P1-P014

Molecular characterization of *TNXA/TNXB* chimeras in *CYP21A2* gene deletions: high frequency of undiagnosed Ehlers Danlos syndrome in congenital adrenal hyperplasia.

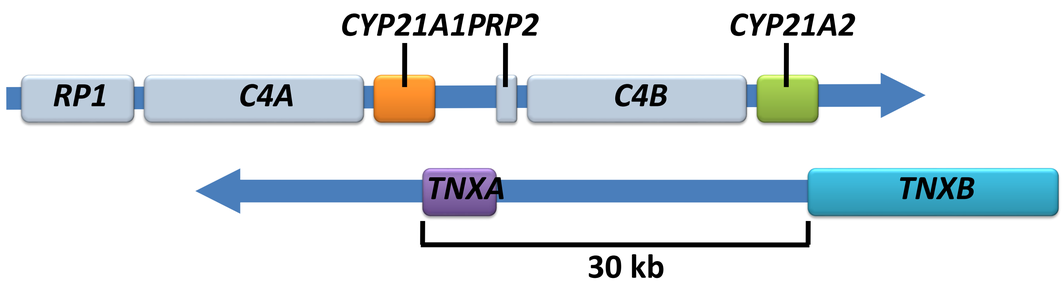
R Marino, G Notaristéfano , N Perez Garrido, P Ramirez , MS Touzon, M Pujana, A Moresco , G Finkielstain , G Obregón , MA Rivarola , A Belgorosky.

Hospital de Pediatría Garrahan, Argentina

Authors have nothing to disclose

Introduction

• The contiguous gene deletion syndrome, CAH-X, was described in 8.5 % of congenital adrenal hyperplasia (CAH) patients with a *TNXA/TNXB* chimera resulting in deletions of *CYP21A2*, and *TNXB*, encoding the extracellular matrix glycoprotein tenascin-X (TNX). There are three *TNXA/TNXB* chimeras described that differ in the junction site, resulting in *TNXB* haploinsufficiency, dominant negative effect, or biallelic forms and an Ehlers Danlos syndrome (EDS) phenotype. (Chen et al. Human Mutation. 2016)

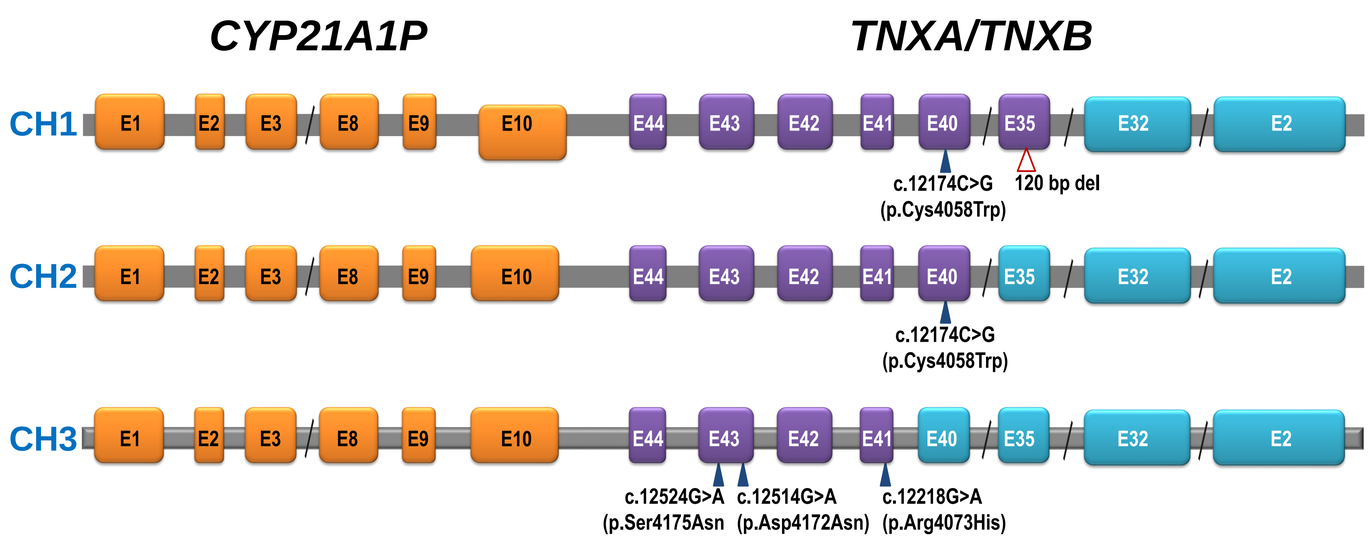


Introduction

• TNXB complete deficiency was first described in a patient diagnosed with CAH and classical EDS, and it was autosomal recessive inherited (Burch et al. Nature Genetics 1997).

