



Sunday, August 4, 2019

Breakout Session G40 • 2:45-3:45 pm • Chantilly Ballroom East

An Interactive Seminar in Genetics: All You Want To Know About the Genetics of CHARGE Syndrome

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Presenter Information

Christa de Geus is a medical doctor in training to become a clinical geneticist. Within clinical genetics she has a particular interest in neurology and neuroradiology. In 2014 she joined the research group of Prof. Conny van Ravenswaaij as a PhD student. Her PhD focuses on neurological symptoms in CHARGE syndrome.

Presentation Abstract

After a short introduction, all questions of the participants regarding genetics, the CHD7 gene, mutations, recurrence risk, et cetera, will be answered using instructive illustrations. A handout that explains the main issues for a lay audience will be provided. We will also present the results of our recent update of the CHD7.org website. CHD7.org aims to be a comprehensive source of clinical and molecular genetic information on known CHD7 mutations. Based on the experience of previous years, we will offer parents the opportunity to discuss the specific genetic test results of their child with us in short sessions after the seminar.

Learning Objectives

- What are chromosomes, genes, DNA and mutations?
- Why perform DNA analysis and what if no CHD7 mutation is found in your child?
- What is the risk that CHARGE syndrome will re-occur in the family?

Handout: Everything you want to know about CHARGE and genetics

By Christa de Geus, adapted from a talk by Conny van Ravenswaaij-Arts
Department of Genetics, University Medical Center Groningen, The Netherlands

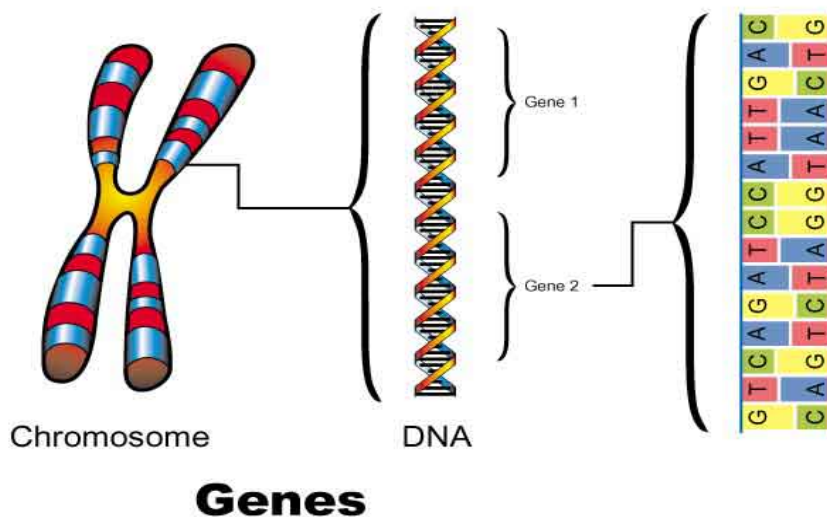
What are chromosomes, genes, DNA and mutations?

Our genetic information is tightly packed up on structures, called chromosomes.

Humans have 46 chromosomes grouped in 23 pairs. Everyone inherited 23 chromosomes from his father and 23 chromosomes from his mother.

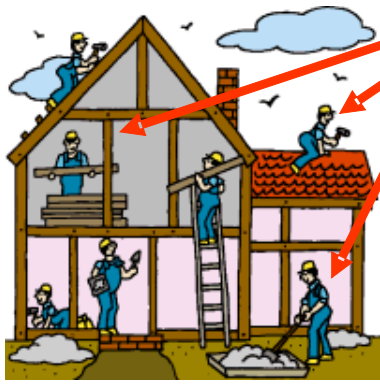
A chromosome consists of tightly packed up DNA. DNA is our hereditary material and is made up of four chemical bases (A,C,T,G). Genes are the pieces of DNA that code for proteins, which are important for all kind of functions in the body.

A mutation is another word for change in the DNA-code, due to such a change in the DNA-code the function of the proteins can be changed.



