Tricho-Rhino-Phalangeal Syndromes (TRPS) - Diagnostic Guidelines

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A Brief Description of the Clinical Features

Three types of the tricho-rhino-phalangeal syndromes have been described in the literature. **All three types share** the following clinical signs, which may vary considerably from patient to patient; even among close family members.
Although the facial appearance may vary also, unrelated patients often resemble each other, whereas patients do not resemble their unaffected relatives.

Clinical Features: (not all of them are necessarily present!)

- hypotrichosis of the scalp with fine, slow-growing hair
- sparse lateral eyebrows
- a long nose with a bulbous tip
- a long flat philtrum (area between nose and upper lip)
- a thin upper lip (lips appear to be pressed together)
- large protruding ears
- brachydactyly (short fingers and toes)
- small and brittle finger nails
- axial deviations of fingers and toes
- retarded bone age in children up to age 13-14
- cone-shaped epiphyses (CSEs) of phalanges (the bones of the fingers and toes) and premature closure of the growth plates in children or
- the resulting abnormal shape of the ends of phalanges in adults
- hip malformations (Perthes-like)
- joint problems (pain, swelling)
- osteoathritis
- short stature
- general muscle weakness
- loose, redundant, extra skin (sometimes during childhood only)
- narrow mouth
- malocclusion
- jaw anomalies (micrognathia, retrognathia, prognathia)
- dental anomalies (missing or extra teeth)
- cleft palate (perhaps submucous)
- obstructions of the respiratory tract
- swallowing problems
- speech problems
- hearing problems
- heart defects
- vesico-ureteric reflux
- excessive sweating

The main difference between **TRPS types I and III** is the degree of brachydactyly and short stature, which are more pronounced in TRPS III. This differentiation is more or less arbitrary!

Patients with **TRPS type II** have **multiple** cartilaginous exostoses in addition to the above mentioned signs. They are in fact affected by two diseases, the TRPS and hereditary multiple exostoses (HME), which can also occur independently of TRPS!
TRPS II is also called Langer-Giedion syndrome, LGS.

Molecular Basis of the Diseases

The genes responsible for development of the TRPSs are known. The *TRPS1* gene and the *EXT1* gene are located close to each other on the long arm of chromosome 8, region q24.1 (8q24.1).

TRPS I can be caused by:
a) complete or partial loss (deletion) of one copy (maternal or paternal) of the *TRPS1* gene
b) disruption of the *TRPS1* gene by a chromosomal abnormality like translocation, inversion etc.
c) a point mutation in the *TRPS1* gene
a) and b) account for 5 to 10 % of cases. Point mutations can be found in approximately 90 % of patients.

TRPS III is almost exclusively caused by a specific type of point mutations (missense mutations) in a specific region (exon 6) of the *TRPS1* gene.

TRPS II (LGS) is a so-called contiguous gene syndrome. All patients have a deletion of the two neighboring genes *TRPS1* and *EXT1* on one of their chromosomes 8. These deletions vary in size between patients. The larger the deletion is the higher is the risk that further neighboring genes are deleted, as well. Such patients may be mentally retarded or may have additional health problems. Additional problems have not yet been investigated systematically.

Inheritance

The TRPSs are inherited dominantly with complete penetrance. This means that every individual carrying a deletion or mutation in one copy of the genes will develop signs of the condition. The risk to pass on the mutant gene(s) is 50 %. This means that statistically 50 % of their children are affected, as well.

Diagnostics

Clinical

The diagnosis of any type of TRPS can be made clinically without any doubt. In most cases, the facial appearance is conclusive. (However, I have already seen several patients with TRPS I -proven by mutation analyses- whose faces were not conspicuous!). Girls with TRPS often present with a male-like appearance.
An X-ray examination of the flat hands and wrists is a must. This will clearly disclose the CSEs in children or the resulting abnormally shaped ends of the phalanges in adults with TRPS. In children younger than two years, epiphyses may not be detectable. However, in these cases the retarded bone age together with the facial appearance has a diagnostic value.
The number of affected bones varies considerably between patients, and in many cases abnormalities are not even symmetrical in both hands. In mildly affected patients, CSEs may be present at the middle-phalanges of fingers 2 and 5, only. But they can develop at any phalanx. All affected phalanges will remain shorter than normal. If the distal phalanges are small, the nails will be small or almost absent.
For a description of the bones of healthy hands and examples of the bone anomalies in the TRPSs see the file "bone abnormalities in the TRPSs" in the files section of the web site of the TRPSA at http://health.groups.yahoo.com/group/TRPSA/.