•*TNXB* haploinsufficiency is associated with hypermobility type EDS (characterized by generalized joint hypermobility and recurrent joint dislocations, chronic arthralgias, mild skin manifestations and cardiac disorders) (Zweers et al. Am J Hum Genet. 2003).

TNXA/TNXB chimeras



Objective

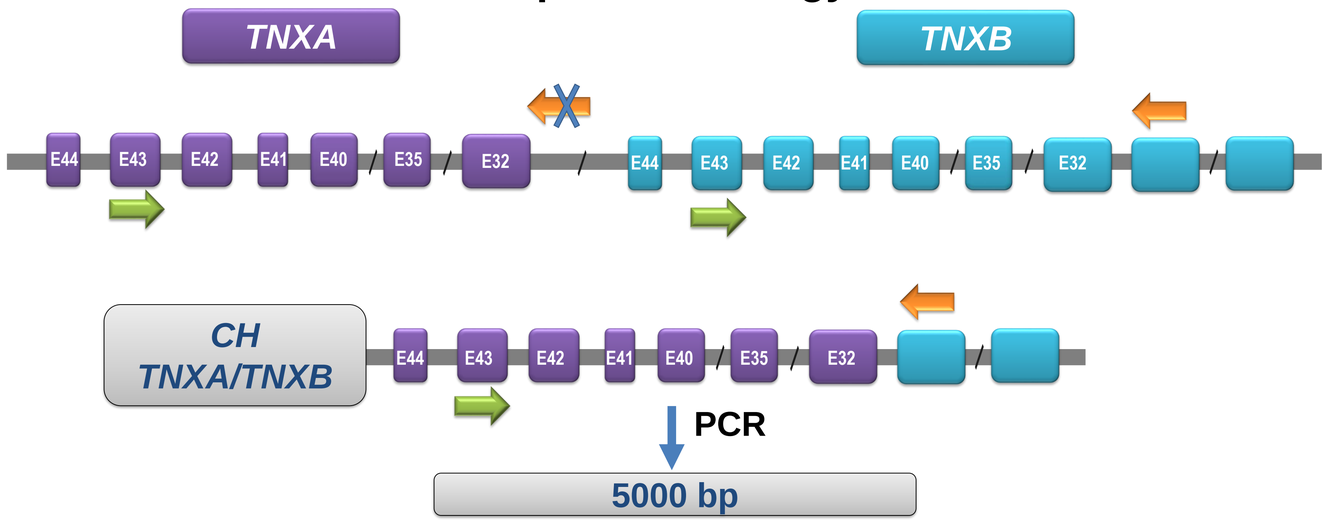
The aim of this study was to analyze copy number variations and genetic status of *TNXB* gene in 58 CAH patients due to *CYP21A2* deletion to determine the frequency of *TNXB* alterations in our population.

