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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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-

ities, which is commonly observed with other microduplication syndromes.[12]

CONFLICT OF INTEREST

Drs Cheung and Stankiewicz are based in the Department of Molecular and Human Genetics at Baylor College of Medicine (BCM), which offers genetic laboratory testing, including use of arrays for genomic copy number analysis, and derives revenue from this activity.

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