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LETTERS

Questionable pathogenicity of *FOXG1* duplication

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Chromosome microarray analysis has revolutionised the diagnosis of patients with neurocognitive impairment and has resulted in the association of many phenotypes with copy number changes in particular genes.

Recently in this journal, Brunetti-Pierri *et al.*[1] published a report of seven patients with duplications at 14q12 that included the *FOXG1* (MIM 164874). These patients presented with relatively severe neurodevelopmental phenotypes comprising intellectual disability, epilepsy and severe speech delay. Previously, we had reported a similarly affected patient with a deletion that also included *FOXG1*,[2] and more recently three patients with West syndrome were reported to have duplications that included *FOXG1*.[3,4] *FOXG1* encodes a brain-specific transcriptional repressor,[5] and deletions and point mutations in *FOXG1* are known to cause the congenital variant of Rett syndrome,[6] making duplication of *FOXG1* a strong candidate for the neurocognitive impairment in patient with 14q12 duplications.

In the course of a research project to identify genetic causes of hemifacial microsomia (MIM 164210), we identified a father–son pair who both have an interstitial duplication of ~88 kb at 14q12 (chr14:28,236,716-28,325,210; UCSC genome browser, NCBI Build 36/hg18) (Figure 1). The duplication was identified using an Illumina CytoSNP-12 microarray (Illumina Inc., San Diego, CA, USA) and

