

Mild Wolf–Hirschhorn Phenotype in a Girl With Unbalanced t(4p;12p) Translocation Without Seizures

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TO THE EDITOR:

Wolf–Hirschhorn syndrome (WHS, OMIM 194190), due to the deletion of critical region within 4p16.3, can be considered a contiguous gene syndrome whose core phenotype includes typical facial appearance, the so-called “Greek warrior helmet profile,” growth delay, mental retardation, seizures (or EEG anomalies), and hypotonia [Zollino et al., 2003].

The critical region for WHS (WHSCR2) falls within a 300–600 kb interval on 4p16.3, comprised between 1.9 Mb and 1.6–1.3 Mb from the telomere. Two genes involved in the WHS phenotype are located within WHSCR-2, *WHSC1* (OMIM 602952), that overlaps the proximal boundary of the region, being a candidate gene for facial characteristics and in part for growth delay, and *LETMI* (OMIM 605507), that lies entirely within WHSCR-2, being a major candidate gene for seizures [Maas et al., 2008; Zollino et al., 2008]. Here we report on a girl with a mild WHS phenotype, in which a derivative chromosome 4 resulting from a de novo unbalanced t(4;12)(p16.3;p13.33) translocation was detected by aCGH.

The girl was born to healthy, nonconsanguineous parents after an uncomplicated full-term pregnancy. Birth weight was of 2,200 g, length 46 cm (both <3rd centile), and head circumference 32.5 cm (5th centile). Apgar scores were 8 and 9 at 1 and 5 min, respectively. Physical examination revealed generalized hypotonia, and a left preauricular fistula. She walked without support at 24 months, and started talking with single words at 32 months. Because of early sexual development at age of 7¹⁰/₁₂ year, short stature, advanced bone age, adult height prevision lower than target height, and high levels of FSH and LH (although without inversion) the patient started treatment with triptorelin depot (3.75 mg i.m. every 28 days), and cyproterone acetate (25 mg once daily for 21 days every 4 weeks) for 3 years. After interrupting therapy the girl demonstrated spontaneous pubertal progression (11¹³/₁₂ years), and attained her menarche.

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The girl corresponds to Patient No. 151 reported by Zollino et al. [2008] and was referred to us at age 11⁵/₁₂ years, because of mental retardation (“Full IQ,” assessment by Leiter-R was 60), short stature (10th centile), and mild but full clinical phenotype compatible with WHS. She had high forehead, prominent glabella, sparse medial eyebrows, hypertelorism, exophthalmus, prominent nose, and micrognathia. Hyperconvex fingernails were also noted (parents did not give permission to publish a picture of their child). She was loquacious, able to write and read, and largely independent in her daily life, with a better level of adaptive behavior in comparison to people with the same degree of mental retardation. Neurological examination was normal except for hypotonia. She never presented epileptic seizures. An awake EEG showed slow background activity, with synchronous and asynchronous bursts of spikes and high-voltage slow waves located in posterior regions. Sporadic medium-voltage slow waves were recorded in frontocentral areas. Brain MRI was normal.

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Cytogenetic investigation was carried out by G banding at 500-band resolution on peripheral blood lymphocytes following standard procedures, resulting to a normal female karyotype.

Array-CGH analysis was performed at a resolution of 75 kb (kit 44k, Agilent Technologies, Inc., Santa Clara, CA) according to the manufacturer's instructions, and results were confirmed by FISH analyses with both 4p and 12p subtelomeric probes (Vysis, Abbott Laboratories, Abbott Park, IL) and with probes pC847.351, 190b4, 247f6, 21f12 mapping on 4p16.3.

A terminal 4p deletion of 3.5 Mb and a terminal 12p duplication of 380 kb were identified by aCGH (Fig. 1a and b, respectively),

caused by a de novo t(4;12)(p16.2;p13.3) translocation, as detected by FISH (Fig. 2). The patient's karyotype was: arrcgh (4p16.3pter)(A_14_P114202 → A_14P119653) × 1; arrcgh(12p13.3)(A_14_P114202 → A_14_P12886) × 3. Both parents had normal FISH results with both 4p and 12p subtelomeric probes.

According to the different size of 4p deletions, Zollino et al. [2008] proposed a new classification of WHS in three different phenotypes: a "mild" form, with mild degree of mental retardation and paucity of major malformations, associated with deletions not exceeding 3.5 Mb; a more common "classical" form, characterized by severe mental retardation and major malformations, due to

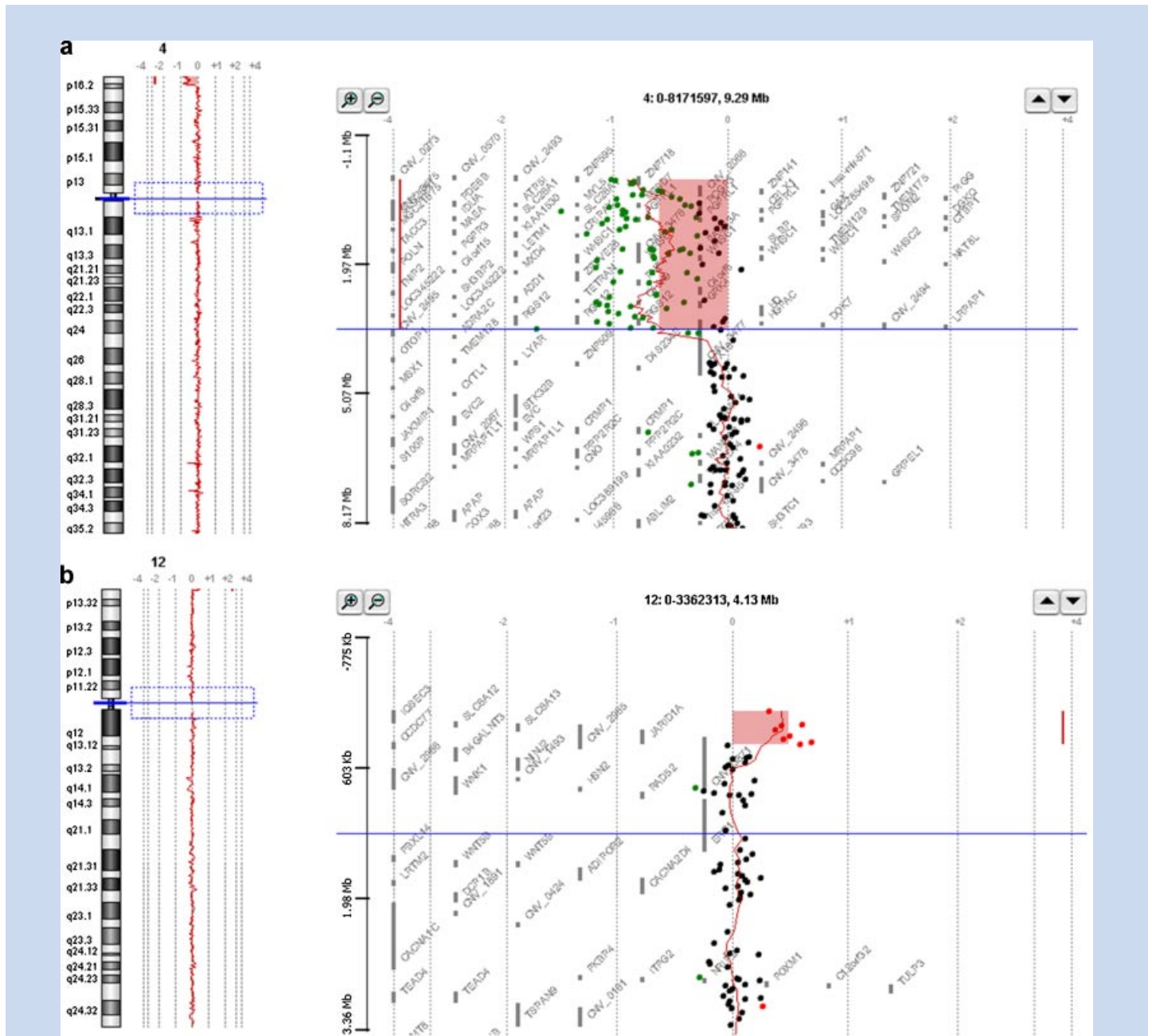


FIG. 1. Array-CGH results showing the 4p deletion (a) and the 12p duplication (b). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

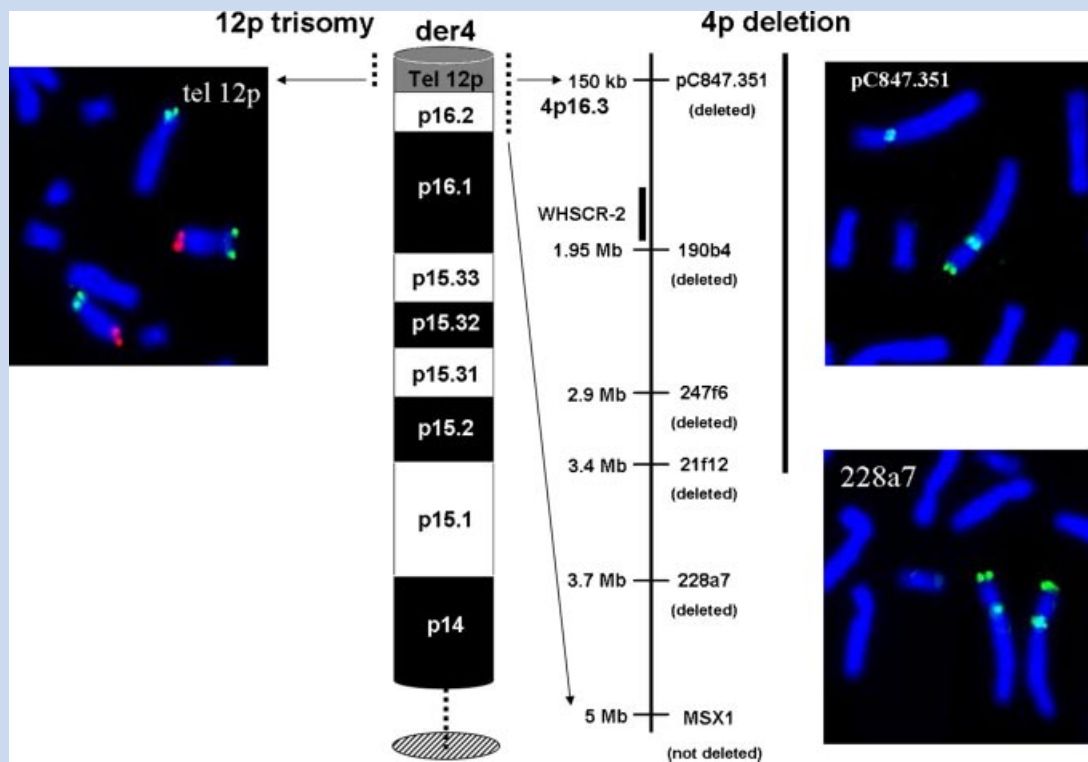


FIG. 2. Ideogram of the derivative chromosome 4 and FISH results on metaphase spreads. Left side: three signals are evident (green) with the 12p subtelomeric probe. Right side: the 4p subtelomeric probe [pC847.351] is deleted on one chromosome 4; probe 228a7, mapping at 3.7 Mb from the telomere, is preserved. Included in the 4p deletion interval is WHSCR-2. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

deletions of 5–18 Mb; a “severe” form caused by deletions of >22–25 Mb not resembling WHS phenotype, with severe mental retardation, seizures, prenatal growth delay, midline defects, hypotonia, and psychotic behavior in the half of cases.

In WHS early onset seizures occur in the majority of cases [Battaglia et al., 2003]. Two EEG patterns are usually observed, consisting of diffuse atypical bursts of spike–wave complexes activated by sleep, or fast spikes–polyspikes and wave complexes triggered by eye closure located in the posterior regions. Sleep organization is constantly absent or very poor. The first type is commonly associated with atypical absences, while the second is also present in WHS patients without seizures [Battaglia and Carey, 2005].

Our patient harbors a deletion of 3.5 Mb encompassing the WHS critical region (WHSCR-2). Consistent with this genetic defect, the girl here reported has a typical facial appearance, mild mental retardation, growth delay, congenital hypotonia, and EEG abnormalities, characterized by posterior spikes and slow waves. Interestingly, our patient did not experience epileptic seizures, even if her deletion encompasses the *LETM1* gene (OMIM 604407), a major candidate gene for the seizure disorder, suggesting that other genes can regulate its biological properties [Dimmer et al., 2008]. Clinical heterogeneity of WHS could be also explained by high frequency of double cryptic chromosome imbalances [South et al., 2008]. In our patient, the aCGH analysis detected successfully the 3.5 Mb deletion of 4p16.3 and the 380 kb duplica-

tion of 12p. The small size of 12p duplication is unlikely to affect the phenotype, that in our case resemble typical WHS features.

To the best of our knowledge, this is the first case of a “mild” complete WHS phenotype caused by a de novo translocation (4p;12p) detected by aCGH, with a 4p deletion size of 3.5 Mb. Some WHS patients with very small 4p deletions, predictive of a mild phenotype, had severe mental retardation associated with early onset seizures [Battaglia et al., 1999; Zollino et al., 2008]. Our patient suggests that early onset seizures independently may impact long-term cognitive outcome in infants with WHS.

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