What is the *CHD7* gene and what does it do?

Since 2004 we know that CHARGE syndrome is caused by a mutation in the *CHD7* gene. 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*.



Body, first weeks of pregnancy

Other genes



CHD7

CHD7 regulates the function of developmental genes during early pregnancy.

How is **CHD7** analysis done?

CHD7 analysis is performed on DNA. DNA is usually extracted from blood cells, but other tissues, e.g. skin, can also 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 these kinds 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 always be found by routine DNA-analysis, but will be identified by other techniques (array, MLPA).

What are reasons to perform DNA analysis?

There are several reasons to perform DNA analysis

- Clarity
- Prove the diagnosis in a child with atypical features
 - o Consequences for clinical follow up
- Prove the diagnosis, so parents or siblings know their recurrence risk
- Prenatal options

What if no mutation is found with **CHD7** analysis in my affected child?

A diagnosis of CHARGE syndrome can be made in a child by identifying a *CHD7* mutation, but also by looking at the clinical criteria made for CHARGE syndrome. If your child fulfills the clinical criteria, he or she has CHARGE syndrome, irrespective of the results of *CHD7* analysis.

If no mutation is found, there may be several different reasons:

- Some other syndromes have overlapping clinical features with CHARGE syndrome. It is important to exclude other syndromes.
- The techniques are not 100% reliable: they are not good enough to identify all *CHD7* mutations.

What is the recurrence risk of **CHARGE** syndrome?

Since familial CHARGE syndrome is extremely rare, in general the recurrence risk for parents who had a child with CHARGE syndrome will be low. If parents 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).

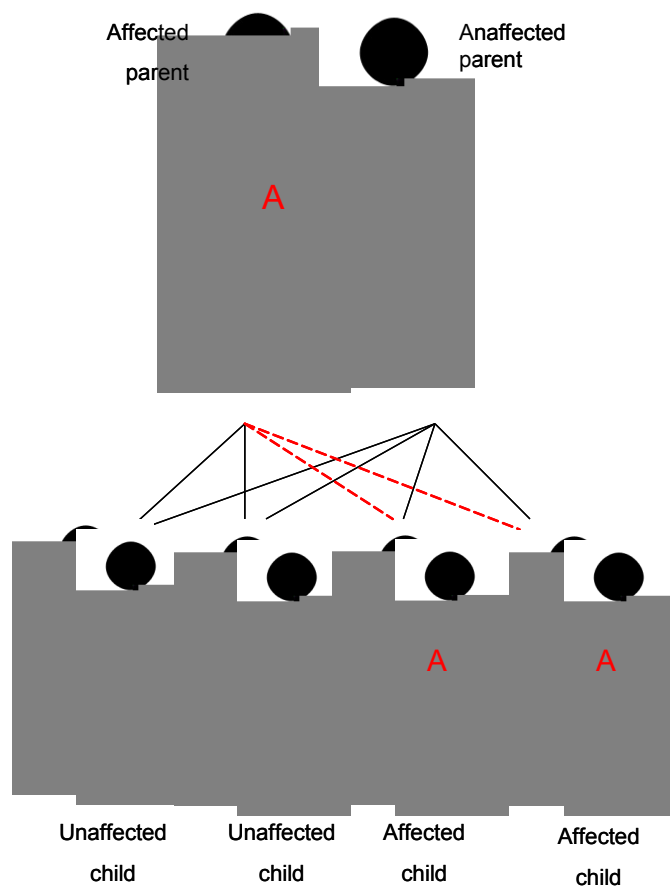
- If a *CHD7* change has been found in the child, offer DNA analysis to the parents as well.

Parent without CHARGE syndrome or *CHD7* mutation

If the *CHD7* change is not found in one of the parents (the most frequent situation), then a small risk for germline mosaicism (carrying a *CHD7* mutation only in germcells) remains. Therefore the recurrence risk is not zero, but 1 to 2 %.