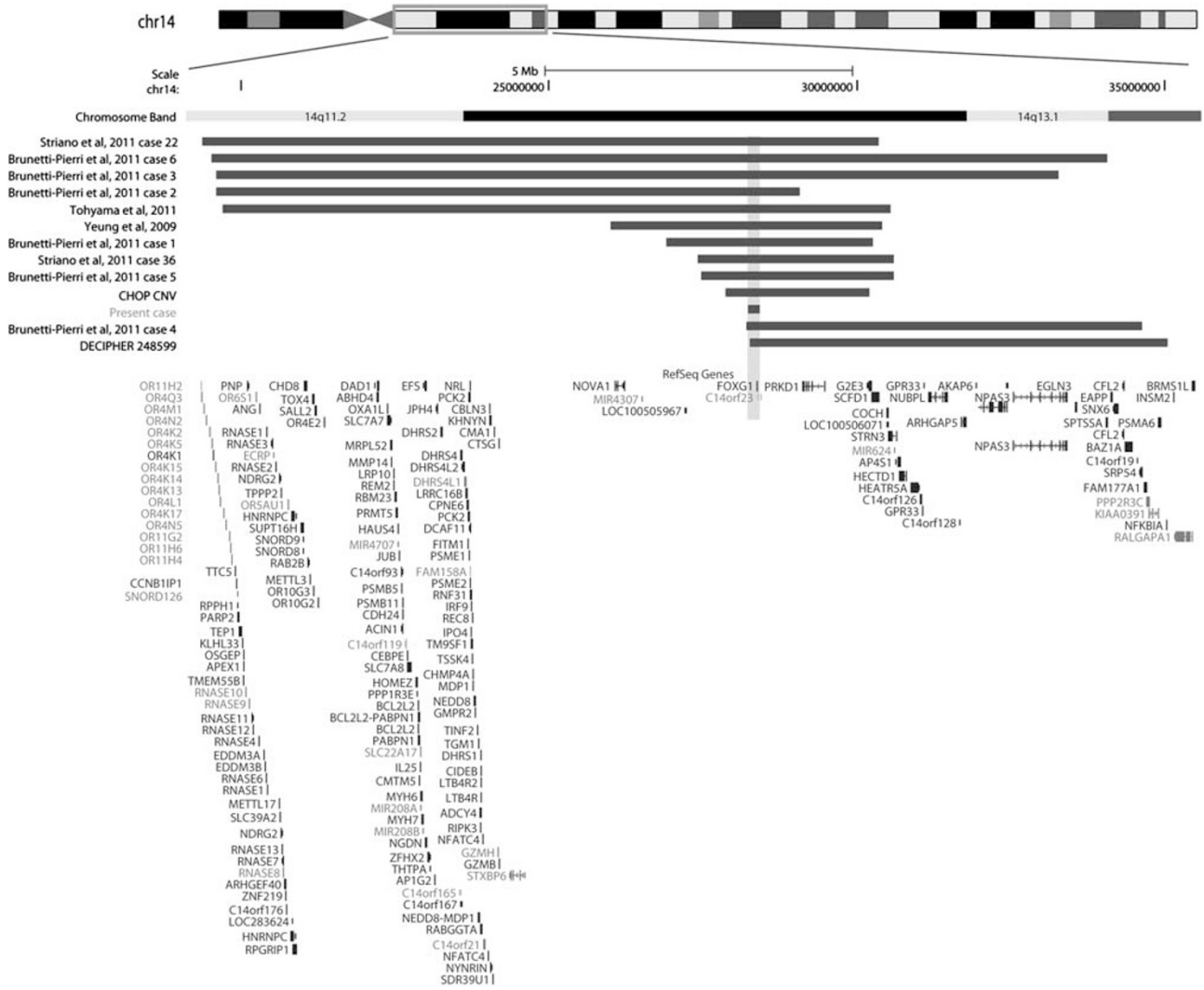

Figure 1 UCSC genome browser (NCBI36/hg18) view of reported proximal 14q duplications (blue bars) encompassing *FOXG1* and neighbouring genes. Grey shadow highlights the duplicated region reported here. The colour reproduction of this figure is available at the *European Journal of Human Genetics* online.

independently confirmed using a synthetic multiplex ligation-dependent probe amplification assay[7] and/or Affymetrix 2.7M microarray (Affymetrix Inc., Santa Clara, CA, USA). The duplication contains only two genes, *FOXG1* and *C14orf23*. Importantly, apart from hemifacial microsomia, the father and son are phenotypically normal, have normal intellect, do not have epilepsy, and have no family history of epilepsy or cognitive impairment.

It is difficult to reconcile the normal neurocognitive phenotype in this father and son pair with the relatively severe impairment reported in other patients with duplications that include *FOXG1*; however, several possible explanations must be considered. First, it remains possible that *FOXG1* duplication is benign, and that the neurocognitive impairment reported in patients with 14q12 duplication is the result of duplication of other genes in the vicinity. Second, *FOXG1* duplication may be incompletely penetrant, manifesting clinical abnormality only in the presence of other genetic or environmental factors. Third, in our father–son pair it is possible that of the three detected copies of *FOXG1*, only two are functional. Finally, *FOXG1* may be subject to long-range regulatory elements, with gene transcription being differentially affected according to the location of the duplication breakpoints.

A duplication at 14q12 that encompasses *FOXG1*is also recorded in the Children's Hospital of Philadelphia CNV database, which comprises CNV data from 2026 healthy children aged 0–18.[8] This duplication is similar in size to the ~3 Mb minimal duplicated region that includes *FOXG1*, *c14orf32* and *PRKD1* described in affected patients reported by Brunetti-Pierri *et al*.[1] Patients carrying these small-sized duplications (cases 1 and 5 in Figure 1) were assessed as non-dysmorphic, so it is possible the healthy CHOP patient is yet to present with developmental problems, infantile spasms or other seizures. Alternatively, this case provides further evidence that *FOXG1* duplication may be benign or incompletely penetrant.

