

Information

Okhiro syndrome

Holt-Oram syndrome

Molecular genetic testing of the genes *SALL4* and *TBX5*

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***SALL4* and *TBX5* mutations in Okhiro/ Holt-Oram and related malformation syndromes**

Dear parents, patients and doctors,

mutations in the gene *SALL4* on chromosome 20q13 are the cause of **Okhiro syndrome**. **Okhiro syndrome alias Duane-Radial Ray syndrome** is an autosomal dominantly inherited malformation syndrome characterized by a combination of radial malformations of the upper extremities and a Duane anomaly, which is a form of strabism (paresis of nervus abducens resulting from lack of the abducens nerve or its nucleus with misinnervation of the ipsilateral lateral rectus muscle of the eye by the oculomotor nerve on the same side). In addition, congenital heart defects, dysplastic ears, hearing loss and anal malformations may occur. If renal malformations are present as well, the clinical diagnosis might be Acro-Renal-Ocular syndrome, which is also due to mutations in the *SALL4* gene.

Holt-Oram syndrome is very similar to Okhiro syndrome with respect to limb and heart malformations. The radial ray malformations are essentially the same as in Okhiro syndrome and include triphalangeal thumbs, hypoplastic thenar eminences, duplication of the thumbs and/ or hypoplasia or aplasia of the radial bone in the forearm. The upper arm may also be affected as well as the shoulder girdle. Heart defects (ventricular or atrial septal defects) are mostly holes in the structure (septum), which separates the big (ventricles) or small heart chambers (atria), but more severe defects may also occur. Often, there are problems with the cardiac conduction system resulting in disturbances of the heart rhythm. The biggest difference between Okhiro and typical Holt-Oram syndrome is that in Holt-Oram syndrome no defects of the ears, kidneys, eyes or hearing loss are observed. Holt-Oram syndrome is also autosomal dominantly inherited (see above for explanation), and the gene, which is mutated in about 74% of typical cases, is *TBX5* on

chromosome 12q24. Although Holt-Oram syndrome can be distinguished from Okihiro syndrome in most cases, in some patients with **Holt-Oram syndrome** a *SALL4* mutation may be found instead of a *TBX5* mutation.

Okihiro, Acro-Renal-Ocular and Holt-Oram syndromes are autosomal-dominantly inherited. 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. The recurrence risk for children of affected persons is considered to be 50%, but there are some families known in which obligate carriers of a mutation do not show the Okihiro syndrome phenotype (reduced penetrance). This is not known for Holt-Oram syndrome. It is also important to know that a mutation carrier may show 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.

We need EDTA blood (5 ml) or a substantial amount (>50 µg, >0.2 µg/µl) of DNA from patients and parents. We might need 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.

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1. I _____, give my consent for my/ my childs blood/ DNA sample to be sent for DNA extraction and *SALL4* and/ or *TBX5* mutation analysis to Prof. 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 Okihiro / Holt-Oram syndrome or related malformation syndrome.

YES NO

3. I wish to be re-contacted regarding the results of any new tests for the Okihiro / Holt-Oram syndrome or related malformation syndrome in the future.

YES NO

4. This sample is to be used for Okihiro / Holt-Oram syndrome 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: