The genetics of CHARGE syndrome

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The CHD7 gene
Since 2004 we know that CHARGE syndrome is caused by a change in the CHD7 gene (=mutation). Every person has two CHD7 genes, one inherited from father and the other one inherited from mother. CHD7 is a regulatory gene. It regulates the expression of developmental genes very early during the development of the unborn child (embryo). If there is insufficient CHD7 the risk for developmental defects in specific organs like the heart, eye, ear, kidney, etcetera, is increased (figure). A change in one of the two CHD7-genes is enough to result in CHARGE syndrome. However, CHARGE syndrome is highly variable and it is not possible to predict the clinical consequences for the child from the specific change in CHD7.

![Function of CHD7](image)

CHD7 regulates the function of developmental genes during early pregnancy.

Effect of CHD7 mutations
CHARGE syndrome is highly variable. That means that even children with the same CHD7 mutation may present with different features. We collected information on 280 persons with a CHD7 mutation and compared these with the features of CHARGE patients who were diagnosed before CHD7 was known. See table on next page. In this table it can be seen that cleft lip/palate occurs more often than previously thought. This is because in the past children were suspected for CHARGE syndrome when they had a choanal atresia (blocked passage from nose to throat). If there is a cleft palate, usually there cannot be a choanal atresia. So in children with cleft palate, CHARGE syndrome used to be under-diagnosed (less well recognised). The increased percentage of genital hypoplasia (micropenis) is mainly due to an increased awareness of this feature in CHARGE syndrome.
Feature | Our CHD7-positive cohort (n=280) | CHARGE patients before CHD7 discovery (n=124)
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External ear anomaly | 97% | 96%
Cranial nerve dysfunction (e.g. facial palsy, abnormal hearing nerve, etc) | 99% | 86%
Semicircular canal anomaly (balance organ) | 94% | 100%
Coloboma (eye defect) | 81% | 77%
Choanal atresia | 55% | 61%
Cleft lip and/or palate | 48% | 18%
Feeding difficulties necessitating tube feeding | 82% | 85%
Facial palsy | 66% | 36%
Inability to smell | 80% | ------
Genital hypoplasia | 81% | 36%
Heart defect | 76% | 85%
Tracheo-oesophageal anomaly | 29% | 18%
Developmental delay | Delayed motor milestones 99% Cognitive delay 74% | Developmental delay 100%
Growth retardation | 37% | 65%

**CHARGE syndrome can be very mild**
Since CHD7 analysis has become available, we learned that CHARGE syndrome can vary from a very mild to a life-threatening condition. Especially in the mildly affected children CHD7 analysis is very helpful in order to make a diagnosis. The diagnosis is important to be able to inform parents about recurrence risk (see paragraph on familial CHARGE syndrome) and to establish an appropriate surveillance program (more about that in the presentation of Nicole Janssen).

However, CHARGE syndrome remains primarily a clinical diagnosis. We know that in 5-10% of patients with typical CHARGE syndrome, no CHD7 mutation can be found. If patients fulfil the clinical criteria of Blake or Verloes, then they have CHARGE syndrome, irrespective of the results of CHD7 analysis. On the other hand, patients who do not completely fulfil the clinical criteria should not be excluded from CHD7 analysis. If a mutation is found in these patients, clinical follow-up and genetic counselling should be performed as in clinically diagnosed patients with CHARGE syndrome.

**When should CHD7 analysis be performed?**
Based on our experience with CHD7 analysis in almost 900 patients suspected of CHARGE syndrome, we wrote a guideline for CHD7 analysis. This guideline is summarised in the figure.
How is CHD7 analysis done?

CHD7 analysis is performed on DNA. DNA is usually extracted from blood cells, but also other tissues, e.g. skin, can be used. Different types of mutations can be present in the CHD7 gene. Most mutations will be detected by routine CHD7 DNA-analysis (called “sequencing”). In the presentation I will give some examples of this kind of mutations. Sometimes a part of or the complete CHD7 gene can be missing (this is called a “deletion”). Deletions of CHD7 are rare and occur in approximately 1% of CHARGE patients. They cannot be found by routine DNA-analysis, but will be identified by other techniques (array, MLPA).

