European Journal of Medical Genetics 55 (2012) 641–645

Contents lists available at SciVerse ScienceDirect

European Journal of Medical Genetics

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

Short clinical report

A 725 kb deletion at 22q13.1 chromosomal region including *SOX10* gene in a boy with a neurologic variant of Waardenburg syndrome type 2

Elisavet Siomou [a,*], Emmanouil Manolakos [b], Michael Petersen [b], Loretta Thomaidis [c], Yolanda Gyftodimou [d], Sandro Orru [e], Ioannis Papoulidis [a]

[a] *Eurogenetica S.A., Adrianoupoleos 7, GR-55133 Thessaloniki, Greece*
[b] *Eurogenetica S.A., Alexandroupoleos 23, GR-11527 Athens, Greece*
[c] *Department of Pediatrics, University of Athens, Aglaia Kyriakou Children's Hospital, GR-11527 Athens, Greece*
[d] *Department of Genetics, Institute of Child Health, Athens, Greece*
[e] *University of Cagliari, Department of Medical Genetics, Binaghi Hospital, Cagliari, Italy*

ARTICLE INFO

Article history:
Received 24 November 2011
Accepted 5 July 2012
Available online 25 July 2012

Keywords:
SOX10
Waardenburg syndrome type 2
Array-comparative genomic hybridization

ABSTRACT

Waardenburg syndrome (WS) is a rare (1/40,000) autosomal dominant disorder resulting from melanocyte defects, with varying combinations of sensorineural hearing loss and abnormal pigmentation of the hair, skin, and inner ear. WS is classified into four clinical subtypes (WS1-S4). Six genes have been identified to be associated with the different subtypes of WS, among which SOX10, which is localized within the region 22q13.1. Lately it has been suggested that whole SOX10 gene deletions can be encountered when testing for WS. In this study we report a case of a 13-year-old boy with a unique de novo 725 kb deletion within the 22q13.1 chromosomal region, including the SOX10 gene and presenting clinical features of a neurologic variant of WS2.

1. Introduction

Waardenburg syndrome (WS) is a rare (1/40,000) autosomal dominant disorder, which belongs to a group of disorders called neurocristopathies and is characterized by pigmentation defects and sensorineural deafness [1]. This syndrome results from abnormal proliferation, survival, migration or differentiation of neural crest derived melanocytes [2,3]. Due to the variety of additional clinical symptoms and genetic heterogeneity, WS is classified into four clinical subtypes (WS1-4). Six genes have been identified to be associated with the different subtypes of WS. The majority of cases with type I WS (WS1) and type III WS (WS3) present with mutations of the *PAX3* gene (paired box 3 transcription factor) [4], while mutations of the *MITF* (microphthalmia-associated transcription factor) and *SNAI2* (snail homolog 2) genes have been documented in patients with type II WS (WS2) [5,6]. Type IV WS (WS4) is associated with mutations within the *EDN3* (endothelin 3) and *EDNRB* [7] (endothelin receptor type B) genes, whereas mutations or deletions of the *SOX10* (SRY bOX10 transcription factor) gene have been described in both WS2 and WS4 [8–10]. *SOX10* is a member of the *SOX* family transcription factors and is a key transcription factor of neural crest development, since it is involved in survival, pluripotency and differentiation of migrating neural crest progenitors [11]. Additionally, *SOX10* mutations have been described in patients with a syndrome called PCWH (peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, WS and long-segment Hirschsprung disease) or PCW (PCWH without Hirschsprung disease) and demonstrate typical WS clinical features along with a neurological phenotype. In most of these cases it has been proposed that nonsense mutations of *SOX10* lead to mutant mRNAs that escape the nonsense-mediated mRNA decay (NMD) pathway and therefore lead to a more severe clinical phenotype [12]. Whole gene *SOX10* deletions have been described by Bondurand et al., [2007] suggesting that haploinsuffiency due to *SOX10* gene deletions should be encountered when testing for WS [10]. In this study we report a case of a 13 year old boy with a unique de novo 725 kb deletion within the 22q13.1 chromosomal region, encompassing *SOX10* and another 13 OMIM listed genes and presenting clinical features of a neurologic variant of WS2.

2. Clinical report

The patient was a 13-year-old boy born to healthy, non-consanguineous parents and delivered at term after a normal uneventful pregnancy. His three older sisters were normal. His

* Corresponding author. Tel.: +30 2310 474414; fax: +30 2310 474415.
E-mail address: cytogenetics@eurogenetica.gr (E. Siomou).

1769-7212/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmg.2012.07.002

birth weight was 3800 g and the only abnormality identified at birth was hexadactyly. During neonatal period and infancy, generalized hypotonia, nystagmus, mild tremor, difficulty to ingest, sensorineural deafness (>90 dB bilateral), broad nasal root, sapphire blue eyes with iris heterochromia, and patchy depigmented areas at thighs and at the abdominal area were observed. Standard G banding chromosomal analyses showed a normal 46,XY karyotype. Additional tests for Prader–Willi, Pallister–Killian and Fragile-X syndromes were performed. All showed normal results. Evaluation at the age of 13 years, showed bilateral deafness, profound intellectual disability (DQ < 25), delayed psychomotor development, hypotonia, autistic-like behaviour, unilateral cryptorchidism, and patchy depigmented areas at thighs and in the abdomen. His weight was at the 70th centile, height at the 80th centile and head circumference at the 10th centile. Speech was severely impaired and limited only to a few single words. He showed difficulty in concentrating and demonstrated aggressive and hostile behaviour. Extensive laboratory investigation followed, including biochemical tests, blood and urine amino acids, organic acids, thyroid function, ACTH, FSH, LH, DHEA-S, prolactin, estradiol e2, progesterone, testosterone, 17a-OH progesterone, IGF-1, muscle biopsy, and kidney-liver-spleen ultrasound, all proved normal. MRI and CT scans performed at the ages of 3, 6 and 12 years did not show any kind of defects.