Parent with CHARGE syndrome

If one of the parents has CHARGE syndrome the recurrence risk is a different story. A parent always passes on one of their two copies of their *CHD7* gene. The parent with CHARGE syndrome thus passes on either the normal *CHD7* gene or the abnormal *CHD7* gene. This means that there is a 50% recurrence risk. However, even if the child inherits CHARGE syndrome, it is not possible to predict how it will affect them.

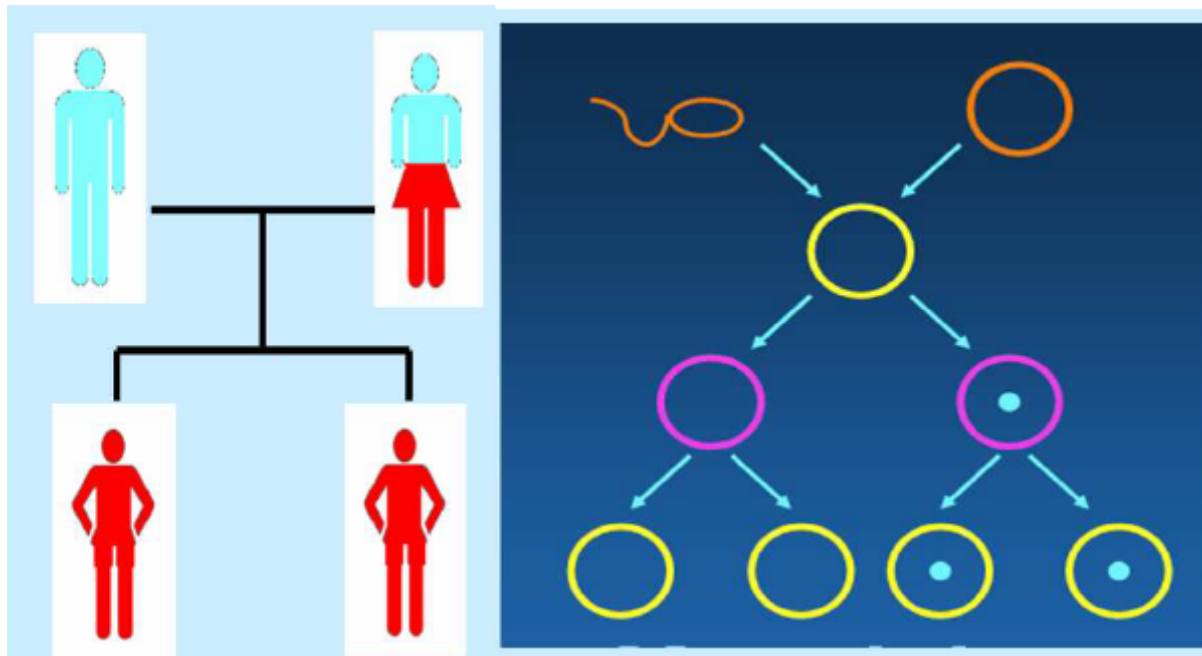


*The parent with (mild) CHARGE syndrome passes on the normal *CHD7* gene (n) or the changed *CHD7* gene (A). Thus the recurrence risk is 50% for each pregnancy.*

Parent with *CHD7* mutation in part of their cells (=mosaicism)

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 mosaicism. 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. If the *CHD7* change is found in the parent in mosaic form the recurrence risk is increased (maximal 50%).



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).

Prenatal diagnosis

Parents who had a child with CHARGE syndrome in whom the *CHD7* mutation is identified, may opt for prenatal diagnosis if they want to. However one should be aware that the severity of CHARGE syndrome can not 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 behavioral 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 counselor is to inform the parents in such a way that they can make the choice that they feel confident with.

If you have any other questions, feel free to ask them to us during the session, at any other time during the CHARGE conference or per email (c.m.de.geus@umcg.nl or c.m.a.van.ravenswaaij@umcg.nl).