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Research Letter

Prenatal diagnosis of directly transmitted benign 4q12-q13.1 quadruplication associated with tandem segmental amplifications of the *LPHN3* gene

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A 38-year-old primigravid woman underwent amniocentesis at 20 weeks of gestation because of advanced maternal age. Her husband was 35 years old and healthy. There was no family history of attention deficit hyperactivity disorder (ADHD). Amniocentesis revealed cytogenetically detectable multiple extra bands between the regions of 4q12 and 4q21.1 in one aberrant chromosome 4. Level II ultrasound findings of the male fetus were unremarkable. Parental cytogenetic analysis revealed that the father had the same chromosome aberration, which was directly transmitted to the fetus (Fig. 1). Oligonucleotide-based array comparative genomic hybridization (aCGH) analysis using CytoChip Oligo Array (BlueGnome, Cambridge, UK) was applied in the paternal blood. The result of aCGH revealed five copies of the 4.41-Mb euchromatic region of 4q12-q13.1 or arr cgh 4q12q13.1 (57,966,988–62,377,421)×5 according to NCBI Build 36, March 2006, UCSC hg18 (Fig. 2). The 4.41-Mb segment containing the *LPHN3* gene had been quadruplicated in the aberrant chromosome 4. For fluorescence *in situ* hybridization (FISH) determination of the quadruplication, the bacterial artificial chromosome clone probes mapping the genomic region of 4q13.1 and a control probe mapping 4p16.3 were used. The bacterial artificial chromosome clone probes RP11-74H5 (red signal, 61,998,695–62,149,756 at 4q13.1) and RP11-69L7 (green signal, internal control, 752,790–906,783 at 4p16.3) were used to determine the quadruplication. Interphase FISH (Fig. 3) showed five red signals and two green signals with four signals closing together. The result was consistent with the aCGH result and indicated quadruplication of 4q13.1 in the aberrant chromosome. Metaphase FISH (Fig. 4) showed multiple amplifications of the red signals in the aberrant chromosome. The parents decided to continue the pregnancy after genetic counseling. At 38 weeks of gestation,

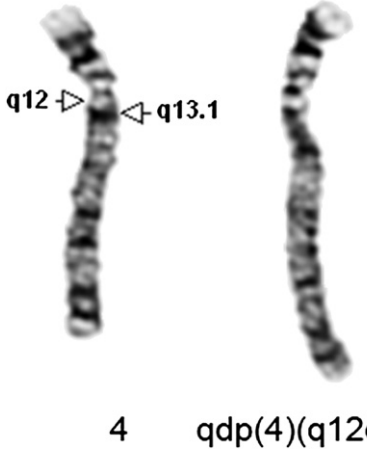

Fig. 1. Partial karyotype shows a normal chromosome 4 and an aberrant chromosome 4 with qdp(4)(q12-q13.1). qdp = quadruplication.

