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Title of the paper:

Chondrodysplasia Punctata (CDPX2) in a Male Caused by Single Gene Mosaicism: A 20-year follow up

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1. Clinic 1(a) - (c)
2. Electrophoretogram figure 2

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Medical Images

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Conflicts of Interest

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Chondrodysplasia Punctata (CDPX2) in a Male Caused by Single Gene Mosaicism: A 20-year follow up

X-linked dominant chondrodysplasia punctata (CDPX2; Conradi-Hünemann-Happle syndrome; CHH; OMIM302960) is a genetic disorder that occurs almost exclusively in females due to intrauterine lethality in hemizygous males. CDPX2 results from mutations within the X-linked gene encoding for $\Delta 8\text{-}\Delta 7$ sterol isomerase, or emopamil binding protein (EBP). Typical syndromic features include spontaneously resolving ichthyosiform erythroderma following Blaschko lines, follicular atrophoderma, cicatricial alopecia, keratosis pilaris and skeletal defects including epiphyseal stippling.¹

A four-year old male initially presented with subtle clinical features of CDPX2, including a two-year history of a patch of cicatricial alopecia, follicular atrophoderma and cutaneous features of Blaschkoid hyperpigmentation. His scalp showed diffusely thinned, coarse hair with an irregular vertical patch of scarring alopecia. Alternating streaks of hyper- and hypopigmentation with prominent follicular atrophoderma followed a Blaschkoid pattern.

Femoral epiphyseal stippling and possible punctate change were evident on x-ray. Plucked abnormal (wavy) hair shafts were short, thinned and twisted on light

microscopy. The diagnosis of CDPX2 was suspected but initially questioned because of the subtlety of the presentation and his male gender.

DNA sequencing detected an 11-base pair deletion in exon 2 of the EBP gene.

Biochemical testing for cholest-8(9)-en-3 β -ol and 8-dehydrocholesterol, shown to be part of the diagnostic work-up for CDPX2,³ suggested that he was a mosaic for CDPX2. The patient was lost to follow up until recently.

Aged 25 years, he sought management of his alopecia; examination revealed cicatricial alopecia (figure 1a) on the vertex of the scalp, Blaschkoid ichthyosis (figure 1b) and palmoplantar keratoderma (figure 1c).

Sequencing of the EBP gene was performed on DNA extracted from blood and affected skin showing mosaicism for a frameshift variant in the EBP gene (c.10_20del), p.(Asn4fs) (figure 2). The level of the mosaicism for the c.10_20del variant within his leukocyte DNA is estimated to be 47%, and higher in the skin (75%), which is consistent with a post-zygotic variant. This result confirms the clinical diagnosis of mosaic X-linked dominant CDPX2.

Despite being assumed to be male-lethal, males with the clinical syndrome have been documented.²⁻⁵ The survival of one individual was attributed to the presence of a 47, XXY karyotype [Klinefelter syndrome]², while others have been either due to post-zygotic mutation or gametic half-chromatid mutations as proposed for other X-linked dominant diseases.³⁻⁵ Both Aughton and Arnold describe young males with clinical, biochemical and molecular features similar to our proband, in the first reported cases of single-gene mosaicism causing CDPX2 in males.^{3,4}

The mutated gene responsible for CDPX2 has been described and localised to Xp11.22-p11.23, coding for EBP - a $\Delta 8$ - $\Delta 7$ sterol isomerase involved in cholesterol synthesis. A defect in EBP results in the accumulation of two cholesterol metabolites, namely cholest-8(9)-en-3 β -ol and 8-dehydrocholesterol which can be detected in serum and other tissues. Cholest-8(9)-en-3 β -ol is converted to lathosterol by $\Delta 8$, $\Delta 7$ -sterol isomerase, which is further converted to 7-dehydrocholesterol, a major precursor for cholesterol and vitamin D synthesis.

Mosaicism of CDPX2 here explains the subtle clinical features in a viable male.

expression in a viable male. Genetic counselling can now be optimised for him and his family.

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References

1. Traupe H., Has C. The Conradi-Hünemann-Happle syndrome is caused by mutations in the gene that encodes a $\Delta 8$ - $\Delta 7$ sterol isomerase and is biochemically related to the CHILD syndrome. *Eur J Dermatol* 2000;10:425-428.
2. Stuphen R., Amar M.J., Kousseff B.G., Toomey K.E. XXY male with X-linked dominant chondrodysplasia punctata [Happle syndrome]. *Amer J Med Gen* 1995;57:489-492.
3. Aughton D.J., Kelley R.I., Metzenberg A. X-lined dominant chondrodysplasia punctata (CDPX2) caused by single gene mosaicism in a male. *Amer J Med Gen* 2003;116A:255-260.
4. Arnold A.W., Bruckner-Tuderman L., Has C., Happle R. Conradi-Hünemann-Happle syndrome in males vs. MEND syndrome (male EPB disorder with neurological defects). *British J of Dermatology* 2012;166:1309-1313.
5. Tronnier M., Froster-Iskenius U.G., Schmeller W. X-chromosome dominant chondrodysplasia punctata (Happle) in a boy. *Hautarzt*. 1992; 43:221–225.

Figure Legend

Clinic Figure 1(a): Stable, patchy cicatricial alopecia over vertex (b): Subtle Blaschkoid ichthyosis on left arm (c): Plantar keratoderma of left foot

Figure 2: Electrophoretogram of proband showing mosaicism for a frameshift variant in the EBP gene (c.10_20del), p.(Asn4fs). The three sequence traces show (a) the

peripheral leukocyte trace (47% mosaicism) and (b) the skin biopsy trace (75% mosaicism), compared to (c) the normal sequence trace for exon 2 of the EBP gene.

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a) EX1712613- DNA extracted from whole blood

b) EX1712614- DNA extracted from skin biopsy

c) Normal exon 2 sequence

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