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**RESEARCH LETTER**
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# Elastin turnover in Williams–Beuren and 7q11.23 microduplication syndromes

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Abnormal elastin metabolism is a pathological hallmark of a group of syndromic vasculopathies due to molecular defects in genes coding for major structural components of the extracellular matrix (ECM).[1] Elastin is particularly present in tissues requiring resilience to deformation such as blood vessels, including the aorta.[1–3] Elastin biosynthesis begins in late embryonic development and is active until adolescence.[3] The *ELN* gene, located on 7q11.23, encodes a precursor protein, tropoelastin, which undergoes posttranslational modifications by lysyl oxidase of specific lysine residues, to form desmosines (DES, including desmosine and its isomer isodesmosine).[2,3] Desmosines are considered to be specific biomarkers of mature elastin breakdown.

Marfan syndrome (MFS), caused by pathogenic variants in the fibrillin 1 (*FBN1*) gene, is characterized by fragmentation and loss of elastic fibres in the aortic tunica media, aortic root dilatation, and significant risk of aortic dissection.[1,4] Iskandar *et al.*[1] have recently investigated DES plasma (pDES) levels in MFS individuals aged between 6 and 40 years and healthy controls: pDES levels were physiologically higher in individuals aged between 6 and 15 years and thereafter gradually decreased. Patients with MFS showed exaggerated elastin turnover in the lower age groups, suggesting an early onset pathophysiology of the MFS aortopathy. A possible correlation of pDES and aortic root diameter in MFS was suggested but not formally confirmed.

7q11.23 chromosomal imbalance vasculopathies represent unique models to evaluate the correlation between elastin biosynthesis, elastin turnover, and aortic involvement. Williams–Beuren syndrome (WBS) is a rare genetic condition (prevalence 1/7500–1/20 000), due to 7q11.23 microdeletions of 1.4–1.8 Mb encompassing 26–28 genes, including *ELN*.[5] Clinical phenotype is characterized by vasculopathy (75% of subjects) including arterial stenosis [notably supravalvular aortic stenosis (SVAS)] and hypertension, multiple congenital abnormalities, and intellectual disability. *ELN* haploinsufficiency in WBS is associated with abnormally thin and disorganized elastic fibres, increased vascular smooth muscle cells, media thickening, and, ultimately, arterial stenosis. The vasculopathy is the main cause of mortality in WBS.[5] A double-blind randomized controlled trial evaluating the effects of a drug stimulating elastogenesis (minoxidil) in children with WBS (NCT00876200) was unfortunately unsuccessful and emphasized the need of specific biological biomarkers of elastin metabolism in this condition.[6] A microduplication of the same chromosomal region causes a 'mirror' syndrome [7q11.23 duplication syndrome (7DUP)], whose phenotype is characterized by aortic dilatation (46%), mild dysmorphic features, and a variable neurodevelopmental involvement.[7] The pathogenesis of aortic dilatation in 7DUP is currently unknown, and no data have been reported to date concerning elastin metabolism in this condition.

Our study aimed to investigate pDES levels and urinary DES/creatinine ratio (uDES) in WBS (characterized by 1 *ELN* copy), normal controls (2 *ELN* copies), and 7DUP (3 *ELN* copies), in order to evaluate whether elastin turnover is correlated with the number of *ELN* copies.

This study was performed according to French laws and approved by the ethical committee of our institution. We recruited 26 individuals with WBS (15 males and 11 females; age range 0.6–32.7 years, median 7.5 years), 10 of them showing variable degree of SVAS, requiring surgery in 3 cases; 8 individuals with 7DUP (3 males and 5 females; age range 3.8–41.6 years, median 14 years), 3 of them showing a significant dilatation of ascending aorta (*Z*-score >3) requiring beta-blocker treatment in 2 cases; and 39 healthy controls matched for age and sex. All affected individuals had diagnosis confirmation by chromosomal microarray and cardiac and aortic ultrasounds scan, as part of their routine multidisciplinary management. Desmosines were determined by liquid chromatography–tandem mass spectrometry, as previously described.[8] Statistical analysis was performed by Mann–Whitney *U* test or Wilcoxon signed rank test, when appropriate (GraphPad Prism version 9.0.0).

In healthy controls, uDES levels were higher in the first year of life and, subsequently, progressively decreased to adult lower levels (*Figure 1A*). Urinary DES were significantly lower in individuals with WBS aged <1 year when compared with controls (*Figure 1A*). Urinary DES levels in 7DUP and pDES levels in both WBS and 7DUP were not significantly different from controls (median uDES 7DUP vs. controls: 5.2 vs. 6.1, $P > 0.999$; median pDES 7DUP vs.

