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CORRESPONDENCE

# Osteopathia striata with cranial sclerosis: a new case supporting the link with bilateral Wilms tumor





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## TO THE EDITOR:

We read with interest the article published by Bach et al. [1], presenting four patients with osteopathia striata with cranial sclerosis (OSCS) and Wilms tumor, one of whom was the first case of bilateral presentation in this syndrome. Here we report on an additional patient with bilateral early onset Wilms tumor and OSCS due to a de novo previously undescribed pathogenic variant in *AMER1* gene.

## CASE REPORT

The proband, a female, was born at term by a spontaneous pregnancy with a regular course. Ultrasound examinations during gestation suspected left cerebral ventriculomegaly, unconfirmed at postnatal targeted controls. She was born by caesarean section. Birth weight was 3450 g and length 49 cm. Head circumference was reported to be high in the percentiles ranks and was monitored by brain ultrasound scans for the first 6–8 months of life. The presence of unspecified heart murmur was reported. She showed delayed developmental milestones; she walked alone at 18 months. Her first words were pronounced at 12 months, but fluent language occurred around 4 years of age. Sphincter control was reached at 3 years.

The only concern noted by her family and family doctor during infancy was macrocephaly. At the age of 4 years she was hospitalized for recurrent abdominal pain. At clinical evaluation, a mass in the inner region of the left part of the gut was detected and a computerized tomography (CT) scan was then planned. The CT scan confirmed two bilateral well-defined renal masses, the bigger one occupying the inferior half of the left kidney. The right lesion was 2 cm for 2 cm superficial and occupied the antero-lateral surface of the kidney. The patient underwent chemotherapy before surgical removal of both tumors. She underwent left heminephrectomy and right renal tumorectomy.

The macroscopic examination of the left $9 \times 7 \times 5$ cm partial nephrectomy showed an oval formation of $8 \times 6$ cm, with defined contours, the appearance was not homogeneous and gross necrosis was present in about 50–60%. At histological examination, mixed nephroblastoma with diffuse anaplasia was observed. Microscopic necrosis accounted for about 60% of the tumor. The growth edges were expansive causing the formation of a fibrous pseudocapsule and hypotrophy of the surrounding renal parenchyma. The macroscopic examination of the right $3 \times 2.5 \times 1$ cm tumorectomy sample included a neoformation, with well-defined contours, surrounded by a thick pseudocapsule, and with a not homogeneous appearance on the cut surface. Histologically it was classified as a mixed nephroblastoma without anaplasia. Microscopic necrosis represented <5% of the tumor. The growth edges were expansive causing the formation of a thick fibrous pseudocapsule.

At the last evaluation the girl was 11 years old. At physical examination, she looked attentive and responsive. She appeared in good general condition, serene, smiling and cooperating during the visit. She had a nasal voice, tended to keep her mouth open and showed hypotonia of the buccal district. She presented inner chantal dystopia, hypertelorism, epicanthus and wide, saddle nose bridge, small, low-set ears with overfolded helices could be noticed and full lips (Fig. 1). Her teeth were crowded with persistence of some deciduous teeth. She showed high-arched palate, short frenulum and slight retrognathia (Fig. 1). Her fingers appeared long. She showed mild clinodactyly of the fourth and fifth finger, bilateral single palmar crease, most noticeable on the left palm. Chest was carinatum.

Skeletal X-ray examination revealed epimetaphyseal striations of the long bones of the upper and lower limbs (Fig. 2) and cranial sclerosis (Fig. 1). Head circumference was 58.5 cm (>>97th centile).

Trio-based clinical-exome sequencing allowed to identify the heterozygous de novo frameshift variant c.1298_1320insACCACGGCTACATGCTCCTTGA resulting in a premature stop codon [p.Pro441ThrfsTer16] in the *AMER1* gene (NM_152424). The variant was neither known in the scientific literature and nor present in the reference population database [dbSNP, Exome Aggregation Consortium and Genome Aggregation Database]. The variant was evaluated by VarSome [2] and categorized in accordance with the American College of Medical Genetics and Genomics recommendations [3] and visualized by the Integrative Genome Viewer.

The present report further supports the predisposition to Wilms tumor in patients with OSCS. Noteworthy, to date in two patients nephroblastoma developed bilaterally, that is in the present case and in the one by Bach et al. [1]. Previously, only somatic variants in *AMER1* were reported in neoplastic tissue of patients with isolated Wilms tumor [4].

Additional syndromes with bilateral Wilms tumor predisposition include malformative diseases as WAGR (Wilms, Aniridia, Genito-urinary anomalies, mental Retardation) and Denys–Drash syndromes, and several overgrowth syndromes as Beckwith–Wiedemann and Perlman Syndromes [5]. OSCS is clinically different from other syndromes with bilateral Wilms tumor, manifesting OSCS as specific skeletal anomaly. Nevertheless, OSCS shares several characteristics with malformative syndromes (i.e., cleft palate, cardiac anomalies) so as with overgrowth syndromes (i.e., macrocephaly) (see Table 1).

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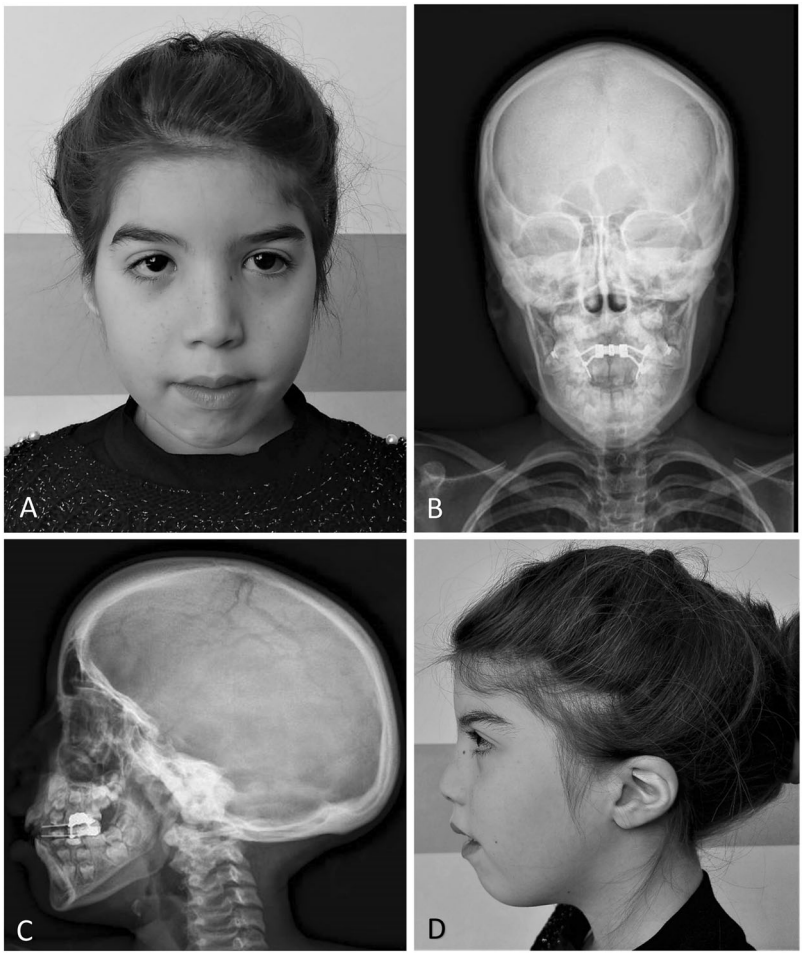


**Fig. 1 Facial characteristics and skull X-rays of the here reported eleven years old girl.** Eleven years old girl affected by OSCS presenting with mouth open with full lips (**A**, **D**), inner chantal dystopia (**A**), hypertelorism, epicanthus, wide, saddle nose bridge (**A**), small, low-set ears with overfolded helices (**D**), overcrowded teeth (**B**, **C**) and retrognathia (**D**). Skull X-ray showed cranial sclerosis (**B**, **C**).

