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LETTER TO THE EDITOR

Wilms tumour occurring in a patient with osteopathia striata with cranial sclerosis: A still unsolved biological question

To the Editor:

Osteopathia striata with cranial sclerosis (OSCS, MIM#300373) is a rare X-linked dominant skeletal dysplasia characterised by linear striations in the metaphyseal region of the long bones and pelvis in combination with cranial sclerosis owing to increased osteoblast activity.[1,2]

The rarity and heterogeneity of its phenotype makes a diagnosis of OSCS challenging, leading to the risk that it can actually be missed for many years. Jenkins et al. found that OSCS is caused by germline deletions/mutations of the *AMER1* gene (MIM#300647, NM_152424.4) located on Xq11.2.[3] Somatic mutations in *AMER1* are found in 7–29% of Wilms tumours (WT).[4–7]

To date, and to the best of our knowledge, just five cases of paediatric tumours, four WT and one hepatoblastoma, have been reported in patients with OSCS[8–10] despite two large studies investigating cohorts of patients (including adults) with OSCS did not find an increased risk of cancer.[3,11]

Herein, we report a clinical and molecular description of an additional girl affected by OSCS who developed a WT.

The girl was born at 35 weeks of gestation to healthy nonconsanguineous parents. At her birth, macrocephaly, a prominent forehead, retrognathia, anteverted nares, hypertelorism and pectus excavatum were all observed. The neonatal audiometry was normal. The brain magnetic resonance imaging was unremarkable except for the evidence of macrocephaly. During follow-up, a mild intellectual disability (ID) became evident in the girl, particularly in speech ability. Later, at the age of 4, the patient began to experience a painless rapid increase in abdominal volume. A computed tomography (CT) scan showed a capsulated polycyclic hypo-vascularised retroperitoneal mass with necrotic areas, compatible with a renal tumour. A chest CT was also performed and resulted negative for metastases, but intriguingly, the chest X-ray inadvertently revealed longitudinal sclerotic striations in the humeral metaphysis (Figure 1). Similarly, the radiographs of her long bones demonstrated prominent linear sclerotic striations in the metaphyses and epiphyses and fan-like striations of the iliac crest (Figure 1).

The girl underwent a core needle biopsy of the lesion, which confirmed our suspicion of WT. After this diagnosis, the girl started neoadjuvant chemotherapy according to the contemporary national protocol. At nephrectomy, pathology inspection revealed a mixed epithelial and blastemal WT, with no associated nephrogenic rests, stage III. Treatment was then completed with adjuvant chemotherapy and abdominal radiotherapy.

At the same time, our geneticists raised the suspicion of OSCS based on the facial dysmorphisms, macrocephaly, ID, and the typical metaphyseal striations of her long bones. We performed a clinical exome sequencing (SOPHiA GENETICS) on the patient's DNA extracted from her peripheral blood, which revealed a heterozygous nonsense mutation c.1072C>Tp. (Arg358Ter) in the *AMER1* gene. The mutation was confirmed by Sanger sequencing and was compatible with diagnosis of OSCS, and was demonstrated to be de novo studying parents' peripheral blood DNA.

This mutation has been previously reported in other cases with OSCS.[3,11] Sanger sequencing performed on tumour DNA obtained from a single formalin-fixed paraffin embedded sample disclosed that the *AMER1* wild-type allele was lost in the tumour; analysis of the tumour cDNA from the same block showed that the mutant allele was expressed (Figure S1). No further genetic tests on the girl's tumour DNA have been performed. Our patient is currently 7 years old and in complete remission, 2 years after the end of treatment.

To the best of our knowledge, among previously reported OSCS patients who developed a childhood cancer, a genetic investigation of *AMER1* in the tumour was performed only in two of those cases, one WT and one hepatoblastoma. In both cases, the authors reported retention of heterozygosity for the germline *AMER1* mutation.[9,10] In our patient, we demonstrated that the *AMER1* wild-type allele was lost in the tumour, which expressed the mutant allele. Ours is the only patient with OSCS where tumour cDNA was investigated, whereas the determination of the presence of the *WTX* mutated/deleted allele on the active or inactive X chromosome (Xa and Xi, respectively) in tumours from female patients with OSCS would be important. Bach et al. proposed a likely association between OSCS and WT.[8]

The prevalence of OSCS is estimated in less than one per million with fewer than 100 cases reported in the literature worldwide. However, these data are probably underestimated, because we should also take into consideration the likelihood of undiagnosed or misdiagnosed cases due to the heterogeneity of OSCS phenotypes. Noteworthy, also our patient was diagnosed with OSCS only after performing chest X-ray for WT. Consequently, calculation of the probability to present both phenotypes (OSCS and WT) based on their related reported prevalence could not precisely estimate the probability of the co-occurrence.

Moreover, literature data demonstrated that in female patients with WT, *AMER1* deletions/mutations can occur on both the Xa and Xi[4,7]; suggesting that *AMER1* alteration is not an essential and early

[Corrections added on 12 June, 2021 after first online publication: The author forenames and surnames names have been adjusted and now appear in the proper order]

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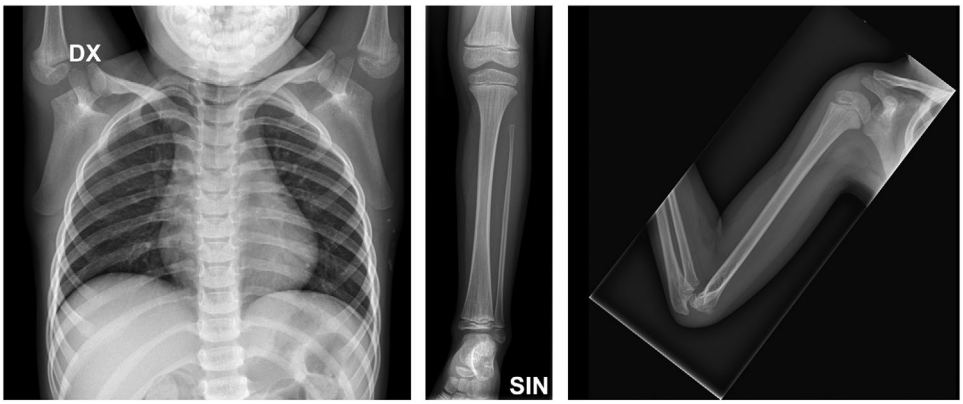

FIGURE 1 Identification of metaphyseal striations. Metaphyseal striations observed in the long bones of upper and lower limbs on X-ray

mutation needed to drive WT tumourigenesis, but rather a later event with unclear clinical relevance[12]; and showed that *Wtx* deletion in mice causes neonatal lethality, somatic overgrowth, and malformations of multiple mesenchyme-derived tissues, but not WT.[13]

All these considerations suggest caution in drawing any conclusion about a possible association between OSCS and WT and underline the need to deeply investigate molecular anomalies that occur in the tumours of OSCS patients to disclose the underlying mechanisms and the role of their germline mutation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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