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A woman with intellectual disability, amenorrhoea, seizures and balance problems

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A 38-year-old woman with intellectual disability (ID), primary amenorrhoea and focal seizures (Fig.1A) described two years of progressive balance difficulties. On examination she had short stature (1.45m), cerebellar ataxia and a visual acuity of 6/60. T2 weighted MR Imaging showed severe cerebellar atrophy, an atrophic corpus callosum and patchy signal change in the corona radiata suggestive of hypomyelination (Fig.1B).

Given the clinical features, a diagnosis of '4H syndrome' (hypomyelination, hypodontia and hypogonadotrophic hypogonadism) was considered. Genetic sequencing of *POLR3B* identified compound heterozygous mutations, which segregated with parents. Detailed endocrine assessment confirmed hypogonadotropic hypogonadism (LH/FSH ratio (<0.5 u/L) and low estradiol (<60 pmol/L)), but not growth hormone deficiency (IGF1 = 13nmol/L (NR 6-29)). Contact with the patient's dentist established the presence of hypodontia (Fig.1C).

4H leukodystrophy typically presents with ID or developmental delay and is associated with motor deterioration, often due to ataxia,^{1, 2} due to recessive mutations in either *POLR3A* or *POLR3B* which code for subunits of RNA polymerase III. Whilst hypomyelination is present in 95% of patients, the extra-neurological features, such as hypodontia and

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Author contributions

AJCH performed the laboratory work and co-wrote the manuscript.

HES evaluated the patient and co-wrote the manuscript.

AP performed and supervised the laboratory work.

YH provided clinical care and critically reviewed the manuscript.

RQ provided clinical care and critically reviewed the manuscript.

PFC provided clinical care and critically reviewed the manuscript.

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hypogonadism, may be absent and are not essential for diagnosis.^{1, 2} Seizures occur in a significant minority (19%),¹ whilst other features including myopia,¹ short stature¹ and growth hormone deficiency³ are also recognised.

A molecular diagnosis led to hormone replacement therapy and vitamin D supplementation to maintain bone mineral density. A definitive diagnosis has obviated the need for ongoing investigation and provided important prognostic information for her family, thereby facilitating appropriate long term care planning.

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References

1. Wolf NI, Vanderver A, van Spaendonk RM, et al. Clinical spectrum of 4H leukodystrophy caused by POLR3A and POLR3B mutations. *Neurology*. 2014; 83(21):1898–905. [PubMed: 25339210]
2. Daoud H, Tetreault M, Gibson W, et al. Mutations in POLR3A and POLR3B are a major cause of hypomyelinating leukodystrophies with or without dental abnormalities and/or hypogonadotropic hypogonadism. *Journal of medical genetics*. 2013; 50(3):194–7. [PubMed: 23355746]
3. Billington E, Bernard G, Gibson W, Corenblum B. Endocrine Aspects of 4H Leukodystrophy: A Case Report and Review of the Literature. *Case reports in endocrinology*. 2015; 2015

Figure 1. Clinical Features of the 4H syndrome

- A. Electroencephalogram (EEG) showing spike activity centred on the fronto-central region.
- B. T2 weighted MRI demonstrating hyperintensity in the corona radiata bilaterally (arrows) suggestive of hypomyelination.
- C. Dental radiograph demonstrating hypodontia with the absence of one pre-molar and two lateral incisors.