Dual function of the retinoic acid catabolizing enzyme CYP26C1: (I) modifying disease severity in SHOX deficiency and (II) underlying idiopathic short stature

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To elucidate the factors that modify disease severity/penetrance in short stature, we have studied a three-generation family with SHOX deficiency. We have found that the retinoic acid degrading enzyme CYP26C1 is a modifier for SHOX deficiency phenotypes towards the more severe clinical manifestations (Leri-Well dyschondrosteosis) and confirmed these findings in independent cases. We also asked whether damaging variants in CYP26C1 alone could lead to short stature. We performed exome and Sanger sequencing to analyze 856 individuals with short stature where SHOX deficiency was previously excluded. Three different damaging missense variants and one splicing variant were identified in six independent individuals. The functional significance of the identified variants was tested in vitro (splicing defect) or in vivo (missense mutations) using Zebrafish as a model. The identified CYP26C1 variants affected the catabolic activity of CYP26C1 in human primary chondrocytes and zebrafish embryos. Together, the genetic and functional data reported here indicate that CYP26C1 represents a novel gene underlying growth disorders with dual function: damaging variants in CYP26C1 in the absence of SHOX mutations can lead to short stature and damaging variants in CYP26C1 modify SHOX deficiency phenotypic outcomes through the retinoic acid signaling pathway.

I. Modifier in Leri-Weill Dyschondrosteosis

II. Idiopathic Short Stature

Figure 1. Identification of CYP26C1 as a genetic modifier

Figure 2. Scheme of SHOX and CYP26C1 and results of Luciferase assays

Figure 3. Modeling SHOX and CYP26C2 interaction in zebrafish embryos

Figure 4. Schematic representation of the CYP26C1 gene with identified variants

Figure 5. Functional significance of the CYP26C2 missense variants identified in zebrafish embryos

References:

Montalbano et al., Retinoic acid catabolizing enzyme CYP26C1 is a genetic modifier in SHOX deficiency. EMBO Mol Med. 2016 Dec 1; 8(12):1455-1469.