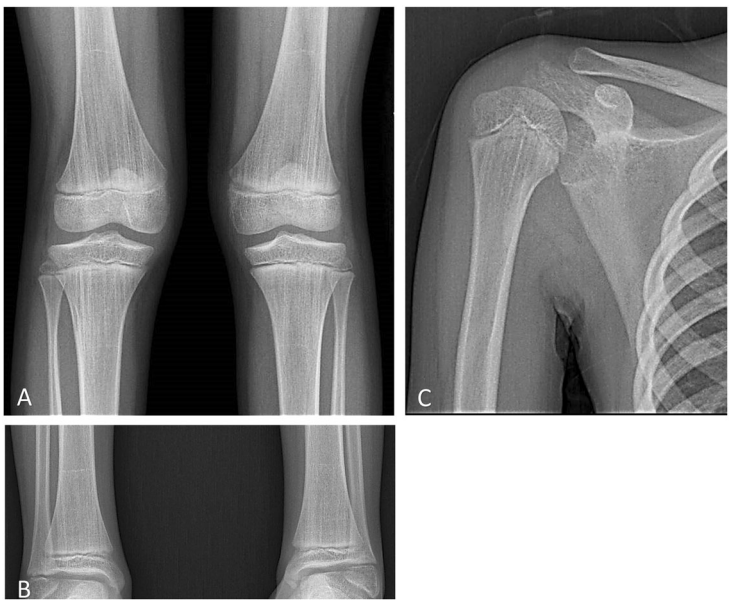


**Fig. 2 Epimetaphyseal striations of the long bones—details. A** Distal femur; proximal tibia and fibula. **B** Distal tibia and fibula. **C** Right proximal humerus.

**Table 1.** Brief summary of the clinical characteristics of tumor predisposition syndromes with bilateral Wilms tumor.

| Clinical features | WAGR association | Denys–Drash syndrome | OSCS syndrome | Beckwith–Wiedemann syndrome | Perlman syndrome |
|---|---|---|---|---|---|
| Wilms tumor | + | + | + | + | + |
| Genital anomalies | + | + | – | + | + |
| Ocular anomalies | + | – | – | – | – |
| Macrocephaly | – | – | + | + | + |
| Overgrowth | – | – | – | + | + |
| Developmental delay | + | – | + (males) | – | + |
| Facial anomalies | – | – | + | + | + |
| Cardiac defect | – | – | + | + | + |
| Hypoglycemia | – | – | – | + | + |
| Omphalocele | – | – | – | + | – |
| Macroglossia | – | – | – | + | – |
| Hearing loss | – | – | + | – | – |
| Cleft palate | – | – | + | – | – |
| Skeletal anomalies | – | – | + | – | – |

*WAGR* Wilms, aniridia, genito-urinary malformations, mental retardation, *OSCS* osteopathia striata with cranial sclerosis.

Therefore, we agree with Bach et al. [1] that OSCS should be included to genetic syndromes with tumor predisposition so that tumor surveillance would be recommended in affected patients from the first years of age.

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## DATA AVAILABILITY

The datasets generated and analyzed during the current study which are not shown in the paper are available from the corresponding author on reasonable request.

## REFERENCES

1. Bach A, Mi J, Hunter M, Halliday BJ, García-Miñaúr S, Sperotto F, et al. Wilms tumor in patients with osteopathia striata with cranial sclerosis. Eur J Hum Genet. 2021;29:396–401.
2. Kopanos C, Tsiolkas V, Kouris A, Chapple CE, Albarca Aguilera M, Meyer R, et al. VarSome: the human genomic variant search engine. Bioinformatics. 2019;35:1978–80.
3. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, ACMG Laboratory Quality Assurance Committee, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.
4. Ruteshouser EC, Robinson SM, Huff V. Wilms tumor genetics: mutations in WT1, WTX, and CTNNB1 account for only about one-third of tumors. Genes Chromosomes Cancer. 2008;47:461–70.
5. Dome JS, Huff V. Wilms tumor predisposition. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. Genereviews. Seattle, WA, University of Washington, Seattle; 1993–2021

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## AUTHOR CONTRIBUTIONS

LS: Clinical diagnosis, writing and elaboration of the text; AM: molecular diagnosis and elaboration of the text; AS: oncological treatment and collection of the oncological treatment data; AC: surgical treatment and collection of the surgical treatment data; FDC: pathological studies; DB: X-ray imaging studies; MLD: elaboration of the text; AT, MM, and AN: molecular diagnosis; and MCD: clinical overview and elaboration of the text.

## COMPETING INTERESTS

The authors declare no competing interests.

## ETHICS APPROVAL

The present study was reviewed and approved by the Institutional Review Board of Bambino Gesù Children's Hospital (RRC-2021-2874811). The study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent from the girl's parents for blood sampling for genetic testing was obtained as part of the diagnostic protocol. Written informed consent for scientific publication of the girl's pictures was also obtained.

## ADDITIONAL INFORMATION

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