

Information Townes-Brocks Syndrome

Molecular genetic testing of the gene *SALL1*

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Townes-Brocks syndrome

In 1998 we found mutations (defects) in the gene called *SALL1* on chromosome 16q12.1 to cause Townes-Brocks syndrome (Kohlhase et al., Nature Genetics 18, 81-83, 1998). This is an autosomal-dominantly inherited disease, characterized by a combination of malformations of the thumbs (thumbs with three bones (triphalaengeal thumbs) or doubled thumbs (preaxial polydactyly)) with those of the external ears and of the anus (imperforate anus, anal stenosis, anal ante-position). Other (less common) symptoms are malformations of the feet, the kidneys and the heart, impaired renal function, hearing loss and developmental delay.

Inheritance is autosomal-dominant. This means: each of our genes – in males with the exception of the ones on the sex chromosomes X and Y – is present in 2 copies (alleles). One allele comes from the mother, the other from the father. Symptoms of an autosomal dominantly inherited disease will occur if one of the two alleles carries a mutation, i.e. a change in the gene, which impairs or destroys its normal function or leads to an abnormal function. The recurrence risk for children of affected persons is considered to be 50%, but there are some families known in which a carrier shows a milder or a more severe phenotype compared to his/ her relatives with the same mutation. In sporadic cases (affected child of non affected parents), the recurrence risk for siblings is low if the mutation is only found in the affected person but not in the parents. In this situation, we give a recurrence risk for TBS in further children of about 1-5%, because unaffected parents can still carry the mutation in the testes or ovaries (called germline mosaicism), and we can never exclude this by testing the gene in the blood, as we do.

What is a chromosome?

It is a structure in the nucleus of a cell, which harbours the genes. It consists of the gene material called DNA and proteins wrapped around the DNA. Humans have about 25000 genes, females have two copies of each, males a bit less. You can imagine a chromosome as a pearl chain with

every pearl being a gene and the space in between being less important (mostly we don't know what it is good for).

What is a gene?

Genes consist of DNA. Most genes are recipes for proteins. Those proteins have specific functions. Collagen is a protein. There are several different types, and those are needed for stability of the skin or the bones for example. A Collagen gene produces the collagen protein.

What is a mutation?

Imagine a gene like a recipe. It is a text and tells you how to make a cake. If you have a mutation in the gene, this would mean that a part of the recipe is missing (deletion). Either you get a wrong cake or none. The whole recipe could be missing, that is also a deletion. Genes are a bit more complicated because just one letter could be missing and still the recipe does not work. You can also add a letter or more and it does not work (insertion). If you exchange a letter for another, this may stop you from reading (nonsense mutation) or give you a different taste of the cake (missense mutation).

What does a *SALL* gene do?

Humans have four *SALL* genes. *SALL* means Sal-like, and Sal stands for Spalt, a mutant in the fly *Drosophila* created in 1980 by C. Nüsslein-Volhard, G. Jürgens and E. Wieschaus (two of them got the noble price for creating thousands of those mutants). In the Sal mutant fly, the embryo does not develop properly. Sal in the fly and the *SALL* genes in humans are making proteins called transcription factors, which work like switches for other genes. They make proteins, which turn other genes off. If they don't work properly, human embryos cannot develop normally.

Why is there more than one *SALL* gene?

They have different functions. *SALL4* is important for the forearm development, and if there is a defect, the forearm bones are shortened (especially the radius, the one on the side of the thumb), *SALL1* is less important for the forearm, more for the thumbs.

How do we get TBS?

If the *SALL1* gene gets a defect in the egg or sperm, which destroys the recipe for making the switch protein, there is either not enough *SALL1* switch protein in the embryo or the *SALL1* protein is shorter than usual and does not work as it should do. We don't know exactly what happens here.

Why do *SALL1* mutations happen?

We know that it is not related to a higher age of the parents, as it is in some other diseases. It can happen because the SALL1 gene like all other genes is copied when cells divide and produce egg or sperm cells. It is like writing a copy of the recipe, where you have to be cautious not to make any spelling mistake. Our copy machine has safety precautions, but sometimes copy mistakes are overlooked. The spelling mistakes can also just happen by accident, and can happen because we are all subject to cosmic radiation, which we cannot prevent. Most of those mistakes are corrected by a repair system, but some do escape.

Testing

We need EDTA blood or a substantial amount (>50 µg, >0.2 µg/µl) of DNA from patients. We prefer to have samples of the parents in order to exclude polymorphisms or mosaicism for a mutation. Once we have found a mutation the results will be communicated to your clinical geneticist or genetic counselor and they will be able to explain them to you. If we don't find a mutation, we would like to keep your sample in order to look for mutations in other genes possibly causing the syndrome as well.

If we find a mutation we will let your doctor/ genetic counselor know. The results should be disclosed only by a person especially trained in medical genetics, such as a genetic counselor or a clinical geneticist.

Declaration:

I/ we have read and understood the text above. I/ we received detailed information on chances and risks of the test as well as on the limitations of the results.

Place, date

Signatures

Local coordinator:

Investigator:

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1. I _____, give my consent for my/ my childs blood/ DNA sample to be sent for DNA extraction and *SALL1* mutation analysis to Dr. Kohlhase's laboratory.

YES NO

2. The DNA may be stored indefinitely so that further tests maybe performed in the future in order to clarify the cause of the Townes-Brocks syndrome or related malformation syndrome.

YES NO

3. I wish to be re-contacted regarding the results of any new tests for the Townes-Brocks syndrome or related malformation syndrome in the future.

YES NO

4. This sample is to be used for Townes-Brocks syndrome clinical testing or related research only and I wish to be contacted regarding the use of my DNA for any other tests or research.

YES NO

5. My/ my childs clinical data may (in anonymized form) be used for research purposes, especially for scientific (medical) publications.

YES NO

6. If provided, my/ my childs photographs may be shown in scientific (medical) publications

YES NO

please encircle your answers

Signed:

Witness:

Print name:

Print name:

Date:

Date: