American Journal of Medical Genetics Part A 146A:2417–2420 (2008)

Clinical Report

A 10.7 Mb Interstitial Deletion of 13q21 Without Phenotypic Effect Defines a Further Non-Pathogenic Euchromatic Variant

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Received 16 April 2008; Accepted 29 May 2008

Chromosome 13 deletions are associated with widely varying phenotypes but the clinical picture nearly almost includes mental and growth retardation, craniofacial dysmorphisms, and/or malformations. Several attempts have been made to link monosomy 13q intervals with specific clinical features, but a genotype–phenotype correlation could not be delineated. We report on a woman with a normal phenotype and intelligence referred for chromosomal analysis because of recurrent abortions followed by reproductive loss. Conventional karyotyping revealed an interstitial deletion of chromosome 13q21. By SNP array analysis and FISH the deletion was shown to comprise nearly 10.7 Mb of euchromatic material. This region harbors several genes but an association with recurrent miscarriages has not yet been reported. This is the second report of a 13q21 deletion without psychomotoric retardation, dysmorphisms and malformations. Both cases indicate that this 13q21 deletion can be added to the growing list of euchromatic imbalances without obvious phenotypic abnormalities.

Key words: chromosome 13q deletions; non-pathogenic euchromatic material; SNP array

How to cite this article: Roos A, Elbracht M, Baudis M, Senderek J, Schönherr N, Eggermann T, Schüler HM. 2008. A 10.7 Mb interstitial deletion of 13q21 without phenotypic effect defines a further non-pathogenic euchromatic variant. Am J Med Genet Part A 146A:2417–2420.

INTRODUCTION

Segmental aneuploidy is often associated with clinical consequences but an increasing number of non-pathogenic copy number variations (CNVs) have been published [Barber, 2005]. However, only a small number of these "harmless" CNVs have been exactly characterized by molecular means [Daniel et al., 2007]. In case of chromosome 13q, deletions are accompanied by widely varying phenotypes, but the clinical picture nearly almost includes mental and growth retardation, craniofacial dysmorphisms, and/or malformations [for review: Schinzel, 2001]. Several attempts have been made to link monosomy of distinct 13q intervals with specific clinical features but an unambiguous genotype–phenotype correlation can currently not be drawn. With the exception of retinoblastoma, proximal deletions of 13q seem to be associated with less striking phenotypes. However, the complete lack of clinical signs associated with a visible euchromatic deletion of 13q is extremely rare. Here we report on a phenotypically normal woman carrying a 10.7 Mb deletion in 13q21; to the best of our knowledge this is the second case of a non-pathogenic euchromatic variant in this band [Couturier et al., 1985].

CLINICAL REPORT

A 32-year-old non-dysmorphic woman of Nigerian origin was referred for genetic counseling and chromosome analysis due to recurrent abortions (n = 5; one in 21st and one in 25th week of gestation due to amniotic infection syndrome and three before the 12th week of gestation) followed by infertility, persisting for 2 years prior to presentation. Multiple

Grant sponsor: Novonordisk Pharma GmbH.
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DOI 10.1002/ajmg.a.32465

factors associated with recurrent abortions, including lupus anticoagulant, thrombophilia (including factor V Leiden) or thyroid disorders, were tested and showed normal biochemical parameters. Her physical appearance was normal (size = 175 cm, weight = 85 kg, circumference = 59 cm, BMI = 27.76 kg/m^2). She has successfully completed school, is self-employed, speaks two languages and is currently adding German as a third one. Unfortunately, parental blood samples and samples of the abortions were not available. There was no family history of abortions or malformed newborns.

CYTOGENETIC AND MOLECULAR INVESTIGATIONS

Conventional chromosome analyses was performed with a resolution of 550 bands (GTG-banding; Shaffer and Tommerup, 2005) and revealed an interstitial deletion of the long arm of chromosome 13 in each of the 50 cells analyzed (Fig. 1): 46,XX,del(13)(q21.1q21.31). The chromosomes of her husband were normal.

To confirm the unbalanced status and to estimate the extent of the imbalance and the exact localization of the breakpoints, further characterization was carried out by DNA array analysis and FISH.

The used 500 K array (Affymetrix, High Wycombe, UK) consists of two arrays, the *Nsp*I kit and the *Sty*I kit which together include >500,000 SNPs. DNA was processed according to the manufacturers instructions. Hybridization and washing was preformed according to the manufacturer's instructions. Arrays were recorded using an Affymetrix Genosensor 4000 scanner. Data processing including quality assessment was performed using the "R" statistical framework (http://www.r-project.org) with dedicated extensions from the "aroma.affymetrix" project [Bengtsson et al., 2008]. For final copy number profile generation, the data from the *Nsp*I array was omitted due to prominent probe level noise.

Fluorescence in-situ hybridization (FISH) was performed using clones localized within the deleted region (RP11-81D19, RP11-218B22 and RP11-37I8; BACPAC Resource Centre, Oakland, CA). BAC-DNA was labeled by nick translation and FISH was carried out according to standard procedures. Slides were counterstained with DAPI (Vector Laboratories, Orton Southgate, UK) and metaphase images were captured and processed with Isis FISH imaging system (Metasytems, Altlußheim/D, Germany).

Both molecular-cytogenetic approaches confirmed the deletion ranging from band 13q21.1 to 13q21.32 (Fig. 2). In the SNP array analysis, the deletion covered 566 SNPs with a total extension of approximately 10.7Mb (chr13:53513760-64180663). As expected, FISH results corroborated the cytogenetic findings as well as the DNA array testing results (Fig. 3).

DISCUSSION

We report on a phenotypically normal woman carrying an interstitial deletion of 10.7 Mb which affects the euchromatic band 13q21. According to the UCSC human genome database and the Human Transcriptome Map [May, 2008] the deleted area encompasses approximately 15 genes/transcripts among them procadherin genes (*PCDH17*, *PCH68*, *PCDH20*), all these genes show a (very) low transcription (http://bioinfo.amc.uva.nl/htm/). This indicates a low gene density (1.4 genes/Mb vs. mean 2.5 genes/Mb). Furthermore, a relatively high ratio of

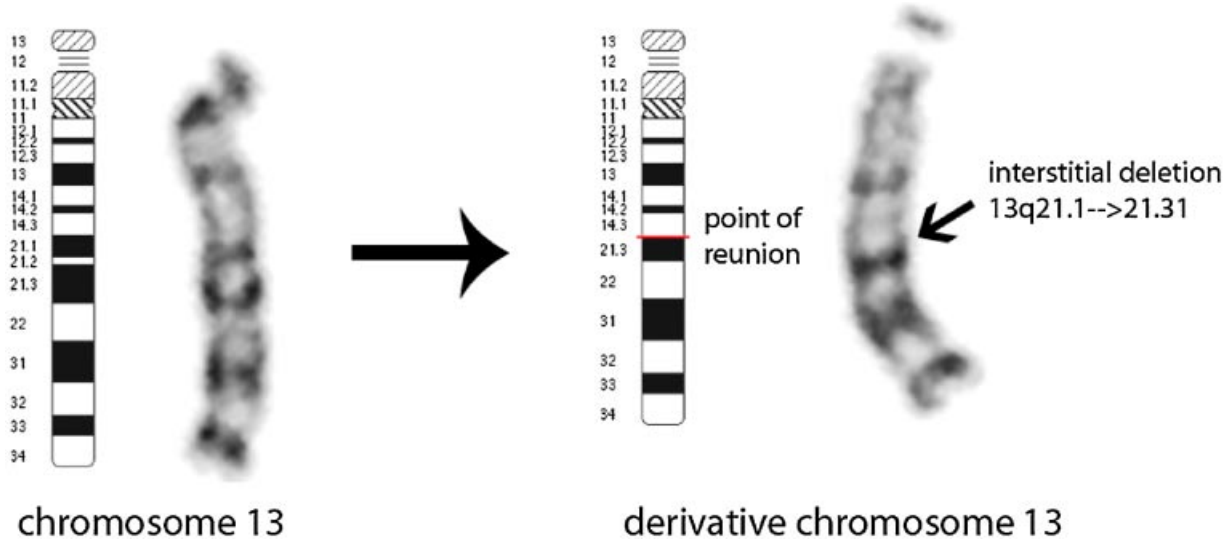

FIG. 1. Ideogram and partial karyotype of the interstitial deletion in 13q21 in our patient.