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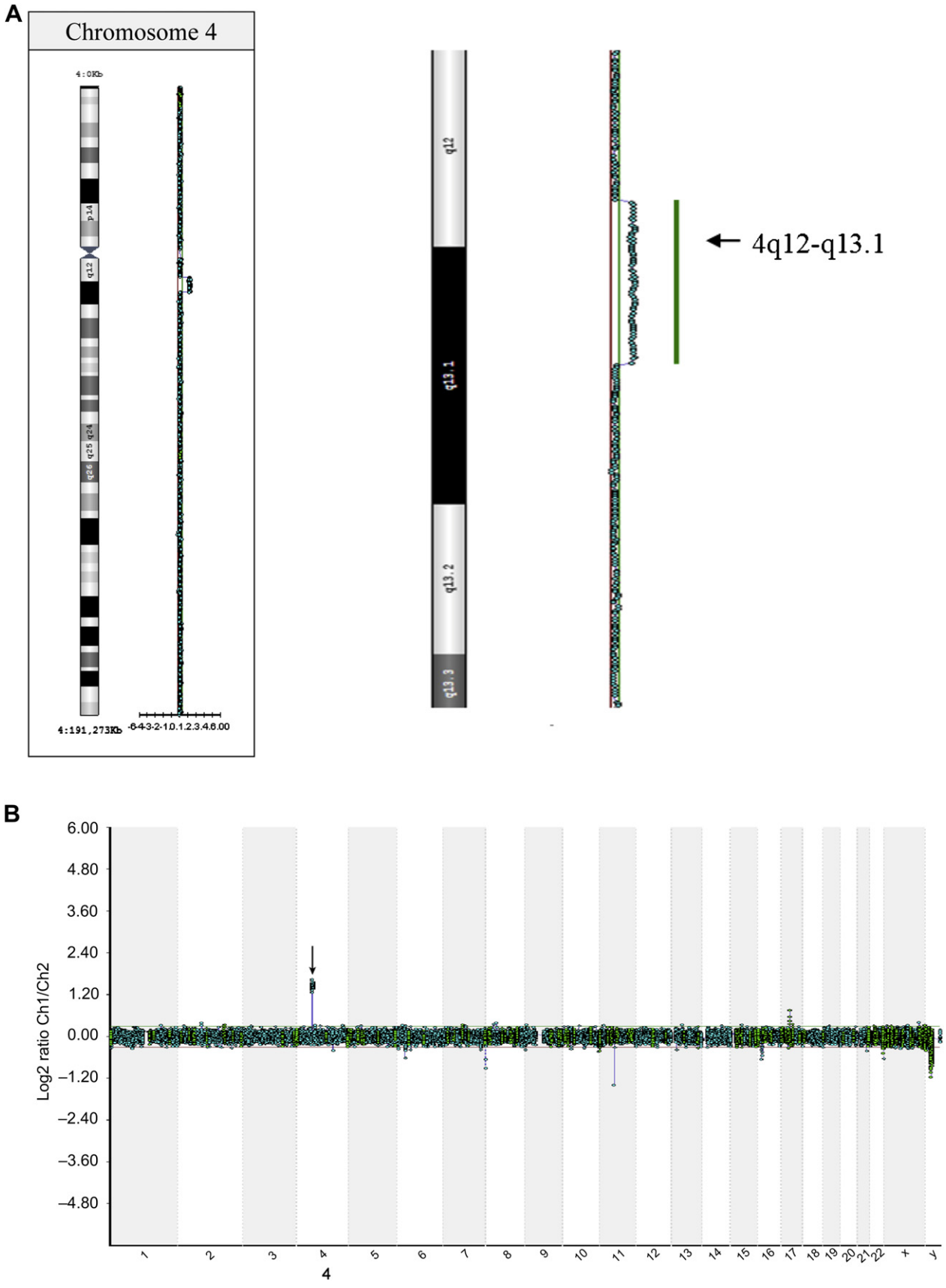

Fig. 2. (A) Array comparative genomic hybridization (aCGH) using CytoChip Oligo array (BlueGnome, Cambridge, UK) shows gene dosage increase in the 4.41-Mb region of 4q12-q13.1. (B) aCGH shows a log2 ratio of 1.47 consistent with five copies of the gene dosage in the region of 4q12-q13.1.

a healthy 3045-g male baby was delivered uneventfully. Pediatric follow-ups at 1 month of age showed normal development and no phenotypic abnormalities in the baby. The karyotype of the father and the son was 46,XY,qdp(4)(q12q13.1).

