prenatal diagnosis, is based on the collection and analysis of amniotic fluid. It can be used from the 15th week of pregnancy. You should know that these two techniques carry risks of complications that can go as far as miscarriage (risk about 1/300).

RESOURCES :

Association québécoise des personnes de petite taille
<https://www.aqppt.org/>

Little People of Ontario
<https://littlepeopleofontario.com/>

Association québécoise des personnes de petite taille, *Recherche médicale sur le nanisme*, Montréal, AQPPT, 1993

Nathalie Boëls, *Le nanisme. Se faire une place au soleil dans un monde de grands*, Montréal, éditions du CHU Sainte-Justine, 2008

Inserm (Institut national de la santé et de la recherche médicale) – dossier « Epigénétique. Un génome, plein de possibilités! »
<https://www.inserm.fr/information-en-sante/dossiers-information/epigenetique>



Please contact us for more information

Association québécoise des personnes de petite taille
6300, avenue du Parc, bureau 430, Montréal (Québec) H2V 4H8
Phone: 514 521-9671 • Fax: 514 521-3369
Website: www.aqppt.org • E-mail: info@aqppt.org

Avec la participation financière de

Office des personnes
handicapées
Québec 