In patients with **TRPS III** almost all phalanges as well as the metacarpals (the bones forming the skeleton of the palm) are short.

Patients with **TRPS II** (LGS) have exostoses at **multiple** sites of their skeleton. Exostoses are visible or palpable lumps located close to the ends of long bones. They may be present at birth but will develop until the age of 5, at the latest. Thus, in very young patients, the **clinical differentiation** between TRPS I and TRPS II may be

difficult. Although exostoses may occur at any tubular bone, they are less abundant on the phalanges, but many patients have exostoses on their ulnae and radii close to the wrist, which should be detectable on the X-ray images (see above). In case of uncertainty, X-ray examination of additional joints like elbow or knee is advisable. Please, keep in mind that not all individuals with **multiple exostoses** have **TRPS II**!

The best diagnostic tool for TRPS is the X-ray examination of the hands and wrists!

X-ray examination is easy, inexpensive and non-invasive. The result is obvious immediately (at least for experienced radiologists).

Although height is rather variable in the general population, the patient's height should be evaluated. There are many patients with TRPS I who appear "normally" tall compared to the "mean" population. However, if taking the heights of the **healthy** parents, which also contribute to the expected height of a patient, into consideration, these patients may be identified as "mildly" affected.

Laboratory Tests

Because the responsible genes are known, the clinical diagnosis **can** be but **need not** to be confirmed by several laboratory tests. **Note: Even if performing all available laboratory tests, there are patients (~ 5 %) in whom the disease causing mutation can not be identified. Such "negative" lab tests do not reject the clinical diagnosis!**
However, the precise determination of the cause of the disease may be advisable to exclude several risks. There is an extremely rare possibility that a **healthy parent** of a sporadic case carries a balanced deletion or insertion mutation. In such a scenario, there is a 50 % risk for further children to be affected, as well.
Furthermore, if a **patient** carries a translocation, an inversion, or an insertion which disrupts the *TRPS1* gene, this patient's children do not only have a risk of developing TRPS I but also for other diseases. These rare situations can not be discussed here, but should be discussed with the caring physician if a chromosomal abnormality has been found.

Cytogenetic Diagnostics

A **conventional cytogenetic analysis** (analysis of banded metaphase chromosomes) can disclose only gross abnormalities like large deletions, translocations, inversions, or insertions. Cytogenetically visible deletions can be found in up to 50 % of patients with **TRPS II** (LGS), and in less than 2 % (my experience) of patient's with **TRPS I**.
A molecular cytogenetic technique, the **fluorescence *in situ* hybridization** (**FISH**) is capable of detecting subtle chromosome abnormalities. Provided that the probes are chosen carefully, FISH discloses the abnormality in 100 % of those patients who have such an abnormality.

Although chromosomal abnormalities are rare in TRPS I, the exclusion of such an abnormality by a conventional cytogenetic and a FISH analysis is reasonable, because chromosomal abnormalities often affect more than one gene and may lead to additional health problems.

Molecular Diagnostics

TRPS1 mutation screening

Because the majority (~ 90 %) of patients with **TRPS I** and all patients with **TRPS III** have point mutations in the *TRPS1* gene, **mutation screening** by sequencing the *TRPS1* gene in the patient's DNA isolated from peripheral blood cells is the method of choice for these conditions.

Deletion mapping

For patients with TRPS II or those with TRPS I, in whom no *TRPS1* mutation could be identified, deletion mapping is advisable. In the past it has mainly been done by **microsatellite analysis** for which one needed DNA samples of patient **and both** parents**.** In recent years, there has been significant progress in finding and describing deletions. Nowadays so-called **SNP-chip hybridization** (GeneChip human mapping arrays) or Microarray-based **Comparative Genomic Hybridization** (aCGH) are available. The new tests give precise results, are not

dependent on the availability of the DNA of the patient's parents, and the analysis is completed fast. However, they are rather expensive. A cheaper test is the **Multiplex Ligation-dependent Probe Amplification** (MLPA). The resolution of the SALSA MLPA Kit P228, TRPS1-LGS, by MRC Holland is sufficient to detect a deletion and to confirm the clinical diagnosis.

Prenatal diagnosis

In general, prenatal diagnosis in subsequent pregnancies is possible if the disease causing mutation has been identified in the index patient.