3. Methods – results

Array-CGH was performed by hybridizing the sample against a male human reference commercial DNA sample (Promega biotech) using an array-CGH platform that includes 60,000 oligonucleotides distributed across the entire genome (Agilent Technologies). The statistical test used as parameter to estimate the number of copies was ADAM-2 (provided by the DNA analytics software, Agilent Techn) with a window of 0.5 Mb, $A = 6$. Only those copy number changes that affected at least 5 consecutive probes with identically oriented change were considered as Copy Number Variations (CNVs). As a consequence, for the majority of the genome, the average genomic power of resolution of this analysis was 200 kilobases.

Array-CGH analyses detected a copy number deletion in band 22q13.1, genomic coordinates chr22:38,202,740-38,927,438(Genomic coordinates are listed according to genomic build NCBI37) (Fig. 1).

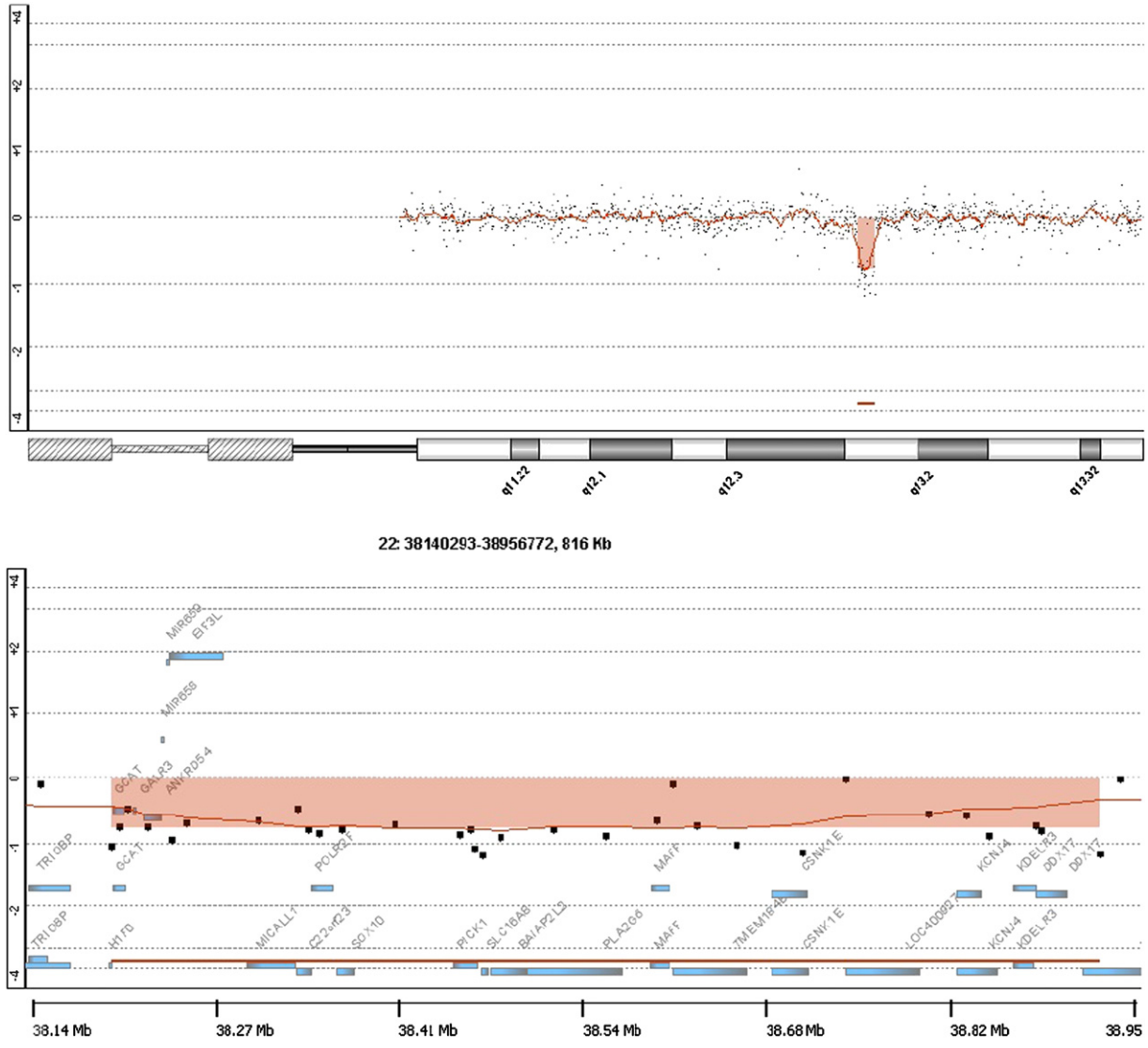

Fig. 1. Ideogram of the deletion at chromosomal band 22q13.1 as detected by array CGH.