CONGENITAL ADRENAL HYPERPLASIA WITH A CYP21A2 DELETION OVERLAPPING TENASCIN-X GENE

Catarina Rodrigues Ivo[1], Ana Laura Fitas[2], Inês Madureira[3], Catarina Diamantino[2], Susana Gomes[4], João Gonçalves[4], Lurdes Lopes[2]

1- Departamento de Endocrinologia, Hospital das Forças Armadas (HFAR), Lisbon, Portugal
2- Unidade de Endocrinologia Pediátrica, Hospital de Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central (CHULC), Lisbon, Portugal
3- Unidade de Reumatologia Pediátrica, Hospital de Dona Estefânia, Centro Hospitalar Universitário de Lisboa Central (CHULC), Lisbon, Portugal
4- Departamento de Genética Humana, Instituto Nacional de Saúde Dr Ricardo Jorge, Lisbon, Portugal

ESPE 2021 The 59th Annual Meeting Online 22-26 September 2021

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a group of genetic diseases characterized by impaired cortisol synthesis. 95% of CAH cases result from mutation in the *CYP21A2* gene encoding 21-hydroxilase.

TNX-B gene partially overlaps *CYP21A2* and encodes a matrix protein called Tenascin-X(TNX). Complete tenascin deficiency causes Enlers-Danlos syndrome (EDS). A variant called CAH-X, has been described, resulting from *CYP21A2* deletions extending into the *TNXB* on at least one allele. This haploinsufficiency of TNX may be associated with a mild hypermobility form of EDS, as well as other connective tissue comorbidities such as herniae, cardiac defects and chronic arthralgia.

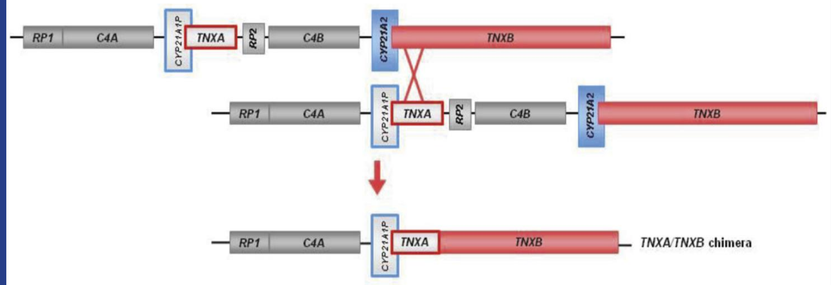


Figure 1: Schematic of the tenascin genes undergoing unequal crossover resulting in a *TNXA/TNXB* chimera. *CYP21A2* encodes the active 21-hydroxylase gene (blue); *TNXB* encodes the active tenascin gene (red). Pseudogenes *CYP21A1P* and *TNXA* are in gray and are framed with the color of the corresponding functional gene. Adapted from *J Clin Endocrinol Metab. 2013;98(2):1-17* [3].

AIM

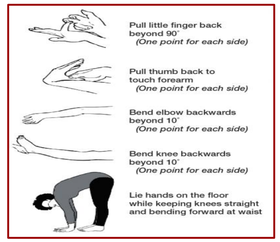
It is our purpose to report four patients heterozygous for a CAH-X allele that do not present clinical manifestations of the Ehlers-Danlos syndrome.

CASE REPORTS

	Case 1	Case 2	Case 3	Case 4
Sex / Age (years)	M/17	M/14	M/12 (Brother of case 2-studied after index case diagnosis)	F/15
Diagnosis	Classic salt wasting CAH	Non-classical CAH	Non-classical CAH	Non-classical CAH
Genetic Test	TNXA/TNXB chimera: CYP21A2 deletion (heterozygosity) overlapping the TNXB gene	CYP21A2 variant and a complete CYP21A2 deletion on the other allele covering the last exons of TNXB.	CYP21A2 variant and a complete CYP21A2 deletion on the other allele covering the last exons of TNXB	CYP21A2 deletion in one allele also affecting TNXB
Beighton score	0	1	0	1
Joint findings	None	Tibiotarsal dislocation x2	None	None
Skin findings	None	None	None	None
Cardiac findings	None	None	None	None
Other clinical features	Testicular adrenal rest tumour (age of 12)	Lie hands on the floor while keeping knees straight	None	Lie hands on the floor while keeping knees straight

Table 1: Clinical characteristics of patients. Abbreviations: ECHO, echocardiogram; F, female; M, male

Beighton Score



Positive if 6 of 9 points

CONCLUSIONS

- These 4 CAH cases with a monoallelic CYP21A2 deletion overlapping the Tenascin-X gene, highlight the importance of additional clinical evaluations related with the recently described CAH-X Syndrome.
- CAH patients, carriers of these TNXA/TNXB chimeras, should be evaluated for clinical manifestations related to connective tissue hypermobility, cardiac abnormalities and other EDS features allowing a better clinical management.

REFERENCES

1. Chen W, Kim MS, Shanbhag S, et al. The phenotypic spectrum of contiguous deletion of CYP21A2 and tenascin XB: Quadricuspid aortic valve and other midline defects. *Am J Med Genet Part A*. 2009;149A(12):2803-2808. doi:10.1002/ajmg.a.33092
2. Miller WL, Merke DP. Tenascin-X, Congenital Adrenal Hyperplasia, and the CAH-X Syndrome. *Horm Res Paediatr*. 2018;89(5):352-361. doi:10.1159/000481911
3. Merke DP, Chen W, Morissette R, et al. Tenascin-X haploinsufficiency associated with ehlers-danlos syndrome in patients with congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 2013;98(2):1-17. doi:10.1210/jc.2012-3148
4. Kolli V, Kim H, Rao H, et al. Measurement of serum tenascin-X in patients with congenital adrenal hyperplasia at risk for Ehlers-Danlos contiguous gene deletion syndrome CAH-X. *BMC Res Notes*. 2019;12(1):1-6. doi:10.1186/s13104-019-4753-7