

Information
CHARGE Syndrome

**Molecular genetic testing of
the gene *CHD7***

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Dear parents,

in 2004, researchers found out that mutations (defects) in gene *CHD7* on Chromosom 8q12.1 are responsible or causative for CHARGE syndrome (Vissers et al., Nature Genetics 36:955-957, 2004).

CHARGE represents the typically combined anomalies seen in children affected with this disease:

Coloboma (defects in the iris or choroidea in the eye)

Heart defects

Choanal Atresia (Choana are the „internal openings of the nose“ and connect the nasal cavities with the throat)

Retardation of growth and/ or mental development

Genital anomalies

and **Ear malformations**.

This combination of multiple birth defects is rather common (ca. 1/ 12000 newborns). Affected children or adults rarely are of normal intelligence.

Inheritance/ genetics

CHARGE syndrome is an **autosomal-dominant inheritable condition**. The cause are autosomal dominante gene defects (mutations) in the *CHD7* gene, which were found in 58 - 65% of patients with typical malformations. Autosomal dominant 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 inherited cases of **CHARGE** are rare. Parents of affected children are mostly unaffected. Nevertheless, there is an empirical recurrence risk of 1-

2% for further children, because even unaffected parents may carry the mutation in some cells of their body or even only in some germ cells in their testes or ovaries.

Clinical diagnosis according to Verloes (2005):

Typical CHARGE = 3 major criteria or 2 major and 2 minor criteria of the following:

Major criteria

- 1) Coloboma (iris or choroid, with or without microphthalmia)
- 2) Atresia of Choanae
- 3) Hypoplastic semicircular Canals

Minor criteria

- 1) Rhombencephalic dysfunction (brainstem dysfunctions, cranial nerve VII to XII palsies and neurosensory deafness)
- 2) Malformation of mediastinal organs (heart, esophagus)
- 3) Hypothalamo-hypophyseal dysfunction (including growth hormone and gonadotrophin (hormones for genital development) deficiencies)
- 4) Abnormal middle or external ear
- 5) Mental retardation

Clinical features of patients with <i>CHD7</i> mutation	Jongmans et al. 2006 J Med Genet	Lalani et al. 2006 Am J Hum Genet
Colobomata	70 %	89 %
Choanal atresia	36 %	60 %
Ear anomaly/ deafness	100 %	
Outer ear anomaly		95 %
Inner ear anomaly		95 %
Deafness		92 %
Anomaly of the facial nerve	21 %	
Facial asymmetry		64 %
Cardiovascular anomalies	66 %	92%
Cleft lip/ palate	36 %	30%
Tracheo-esophageal fistula	17 %	18 %
Growth retardation	66 %	
Renal anomalies	19 %	
Genital hypoplasia (males)	77 %	
Urogenital anomalies		55 %
Spinal involvement	19 %	

This table gives percentages as for how many patients with a mutation in *CHD7* show specific anomalies. Very common anomalies are **too small or missing semicircular canals** in the inner ear, which can be detected with a computer tomography (CT scan) of the head (especially showing the temporal bones). Such anomalies were seen in 100% (Jongmans 2005) or 95% (Lalani 2006) of patients in two independent investigations (in such patients who were examined with a CT scan).

Gene test/ investigation of the *CHD7* gene

Why do a gene test? The test may confirm the diagnosis and the cause of the anomalies, and thereby allow more precise counseling of parents. Not all children with a *CHD7*-Mutation are affected by all possible anomalies. Therefore, CHARGE is mostly only one out of several possible diagnoses. Similar diseases are for example Townes-Brocks syndrome (malformations of thumbs, ears, anus, but such of genitals, heart defects and coloboma may also be seen) or VACTERL association (malformations of spine, anus, heart, trachea and esophagus, kidneys and limbs). The gene test may confirm the diagnosis CHARGE, but it cannot exclude it if no mutation is found. If a mutation is found, it is possible to detect or exclude it prenatally in further pregnancies.

For *CHD7* testing we need EDTA-blood (5-10 ml, for small children 2 ml will do), to be sent by express airmail within the European union or by express airmail courier from other countries. We need blood of the parents to further investigate unclear results. **Medical information on the malformations of the child will be very helpful.** Even if the diagnosis CHARGE syndrome is clinically clear, we may not find a mutation. In such cases (35-42 % in the literature) a mutation might be in regions of the gene, which were not analyzed (regions not coding for protein) or a causative mutation is present in another, yet unknown gene.

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 *CHD7* 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 CHARGE syndrome or related malformation syndrome.

YES NO

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

YES NO

4. This sample is to be used for CHARGE syndrome 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: