European Journal of Medical Genetics 56 (2013) 331–335

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Chromosomal imbalance report

Behavioural phenotype of a patient with a *de novo* 1.2 Mb chromosome 4q25 microdeletion

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ARTICLE INFO

Article history:
Received 13 December 2012
Accepted 11 March 2013
Available online 29 March 2013

Keywords:
SNP array
de novo 4q25 microdeletion
4q25
Intellectual disability
Dysmorphic features
Behavioural phenotype
Neuropsychological phenotype

ABSTRACT

A female patient, 20 years of age, is reported with a history characterized by developmental and psychomotor delay, and during grammar-school period increasing learning problems, ritualistic behaviours and social withdrawal. Subsequently, challenging and autistic-like behaviours became prominent. The patient showed mild facial dysmorphisms, long thin fingers with bilateral mild short V metacarpals, and hyperlaxity of the joints. Neuropsychiatric examination disclosed obsessive, ritualistic behaviours and vague ideas of reference. Neuropsychological assessment demonstrated mild intellectual disability, mental inflexibility and incongruent affect. MRI-scanning of the brain showed no relevant abnormalities. Genome wide SNP array analysis revealed a 1.2 Mb *de novo* interstitial microdeletion in 4q25 comprising 11 genes, that was considered to be causative for the developmental delay, perseverative cognitive phenotype and dysmorphisms.

To the authors knowledge, this is the first report of a *de novo* 4q25 microdeletion that presents with a specific behavioural phenotype.

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1. Methods of detection

1.1. Genome wide SNP array analysis

Array analysis with an average genome wide resolution of ~200 kb was performed using the Affymetrix 250 k Nsp1 SNP array platform, following the protocols provided by the manufactures (Affymetrix Inc., Santa Clara, CA, USA). Copy number estimates were determined and data were analysed using version 3.0 of the CNAG (Copy Number Analyzer for Affymetrix GeneChip mapping) software package [1,2].

1.2. Chromosomal anomaly

Conventional cytogenetic analyses at 500 band resolution level revealed a normal female karyotype. MLPA of the telomeres disclosed no abnormalities. Subsequent SNP array analysis demonstrated a 1.2 Mb microdeletion in chromosome 4q resulting in the karyotype: 46,XX.arr 4q25(110,320,625-111,557,313)x1 (GRCh36/hg18 assembly). This microdeletion encompasses 11 known protein coding genes (Fig. 1). At the proximal breakpoint the last non-deleted SNP probe is rs17040017; the first deleted probe is rs2526456. At the distal breakpoint, the last deleted probe is rs6533515 and the first non-deleted probe is rs1318244.

1.3. Causative of the phenotype

Carrier testing in the parents with 250k SNP array analysis resulted in normal outcomes and showed that the 4q25 microdeletion had occurred *de novo* in their child. No consent from the parents was obtained to perform additional FISH analysis of the

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http://dx.doi.org/10.1016/j.ejmg.2013.03.012