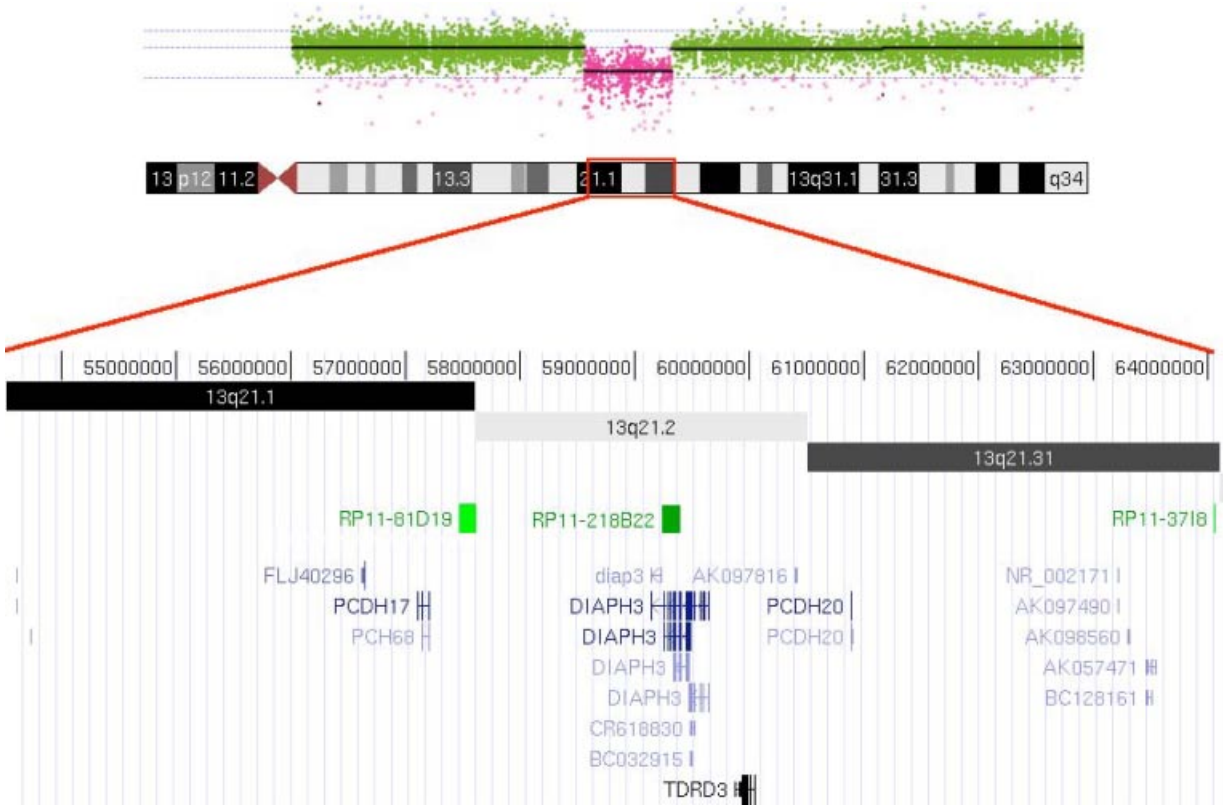

FIG. 2. 500 K array profile of the deletion in 13q21 in our patient and overview of the genes affected by the imbalance. Furthermore, the FISH-probes used for confirmation are listed. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

CNVs (28.1% vs. mean 12%) has been detected in this genomic segment [Daniel et al., 2007].

With an improved resolution of diagnostic methods in (molecular) cytogenetics an increasing number of non-pathogenic euchromatic anomalies becomes apparent. To the best of our knowledge this is the second report of a deletion of band 13q21 compatible with a normal phenotype [Couturier et al., 1985] and the first with breakpoint determination using a high-resolution genomic array technique. Both cases indicate that imbalances in 13q21 belong to the growing list of euchromatic polymorphisms, e.g., euchromatic variants that have no phenotypic effect. The only clinical observation in our patient is the history of recurrent abortions/infertility thus our case does not support the theory of Kogan et al. [2008] who hypothesized that haploinsufficiency of procadherin genes in 13q21 is associated with polymicrogyria and other malformations. However, with limited knowledge about the functional haploinsufficiency of the genes affected in our case, an association between the deletion and reproductive impairment cannot be excluded.

Recently, Ballarati et al. [2007] reported on a detailed karyotype–phenotype analyses of 14 13q deletion carriers. Among them, at least 4 patients

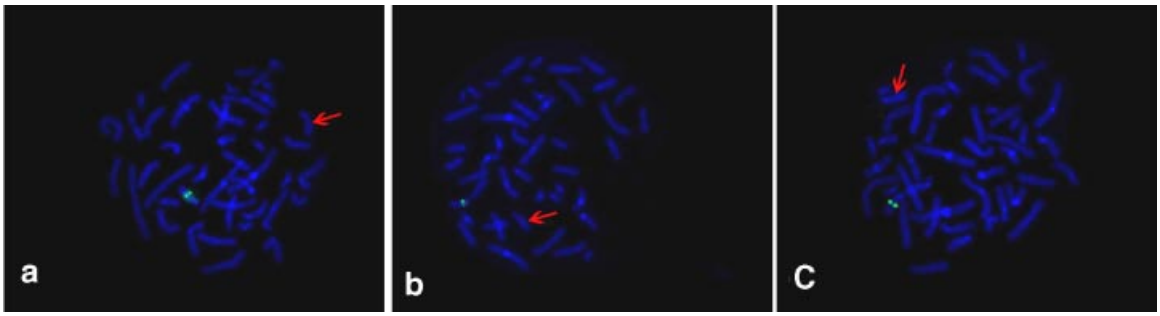

FIG. 3. The FISH analysis indicated the rearranged chromosome to be deleted for: **a**: 13q21.1 (RP11-81D19; deleted chromosome marked by an arrow). **b**: 13q21.2 (RP11-218B22; deleted chromosome marked by an arrow). **c**: 13q21.31 (RP11-3718; deleted chromosome marked by an arrow). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

showed imbalances affecting 13q21. The identification of a 10.7 Mb deletion in 13q21 as a non-pathogenic variant in our patient now allows to further narrow down genomic regions critical for the abnormal phenotypes in the patients reported by Ballarati et al. [2007] and Kogan et al. [2008].

In conclusion, our case impressively illustrates that phenotypically irrelevant genomic imbalances may not only consist of small "gaps" but also of large "holes" and that asymptomatic large scale CNVs may be underestimated.

ACKNOWLEDGMENTS

We thank the family for nice cooperation and Mr. Dirk Kamitz for kindly arranging the figures. This study was supported by Novonordisk Pharma GmbH.

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