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Different Phenotypes Among Lesch-Nyhan Variants: Clinical Reality or Limitation of Ascertainment?

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The recent article by Sarafoglou and colleagues¹ includes several statements that deserve further attention. First, the G550>T mutation described is incorrect. Position 550 falls in exon 8, not exon 7, and G550>T would not cause the R167>M substitution claimed. Based on the DNA sequence provided in Figure 2, the actual mutation should be G500>T.²

Next, the index case was reported to have a uric acid level of 231.5 mg/dL, which exceeds the physiological limit of solubility of uric acid in any body fluid by more than 20-fold.³ This should be clarified.

Third, the pedigree has many details that do not match the text, and designates the mother of one affected boy as unaffected, which seems improbable.

Fourth, the units for enzyme activity vary from pmol/μmol to pmol/nmol, an unlikely 1000 fold difference. Even assuming a typographical error, are the differences meaningful in single measures with no measurement variability?

Fifth, descriptions of the motor problems are difficult to decipher. One case was described with “bilateral focal dystonia of his lower extremities” and dysarthria. We assume the authors are describing generalized dystonia, similar to all patients with classic Lesch-Nyhan disease⁴ and most of variants.⁵ However, another case was described with increased muscle tone, flexion contractures, and “mild intoeing and a rolling alternating hip motion.” We assume again this is dystonia, yet have difficulty understanding why it was interpreted in the discussion as spasticity.

Finally, considering the limitations of the precision of clinical ascertainment, clinical differences seemed minor between the two children, but more obvious when comparing the adult. Are claims of clinical variability meaningful when comparing motor skills of 2- to 3-year-old toddlers with a 65-year-old?

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