Gene identification through array CGH: The CHARGE syndrome

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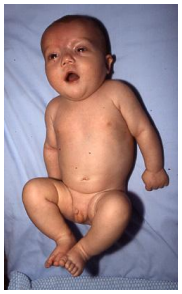
Abstract



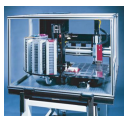
C oloboma
H eart malformation
A tresia of choanae
R etardation of growth/development
G enital hypoplasia
E ar abnormality including deafness

CHARGE syndrome (OMIM#214800) is a common cause of congenital anomalies with an estimated birth incidence of 1:12,000[ref 1].

In this study we have used high-resolution genome-wide DNA copy number screening by array-based comparative genomic hybridization (array CGH)[2-3] to identify the underlying genetic cause of this malformation syndrome. Through this screening we identified overlapping microdeletions on chromosome 8 in two CHARGE patients. These microdeletions pointed us to CHD7, the gene mutated in the majority of cases. These results were published in **Nature Genetics**[4].

This study demonstrates an effective novel approach to identify disease-causing genes. This approach is of special interest for sporadic malformation syndromes that cannot be tackled by other mapping approaches because of reproductive lethality[4].

Patients and Methods



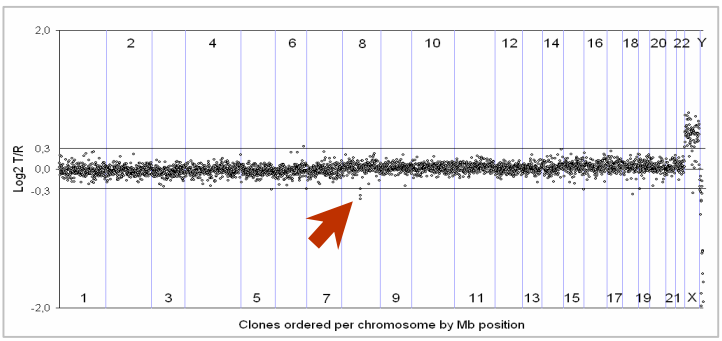
18 patients diagnosed with CHARGE syndrome having normal karyotypes upon routine cytogenetic investigation and 1 patient with an apparently balanced translocation[5] t(6;8)(6p8p;6q8q) were subjected to array CGH on:

(1) A genome-wide BAC array: 3569 BAC clones with an approximate average spacing of 1 clone per megabase

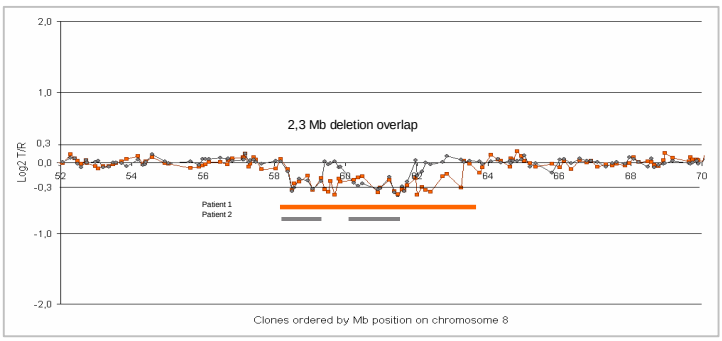
(2) A tiling chromosome 8 BAC array: 918 BAC clones resulting in an average of 1 clone per 159 kilobases

Arrays were printed using an Omnigrid 100 arrayer (Genomic Solutions). The array CGH profiles were established through co-hybridization of 500 ng Cy3-dUTP and Cy5-dUTP (Amersham Biosciences) labeled test and reference DNA, using a GeneTac Hybridization station (Genomic Solutions). Data-analysis was performed as described before[3].

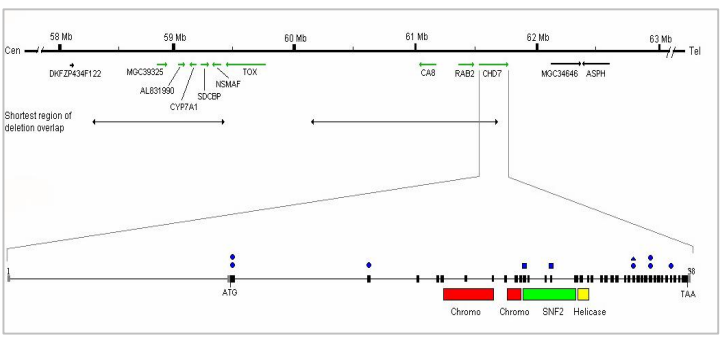
Results



Genome-wide array CGH profile of patient 1 showing a microdeletion of 3 adjacent clones on 8q12 (arrow)



Identification of a 2,3 Mb deletion overlap in two patients on a tiling resolution chromosome 8 array. Subsequent screening of 17 additional patients revealed no deletions.



Mutation analysis of the genes localized at 8q12 in these 17 patients identified 10 heterozygous mutations in the novel gene *CHD7:*

- 7 nonsense mutations (circles)
- 2 missense mutations (squares)
- 1 splice-site mutation (triangle)

CHD7: New member of the chromodomain helicase DNA binding protein family important for early embryonic development by affecting chromatin structure and gene expression.

CHD7 shows ubiquitous expression in several fetal and adult tissues, including those affected in CHARGE syndrome.

References

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4. Vissers *et al.* (2004) *Nat. Genet. 36: 955-957*
5. Hurst *et al.* (1991) *J. Med. Genet. 28: 54-55*