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for deafblind people

Factsheet 4

# Genetics abridged

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Since 2004, we have known that CHARGE syndrome is caused by a mutation or deletion of one of two copies of the CHD7 gene on chromosome 8 (Vissers *et al.* 2004); it is therefore an autosomal dominant disorder.

## Genetics

- Most cases occur sporadically, i.e. due to a new mutation in the child
- Familial occurrence of CHARGE syndrome, whilst rare, does occur (Jongmans *et al.* 2008)
- Parent-to-child transmission occurs, when a relatively mild (missense) mutation runs in the family (Jongmans *et al.* 2008, Bergman *et al.* 2011)
- The CHD7 gene codes for a protein – chromodomain helicase DNA binding protein 7 – which regulates expression of developmental genes very early during embryonic development
- If there is insufficient CHD7, the risk for developmental defects in specific organs (e.g. brain, heart, eye, ear and kidney) is increased
- To date, over 500 different mutations of the CHD7 gene have been described (Janssen *et al.* 2012 and www.CHD7.org)
- Generally, it is not possible to predict the clinical consequences for the child from the specific change in CHD7
- Mutations with a presumed milder effect occur less frequently.

## Genetic testing

- CHD7 analysis is usually performed on DNA extracted from blood cells, although other tissues, e.g. skin, can be used
- Most mutations can be detected by routine DNA-analysis (sequencing)
- Complete or partial CHD7 deletions require other techniques (MLPA, array)
- An aid for interpretation of mutations was developed by Bergman *et al.* (2012) with results being collated in www.CHD7.org
- As CHARGE syndrome can vary from a very mild to a life-threatening condition, especially in mildly affected children, CHD7 analysis is very helpful diagnostically.

## 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 *et al.* (1998) or Verloes (2005), then they do have CHARGE syndrome irrespective of the CHD7 results
- Conversely, patients who don't completely fulfil the clinical criteria shouldn't be excluded from CHD7 analysis; if a mutation is found in these patients then clinical follow-up and genetic counselling should

be performed as in clinically diagnosed patients with CHARGE syndrome
- If no CHD7 mutation is found in a patient with atypical CHARGE syndrome, another diagnosis should be considered (e.g. 22q11.2 deletion and Kabuki syndromes).

### Genetic counselling

- CHARGE syndrome occurs in approximately 1-in-15,000 newborns (Janssen *et al.* 2012), with approximately 3% of affected people having a sibling or parent who also has CHARGE syndrome
- If an adult with CHARGE syndrome has normal fertility the risk of passing on the mutated CHD7 gene to their children is 50%
- If parents have a child with CHARGE syndrome and want to be informed about future pregnancies, we would recommend the following:
    - Investigate parents for mild symptoms of CHARGE.
    - If a CHD7 mutation has been found in the child, perform DNA analysis in the parents
- Prenatal diagnosis can be performed in future pregnancies, although the severity of CHARGE syndrome cannot be predicted by DNA-analysis
- Prenatal diagnosis will always remain a personal choice, 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.

**Note: For a more detailed version of this article, contact Sense's Information and Advice Service at: info@sense.org.uk**

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