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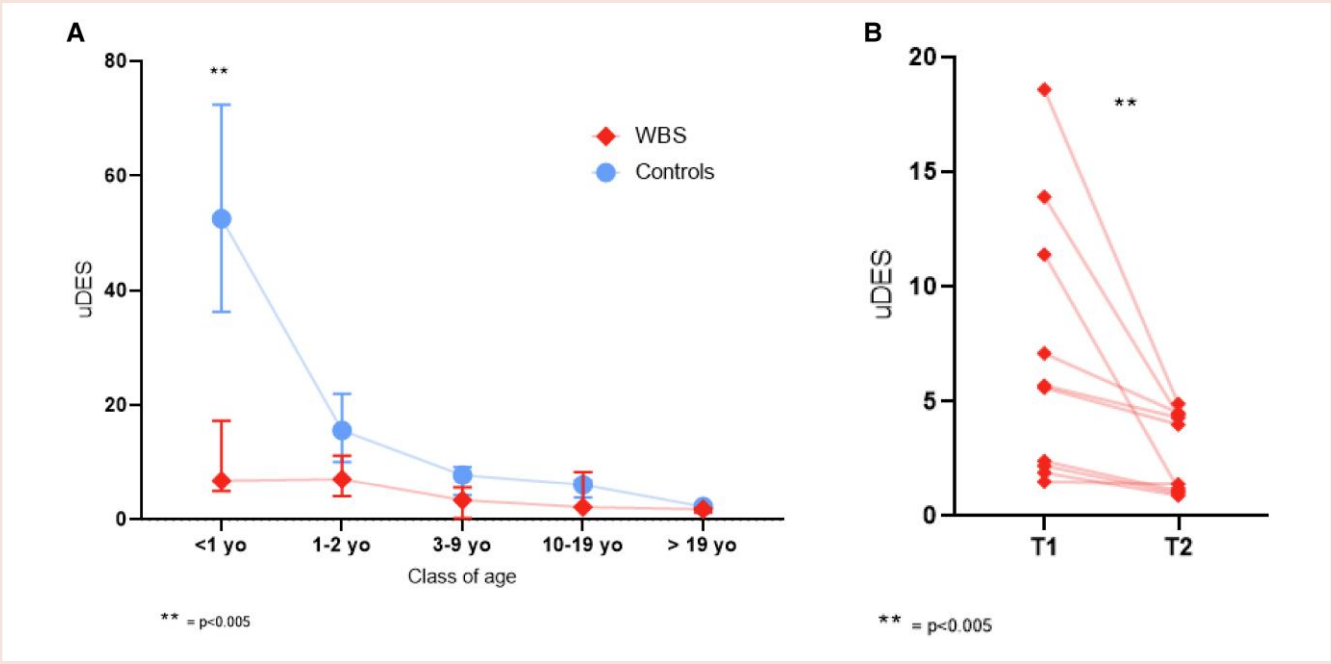


**Figure 1** (*A*) Ratio of desmosine and isodesmosine/creatinine in urine (urinary desmosines) in patients affected by Williams–Beuren syndrome and controls. Median and interquartile range by class of age. Statistical analysis by Mann–Whitney *U* test, corrected by false discovery rate. (*B*) Evolution of urinary desmosines in a subset of 10 patients with Williams–Beuren syndrome. Median age: 10.15 years (range 0.8–29) at the first assessment (T1) and 13.50 years (range 5.5–31.2) at the second assessment (T2). Statistical analysis by Wilcoxon signed rank test.

controls: 0.32 vs. 0.19 nmol/L, $P = 0.078$; median pDES WBS vs. controls: 0.323 vs. 0.212 nmol/L, $P = 0.055$). Repeated analyses were performed at a time interval of at least 6 months in 10 patients with WBS, showing a progressive uDES decrease (*Figure 1B*).

Our findings confirmed that developmental age has a significant effect on elastin turnover, as previously reported,[1] but show also that elastin turnover appears to be higher in children, especially within the first year of life, when elastin biosynthesis is particularly active. Desmosines are excreted in urines:[8] in our study, uDES appeared to be a more sensitive marker of elastin turnover than pDES.

Our study suggests that prepubertal children with WBS have low elastin turnover, which is likely to be the consequence of elastin biosynthesis defect caused by *ELN* haploinsufficiency. Interestingly, the abnormal structure of arterial walls in WBS, including abnormally thin and disorganized elastic fibres, does not appear to be associated with exaggerated elastin turnover. In conclusion, our study suggests that (i) uDES might be considered as a marker of elastin turnover in syndromic vasculopathies due to molecular defects in genes coding for major ECM structural components; (ii) elastin turnover is physiologically higher in the first year of life and, thereafter, progressively decreases to lower adult levels; and (iii) elastin turnover is reduced in WBS, which is likely to be the consequence of elastin biosynthesis defect. This study was limited by the small number of patients recruited due to the rarity of 7q11.23 chromosomal imbalance. Further studies on a larger number of patients are needed to better characterize elastin metabolism in 7DUP, to evaluate the correlation between elastin turnover and the presence of aortopathies in 7q11.23 chromosomal imbalance, and the clinical relevance of uDES as a biomarker of elastin metabolism in ECM diseases with vascular involvement.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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**Conflict of interest:** All the authors declare no conflict of interest.

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