Directly transmitted unbalanced chromosome abnormalities (UBCAs) and euchromatic variants (EVs) may be detected at prenatal diagnosis [1,2]. In instance of UBCAs, copy number of one or more genes is either reduced or increased, whereas in instance of EVs, copy number variation of segment contains paralogous genes and pseudogenes and is polymorphic in the normal population and cytogenetically detectable [1]. The reported EVs include 8p23.1, 9p12, 9q12, 15q11.2, and 16p11.2. In 70 families with directly transmitted EVs, Barber [1] found that 54% (38/70) had no phenotypic effect, 43% (30/70) had affected probands and phenotypically normal family members, and 3% (2/70) had consistent mild phenotypic anomalies. In contrast, in 130 families with directly transmitted UBCAs, Barber [1] found that 18% (23/130) had no phenotypic effect, 23% (30/130) had affected probands and phenotypically normal family members, and 59% (77/130) had consistent mild phenotypic anomalies. In a review of chromosome 4, Barber [1] found dup(4)(q31.3-q33) in the category of Group 2 in which the phenotypically unaffected parents had the same UBCA as their affected children, and del(4)(p15.2-p16.1), del(4)(q33-qter), del(4)(q33-q35.1), del(4)(q33-q33), del(4)(q32-q33), dup(4)(q31.22-q33), and dup(4)(q31.3-q32.3) in the category of Group 3 in which the phenotypically affected parents had the same UBCA as their affected children. Rodríguez et al [10] additionally reported a 3.3-Mb interstitial duplication of 4p16.1 in a phenotypically normal father and a healthy 5-year-old daughter.

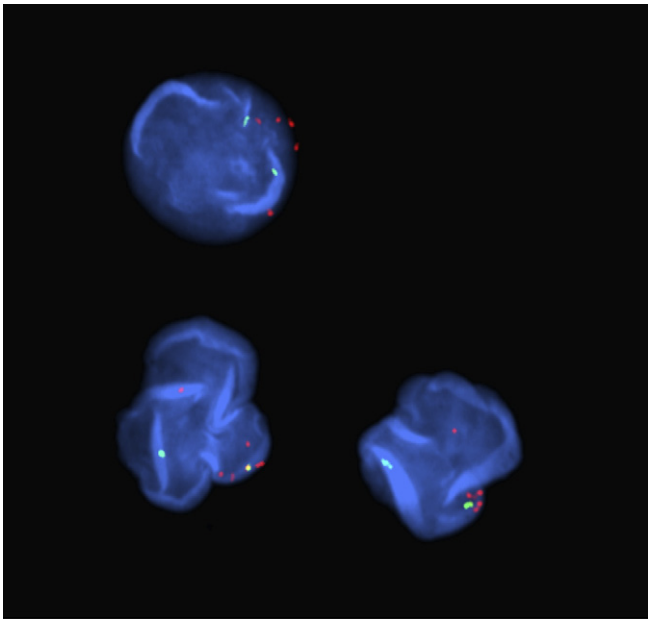

Fig. 3. Interphase fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-74H5 (61,998,69–62,149,756) (spectrum red) at 4q13.1 and RP11-69L7 (752,790–906,783) (spectrum green) at 4p16.3 as internal control shows the presence of five red signals with four signals closing together on one side of the cell.

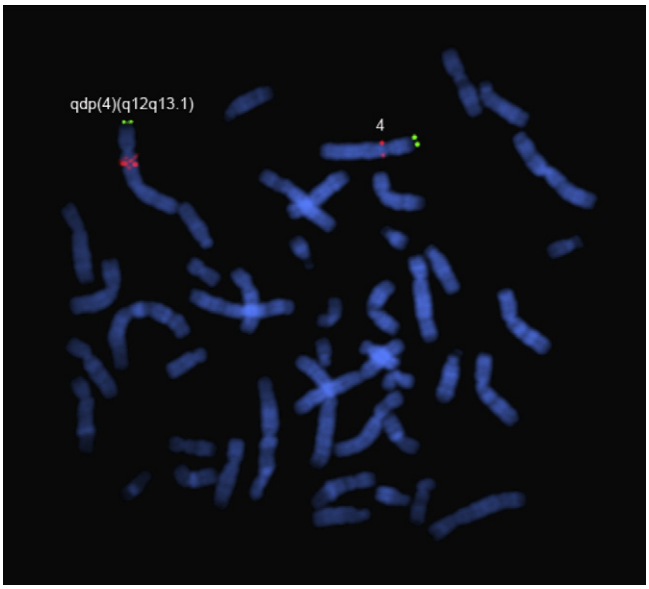

Fig. 4. Metaphase fluorescence *in situ* hybridization using bacterial artificial chromosome clone probes RP11-74H5 and RP11-69L7 shows multiple amplifications of the red signals in the aberrant chromosome. qdp = quadruplication.