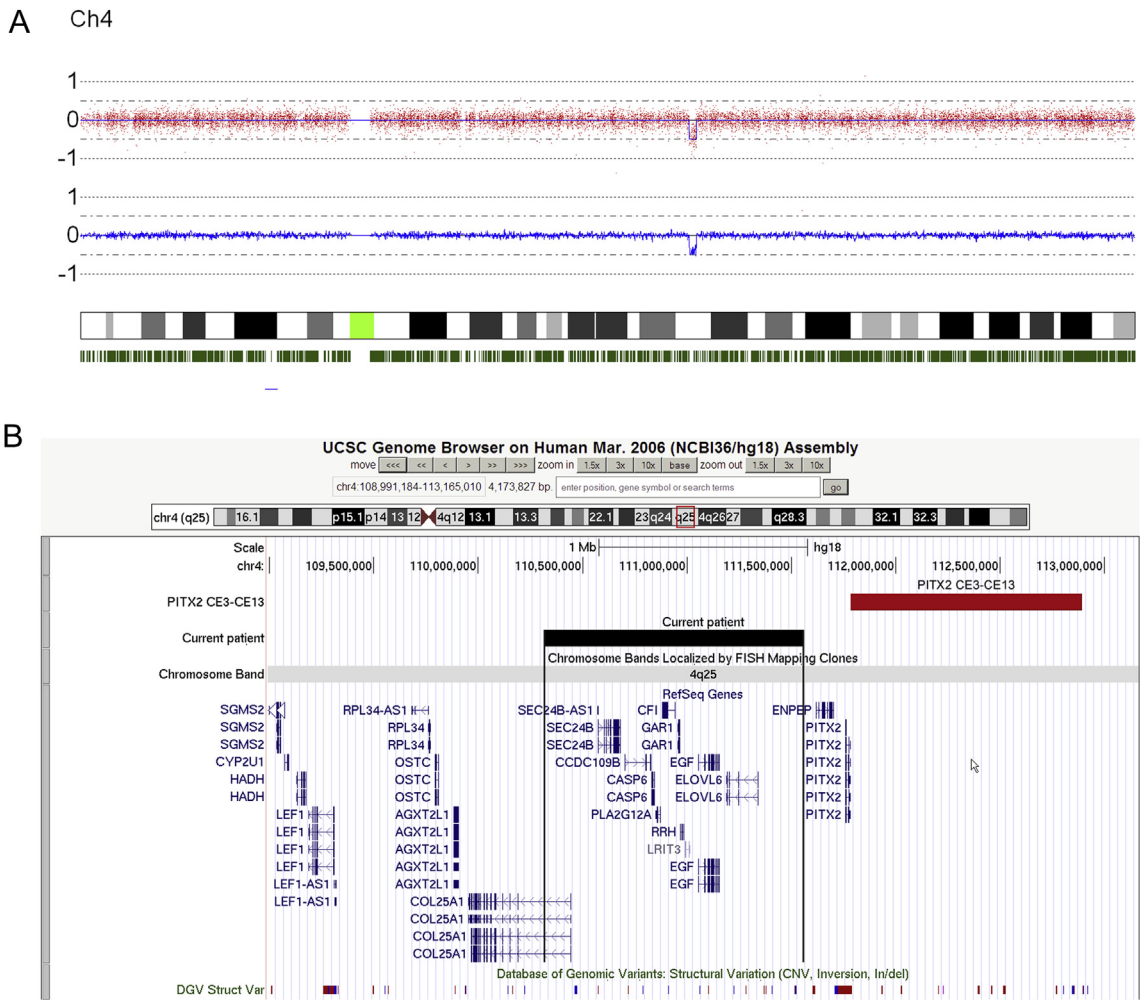

Fig. 1. (A) Log2 intensity ratio of the SNP probes on chromosome 4 obtained with 250K SNP array analysis, showing the 1.2 Mb interstitial microdeletion in 4q25 (46,XX.arr 4q25(110,320,625-111,557,313)x1 (GRCh36/hg18 assembly)) detected by significantly lowered values of 221 consecutive probes. (B) Screen shot of the UCSC genome Browser (http://genome.ucsc.edu/; Human Genome, GRCh36/hg18 assembly) showing the deleted region 4q25 in the patient (black horizontal bar) and the genes included in the deleted area (between the vertical lines). The red horizontal bar indicates the position of the *PITX2* regulatory region (*PITX* CE3-CE13) upstream of the *PITX2* open reading frame (transcribed in telomere-to-centromere direction). At the bottom the position of the common variants reported in the database of Genomic variants (http://projects.tcag.ca/variation/) is depicted. None of the common variants overlaps the entire deleted area.

4q25 locus. At this moment, no losses of similar size have been reported in healthy individuals (Database of Genomic Variants; http://projects.tcag.ca/variation).

2. Clinical description

The referred patient, a 20-year-old female, is the first child of non-consanguineous parents. She has one younger sister who underwent surgical extirpation of a nephroblastoma at the age of 12. Their younger brother is 14 years old and healthy. There is no family history of intellectual disability, congenital anomalies or neuropsychiatric disorders. Her mother as well as a cousin from mother had developed breast carcinoma at their mid forties.

The patient was born after an uncomplicated pregnancy and had normal (0 SD) birth weight and length (3750 g and 53 cm, respectively). No congenital anomalies were observed. During the first months, accelerated growth of the head was noticed that, however, turned out not to be caused by hydrocephalus. There were no feeding problems or sleep disturbances. From early infancy on, developmental and psychomotor delay became apparent, in that walking occurred at the age of two and there were learning problems whereas speech development was normal. She could follow normal pre-school and primary education albeit with intensive additional tutoring. Aged ten, she was referred to a neurologist because of increasing learning problems accompanied by obsessive ritualistic behaviours and social withdrawal. A probable diagnosis of tic disorder was made. Psychopharmacotherapy with several antipsychotics, however, did only induce motor and sedative side effects and was therefore discontinued. From the age of 13, the patient followed special education.

Four years later she was referred to a psychiatrist for evaluation of flattened affect and withdrawal behaviour. A provisional diagnosis of dysthymic disorder was made for which treatment with escitalopram was given that did not improve her apathetic presentation. Aged 18, child neurological examination, including CT-scanning of the brain and EEG-registration, disclosed no abnormalities. At that moment she was treated symptomatically with a low dose of risperidone, prescribed for her challenging behaviours. Because no explanation could be given for her developmental delay, she was subsequently referred to clinical geneticist for etiological diagnosis, especially since also an autistic-like disorder was suggested to be present.

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