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LETTER TO THE EDITOR

Expanding the phenotype of *SETD5*-related disorder and presenting a novel association with bone fragility

Patients with *SETD5*-related disorder have variable features of intellectual disability (ID), facial dysmorphism, cardiac and skeletal abnormalities, behavioural problems, and short stature.¹ We present two patients with pathogenic *SETD5* variants and bone fragility, a new associated phenotype. Both patients were recruited via the deciphering developmental disorders (DDD) study (<https://www.deciphergenomics.org/>) and informed consent for publication was obtained.

Patient 1: 14-year-old male (see Figure 1) with a pathogenic heterozygous c.1381_1388del, (p.Asn461fs) variant in exon 12 of *SETD5*.² At 13 years of age, he was found to have multiple thoracic vertebral crush fractures following a minor fall from a swing at a low height onto his buttocks with resulting back pain which was investigated 10 days later. Radiographs showed multiple wedging of his thoracic spine both new and old which was confirmed on MRI-spine imaging. A transiliac bone biopsy showed mild osteopenia with increased cortical resorption and formation. Treatment with zoledronic acid (dose escalation over 9 months up to 0.05 mg/kg 6 monthly) resulted in improvement in DXA-measured bone parameters after 10 months: L2-4 and total body less head (TBLH) BMD increased by 13% and 7%, respectively; corresponding Z-scores increased from -2.8 to -2.7 and from -1.7 to -1.5 , respectively.

Patient 2: 10-year-old female (see Figure 1) in whom there were concerns with feeding difficulties, global developmental delay and poor weight gain in the first year of life. Her mother has mild-moderate ID with no bone fragility. She was found to carry a maternally inherited pathogenic nonsense variant in *SETD5* c.3214C > T (p.Arg1072*).

At 8 years of age, the patient developed acute lower back pain following a forward fall onto laminate kitchen flooring. Spinal radiographs identified wedging of T11 and L1 (10%–24%) and mild wedging of multiple other thoracic vertebrae (<10% anterior height loss). Treatment with zoledronic acid (dose escalation over 10 months up to 0.05 mg/kg 6 monthly) resulted in improvements in vertebral shapes, and in DXA-measured bone parameters after 20 months: L2-4 and TBLH MD increased by 14% and 11%, respectively; although

corresponding Z-scores changed a little, from -1.4 to -1.5 and from -2.1 to -2.0 , respectively.

Bone-related biochemistry in both patients was normal (serum calcium, phosphate, alkaline phosphatase and 25-hydroxyvitamin D concentrations). There was no significant history of medication use impacting bone health or evidence of a connective tissue disorder in either patient.

Patients reported here have features in keeping with a *SETD5*-related disorder. The key feature that has not previously been highlighted is bone fragility in the absence of a relevant family history of fractures. This suggests previously unrecognised, phenotypic association with *SETD5*-related disorder especially in the context of trio exome sequencing which has not identified any other cause for bone fragility.

SETD5 is a ubiquitously expressed, highly conserved histone methyltransferase.³ There is evidence highlighting the important role of histone methyltransferase activity in osteogenic differentiation of mesenchymal stem cells (MSC).⁴ SET-domain containing histone lysine methyltransferases have been shown to contribute to the balance between osteogenesis and adipogenesis in MSCs and mice with loss of *Setd2* causes a propensity for adipogenesis and loss of osteoblasts, thus raising the possibility of other SET-domain containing histone methyltransferases also having an impact on bone density.⁵

Compression fractures of spine can occur as a result of trauma, osteoporosis and heritable bone fragility conditions such as Osteogenesis Imperfecta (OI). Back pain and kyphosis can be initial presenting features although it may remain a late diagnosis. *SETD5*-related disorder remains a rare genetic condition; future systematic clinical and radiological phenotyping of these patients will be required to confirm this association. This paper highlights a need for a low threshold for bone health assessment in *SETD5*. Clinical screening and judicious use of imaging (e.g., lateral spine imaging with DXA) may enable early identification of bone fragility and ensure timely initiation of bone-targeted medication.

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FIGURE 1 Photographs of Patients 1 and 2. Patient 1 at the age of 3 years (A, B), 6 years (C), 9 years (D, E), 13 years (F). Patient 2 aged 10 photographed with her mother (G) demonstrating common facial dysmorphism including prominent forehead, upslanting palpebral fissures and smooth philtrum [Colour figure can be viewed at wileyonlinelibrary.com]

CONFLICT OF INTEREST



The authors declare no potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/cge.14014>.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analysed during the current study

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