Our case is the first report of directly transmitted UBCA involving tandem segmental amplifications of the 4q12-q13.1 segment and the *LPHN3* gene. Clinical information regarding duplication involving the proximal region of 4q is very little. Mattei et al [3] first reported a 6-year-old girl with dup(4)(q12→q13) resulting from an insertion of 4q12-q13 into a chromosome 18 because of a maternal complex chromosome rearrangement with translocation between chromosomes 2 and 4 in addition to an insertion of 4q12-q13 into the long arm of chromosome 18. The girl manifested short stature, psychomotor retardation, microcephaly, expicanthic folds, a broad nose, a large mouth, a left preauricular fistula, and clinodactyly. Shashi et al [4] reported a 2-year-8-month-old boy with a dup(4)(q12q13), microcephaly, mental retardation, and minor facial anomalies. However, the present case did not have phenotypic abnormalities, indicating a benign nature of gene dosage increase of the *LPHN3*. *LPHN3* or latrophilin 3 gene encodes a member of the latrophilin subfamily of G-protein coupled receptors responsible for mediating extracellular to intracellular signaling. Recent studies have suggested *LPHN3* is a candidate gene for ADHD [5–8], and *LPHN3* common variants of *LPHN3* confer susceptibility to ADHD [5,8,9]. The present case had gene dosage increase of the *LPHN3* gene but manifested no phenotype of ADHD. The aCGH study to define the exact nature of gene dosage increase of the *LPHN3* gene in our UBCA carrier will provide us relevant information for genetic counseling concerning tandem segmental amplifications of 4q12-q13.1.

Acknowledgments

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References

[1] Barber JCK. Directly transmitted unbalanced chromosome abnormalities and euchromatic variants. J Med Genet 2005;42:609−29.

[2] Chen C-P, Lee C-C, Town D-D, Chen W-L, Chen L-F, Lee M-S, et al. Detection of euchromatic variants and unusual C-band heterochromatin variants at genetic amniocentesis. Genet Couns 2006;17:91−5.

[3] Mattei MG, Mattei JF, Bernard R, Giraud F. Partial trisomy 4 resulting from a complex maternal rearrangement of chromosomes 2, 4, and 18 with interstitial translocation. Hum Genet 1979;51:55−61.

[4] Shashi V, Berry MN, Santos C, Pettenati MJ. Partial duplication of 4q12q13 leads to a mild phenotype. Am J Med Genet 1999;86:51−3.

[5] Arcos-Burgos M, Jain M, Acosta MT, Shively S, Stanescu H, Wallis D, et al. A common variant of the latrophilin 3 gene, *LPHN3*, confers susceptibility to ADHD and predicts effectiveness of stimulant medication. Mol Psychiatry 2010;15:1053−66.

[6] Domené S, Stanescu H, Wallis D, Tinloy B, Pineda DE, Kleta R, et al. Screening of human *LPHN3* for variants with a potential impact on ADHD susceptibility. Am J Med Genet B Neuropsychiatr Genet 2011;156B:11−8.

[7] Jain M, Vélez JI, Acosta MT, Palacio LG, Balog J, Roessler E, et al. A cooperative interaction between *LPHN3* and 11q doubles the risk for ADHD. Mol Psychiatry; 2011. doi:10.1038/mp.2011.59.

[8] Ribasés M, Ramos-Quiroga JA, Sánchez-Mora C, Bosch R, Richarte V, Palomar G, et al. Contribution of *LPHN3* to the genetic susceptibility to ADHD in adulthood: a replication study. Genes Brain Behav 2011;10:149−57.

[9] Arcos-Burgos M, Muenke M. Toward a better understanding of ADHD: *LPHN3* gene variants and the susceptibility to develop ADHD. Atten Defic Hyperact Disord 2010;2:139−47.

[10] Rodríguez L, Zollino M, Mansilla E, Martínez-Fernández ML, Pérez P, Murdolo M, et al. The first 4p euchromatic variant in a healthy carrier having an unusual reproductive history. Am J Med Genet 2007;143A:995−8.