On the basis of these data, the role of duplication of FOXG1 in the pathogenesis of cognitive impairment and epilepsy remains uncertain. This case is a salient reminder that our understanding of the relationships between CNVs and phenotype is far from complete, and of the importance of reporting CNVs that are found in the presence of normal phenotypes. This is particularly important in the context of the increasing use of molecular karyotyping for prenatal diagnosis, where decision-making may be based on evidence of questionable validity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Brunetti-Pierri N, Paciorkowski AR, Ciccone R *et al*: Duplications of FOXG1 in 14q12 are associated with developmental epilepsy, mental retardation, and severe speech impairment. *Eur J Hum Genet* 2011; **19**: 102–107.
2 Yeung A, Bruno D, Scheffer IE *et al*: 4.45 Mb microduplication in chromosome band 14q12 including FOXG1 in a girl with refractory epilepsy and intellectual impairment. *Eur J Med Genet* 2009; **52**: 440–442.
3 Striano P, Paravidino R, Sicca F *et al*: West syndrome associated with 14q12 duplications harboring FOXG1. *Neurology* 2011; **76**: 1600–1602.
4 Tohyama J, Yamamoto T, Hosoki K *et al*: West syndrome associated with mosaic duplication of FOXG1 in a patient with maternal uniparental disomy of chromosome 14. *Am J Med Genet* 2011; **155**: 2584–2588.
5 Hanashima C, Li SC, Shen L, Lai E, Fishell G: Foxg1 suppresses early cortical cell fate. *Science (New York, NY)* 2004; **303**: 56–59.
6 Ariani F, Hayek G, Rondinella D *et al*: FOXG1 is responsible for the congenital variant of Rett syndrome. *Am J Hum Genet* 2008; **83**: 89–93.
7 Stern RF, Roberts RG, Mann K, Yau SC, Berg J, Ogilvie CM: Multiplex ligation-dependent probe amplification using a completely synthetic probe set. *Biotechniques* 2004; **37**: 399–405.
8 Shaikh TH, Gai X, Perin JC *et al*: High-resolution mapping and analysis of copy number variations in the human genome: a data resource for clinical and research applications. *Genome Res* 2009; **19**: 1682–1690.

Reply to Amor *et al*

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Microduplications on chromosome 14q11.2 including the *FOXG1* gene have been reported in patients with developmental delay, cognitive impairment with speech delay, and epilepsy.[1–2] Such association has been confirmed subsequently in other patients.[3–4] However, Amor *et al*[5] have found an ~88 kb duplication at 14q12, encompassing the *FOXG1* and *C14orf23* genes in a father-son pair with isolated hemifacial microsomia. Neither the son nor the father exhibited mental retardation or epilepsy. They also identified an ~3 Mb duplication of the 14q12 region, including *FOXG1*, in a child enrolled as a control subject in the CHOP CNV database[6] and questioned the pathogenicity of *FOXG1* duplication.

We believe it is important to highlight that the clinical phenotypes observed in the seven patients in the original description of the syndrome include a relatively wide spectrum of neurodevelopmental abnormalities, ranging from mild to severe intellectual disability and variable presence of epilepsy (in four out of the seven patients).[1] Thus, it is not surprising that subjects at the mildest end of the spectrum may present with few or no clinically evident manifestations of the disease.

Moreover, the duplicated copy of *FOXG1* reported by Amor *et al*[5] is small and may be devoid of its distant regulatory elements, which may explain the lack of neurocognitive phenotype. In support of this notion, two other *FOX* genes, *FOXF1* and *FOXL2*, encoding for the evolutionarily conserved family of transcription factors with a central role in development have been shown recently to be upregulated by non-coding copy-number variants mapping over 250 kb 5′ from these genes.[7–8] Of note, FOXG1 expression is restricted to the brain, and thus more likely to be finely regulated by such distant enhancer(s) in a tissue-specific manner.

With regard to the individual in the CHOP CNV database with a *FOXG1* duplication, we agree with the authors' suggestion that the CHOP subject with the duplication of *FOXG1* may have not manifested yet the neurodevelopmental abnormalities.

On the basis of the well-established causative role of genomic deletions and point mutations of *FOXG1* in determining a Rett-like phenotype[9–10] and the studies generated in animal models,[11] the evidence of *FOXG1* as a dosage sensitive gene is compelling. Thus, we believe microduplications involving *FOXG1* should not be considered of questionable pathogenicity but rather highly likely to be pathogenic, albeit associated with a wide spectrum of abnormal-