Advanced bone age and accelerated dental development associated with elevated retinoic acid levels and haploinsufficiency of CYP26A1 and CYP26C1

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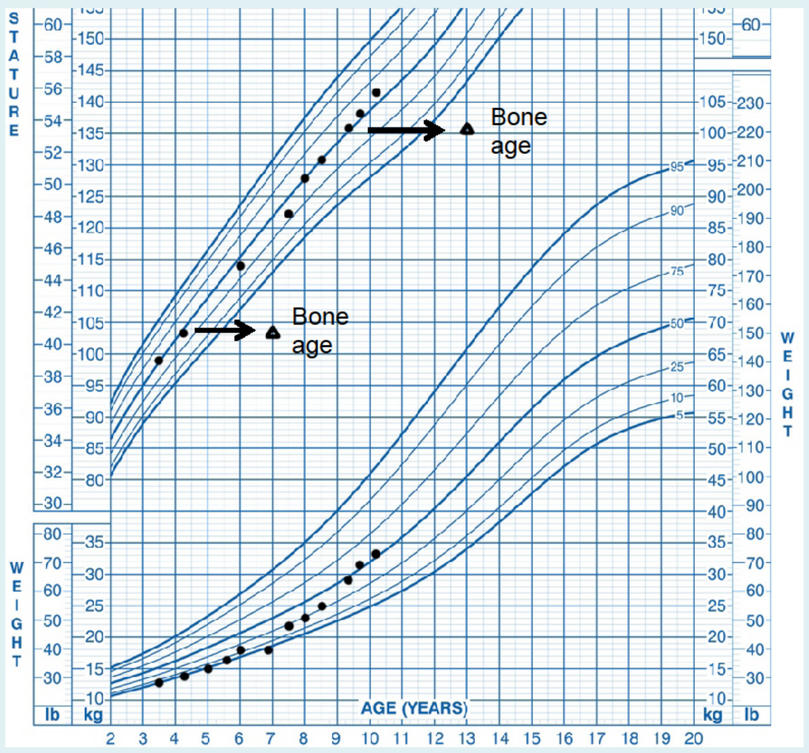

Fig 1 Growth Chart for the patient showing height, weight , and bone age

Conclusions:

- The findings of elevated total retinoic acid (RA) and 13-Cis RA support the hypothesis that elevated RA levels accelerate bone and dental maturation in humans.
- CYP26A1 and C1 haploinsufficiency may contribute to the elevated retinoic acid levels of our patient.

Introduction

Nutritional excess of vitamin A, a precursor for retinoic acid (RA), causes premature epiphyseal fusion, craniosynostosis, as well as light-dependent retinopathy. Similarly, homozygous loss-of-function mutations in one of the major RA-metabolizing enzymes CYP26B1 causes advanced bone age, premature epiphyseal fusion, and craniosynostosis. We studied a 10-yr old prepubertal male with bone age advanced 3.5 yrs over chronologic age. Anterior fontanel was largely closed at age 2 months. Dental age was also markedly advanced with 16 primary teeth present at age 12 months and shedding beginning at age 3 yrs. Linear growth normal along the 50th percentile since age 3 yrs. He also has photophobia, chorioretinal scarring, and developmental delay.

Objective and hypotheses:

To characterize and identify the cause of the markedly accelerated skeletal and dental development, retinal scarring, and autism-spectrum disease in this patient

Methods:

Genetic studies using comparative Genomic Hybridization (CGH) array and whole exome sequencing. RA metabolites were assessed in patient as well as in 10 age-matched boys and 10 girls using high-performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (MS/MS).

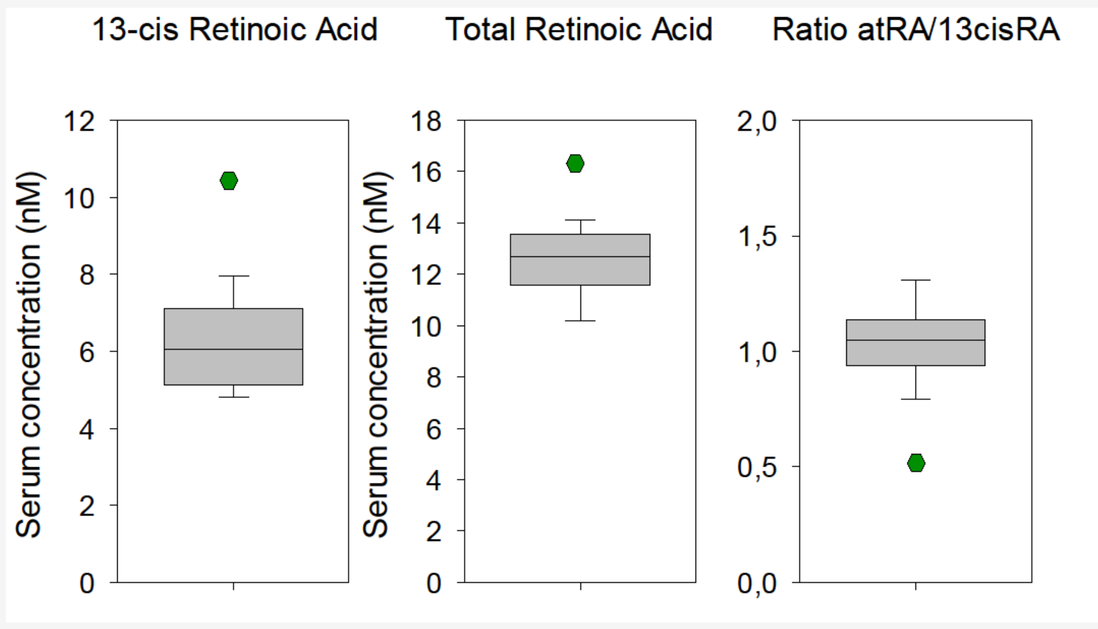

Fig 2. 13-cis retinoic acid (RA), total RA, and Ratio all-trans RA/13-cisRA in healthy age-matched controls (n=20) and the patient (●) were assessed by HPLC-MS/MS.

Results:

CGH array identified a novel 8.3 megabase microdeletion on chromosome 10Q23.2-23.33. The 79 deleted genes include CYP26A1 and C1, both major RA metabolizing enzymes. Whole exome sequencing did not detect any variants that are predicted to be deleterious in the remaining copies of these genes, in CYP26B1, or other known retinoic acid-metabolizing enzymes. The patient exhibited elevated serum levels of total RA (16.5 nM vs. 12.6 ± 2.9; patient vs. controls (mean ± 2 SD)) and 13-Cis RA (10.7 nM vs. 6.1 ± 2.2; patient vs. controls (mean ± 2 SD)) (Fig 2).

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