**Familial CHARGE syndrome**

Rarely two children with CHARGE syndrome are born within one family. CHARGE syndrome has a birth prevalence of approximately 1 in 10,000 newborns. About 3% of all persons with CHARGE syndrome have a sib or parent who also has CHARGE syndrome. We have collected as much as possible information of such families because this reveals important information on the variability of CHARGE syndrome. Within families all affected family members have the same change in CHD7, while their clinical problems may differ a lot. Moreover, we discovered that within families often an unexpectedly mild form of CHARGE syndrome can be found. In such families mildly affected persons were identified through a child with typical CHARGE syndrome.

**A parent with CHARGE syndrome**

Parents always give half of their genetic information to their children. The parent with CHARGE syndrome thus passes on either the normal CHD7 gene or the changed CHD7 gene. This means that there is a 50% recurrence risk.
The parent with (mild) CHARGE syndrome passes on the normal CHD7 gene (a) or the changed CHD7 gene (A). Thus the recurrence risk is 50% for each pregnancy.

Two children with CHARGE syndrome and healthy parents
Very rarely in a family the same CHD7 change is found in two affected children, while the parents do not have any features of CHARGE syndrome. How is that possible?
One of the parents may carry a change in the CHD7 gene in part of his/her body cells. This is called a mosaic. A mosaic situation can occur if in the fertilized egg no CHD7 change is present, but this change occurs after a few cell divisions (figure). Only the cells that arise from the cell with the altered CHD7 gene will carry this change. If these cells are also present in the ovaries or testes, egg or sperm cells with the CHD7 change can be formed and, if these are involved in a pregnancy, a child with (non-mosaic) CHARGE syndrome will be born.

In this example mother has a CHD7 change in part of her body cells (mosaic). The scheme on the right side explains that this can occur when the CHD7 change arises during a cell division after fertilization. Mother will not have CHARGE syndrome herself, but she has an increased risk for children with CHARGE syndrome (she can pass on the CHD7 change via an egg cell, and subsequently the child will have the CHD7 change in all cells).

What is the recurrence risk in CHARGE syndrome?
Familial CHARGE syndrome is extremely rare. This already demonstrates that in general the recurrence risk will be low. If parents have a child with CHARGE syndrome and want to be informed about future pregnancies we recommend the following:
- Investigate parents for mild symptoms of CHARGE syndrome (hearing, balance, smell, shape of the ears).
- If a CHD7 change has been found in the child, offer DNA analysis to the parents as well.

If the CHD7 change is found in the parent, either in mosaic form or in all cells, than the recurrence risk is increased (maximal 50%). If the parents want to, prenatal diagnosis can be performed in future pregnancies. However one should be aware that the severity of CHARGE syndrome cannot be predicted by DNA-analysis.

If the CHD7 change is not found in one of the parents (the most frequent situation), than a small risk for germline mosaicism remains. Therefore the recurrence risk is not zero, but 1 to 2 %. Also parents without CHD7 change may opt for prenatal diagnosis if they want to.

As mentioned before, the severity of CHARGE syndrome cannot be predicted by DNA-analysis. Fetal ultrasound examination can give extra information, for example on the presence of a heart defect. But not everything can be seen by ultrasound, for instance deafness, developmental delay and behavioural problems will remain undetected.

The choice for prenatal diagnosis will always remain a personal one, and the task and challenge of the clinical geneticist/genetic counsellor is to inform the parents in such a way that they can make the choice that they feel confident with.

Are there more genes involved in CHARGE syndrome?
In 5-10% of patients with typical CHARGE syndrome no mutation in CHD7 can be found. This percentage is higher in patients with an atypical presentation of the syndrome. Thus it might be that another gene is also responsible for CHARGE or a CHARGE-like syndrome. A few candidate genes, like CHD8, have been studied, but no mutations were found in CHARGE syndrome patients. Recently we started the search for other genes using a new technique: next generation sequencing or whole exome sequencing. With this technique it is possible to look for mutations in all known genes in one single test run. All patients known to us with CHARGE syndrome but no CHD7 mutation will be analysed by this new technique in spring 2011.

References

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