Clinical Material and Methods

Molecular analysis

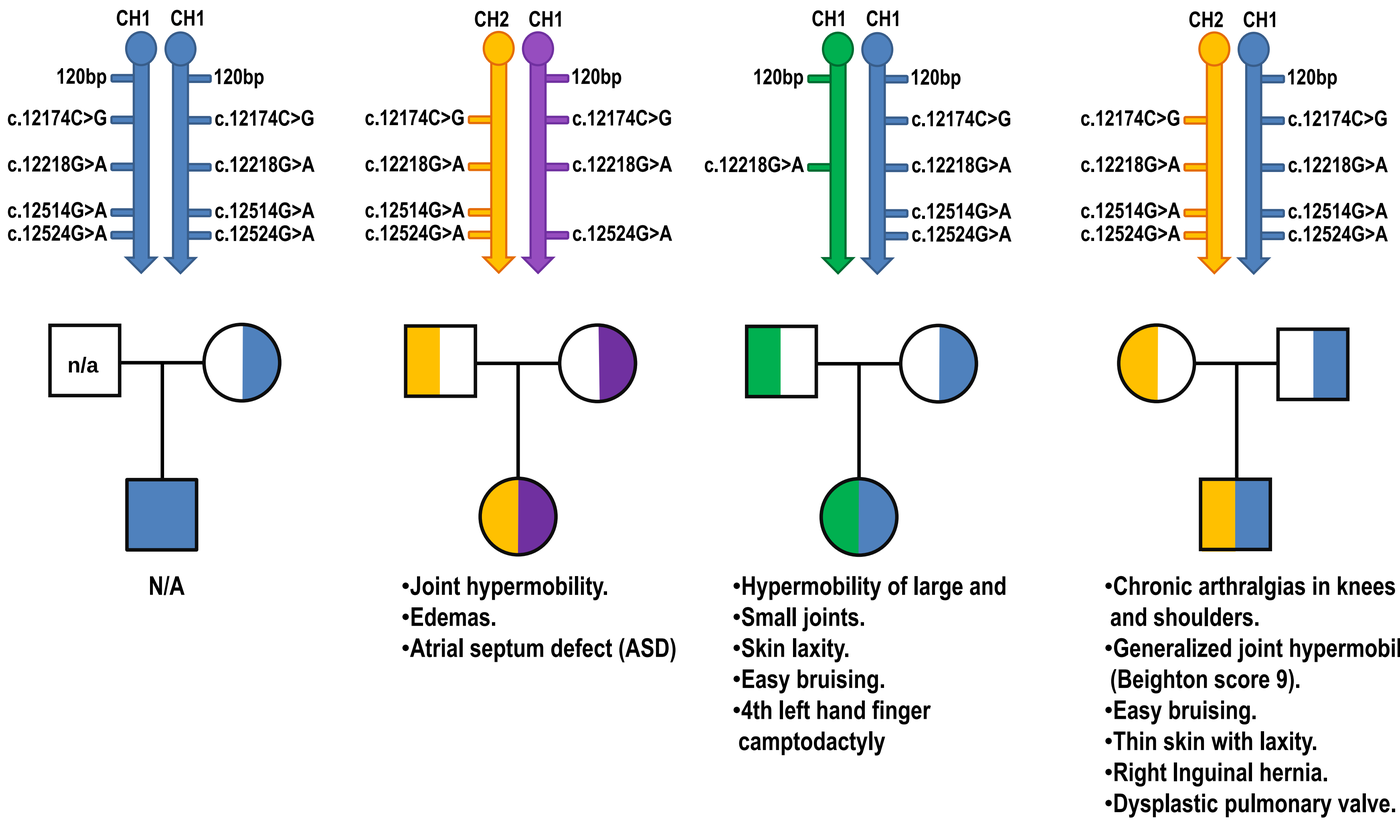
• A total of 58 unrelated CAH patients carriers of *CYP21A2* gene deletion (65 alleles) were screened for *TNXB* defects.
• All the patients were analyzed for the presence of CH1 by MLPA analysis (P050-CAH version C1, MRC Holland) evidenced by a 120 bp deletion in *TNXB* exon 35, and confirmed by exon 35 sequence analysis.
• In addition, all of them were screened for other *TNXB* alterations related to CH2 and CH3 by exon 40, 41 and 43 Sanger sequencing.

Sequence strategy



Results

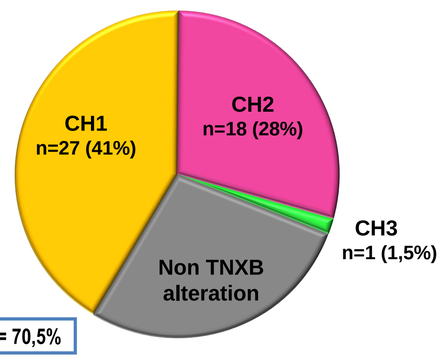
Biallelic CAH-X genetics and pedigrees



Genetic status of *TNXA/B* chimeras

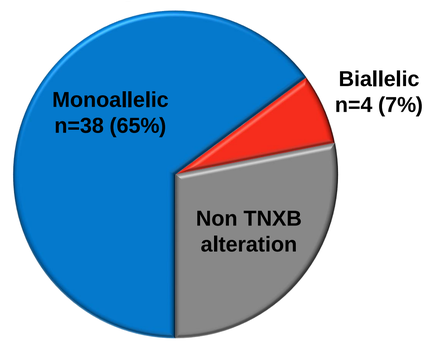
HAPLOTYPE	chimera	VARIANTS					ALLELES (n) Total	ALLELES (n) Biallelic forms
		120 bp deletion	c.12174C>G (p.Cys4058Trp)	c.12218G>A (p.Arg4073His)	c.12514G>A (p.Asp4172Asn)	c.12524G>A (p.Ser4175Asn)		
1	CH1	X	X	X	X	X	19	4
2	CH2		X	X	X	X	12	2
3	CH2		X				4	
4	CH1	X	X	X		X	3	1
5	CH2		X	X		X	2	
6	CH1	X		X	X	X	1	
7	CH1	X		X			1	
8	CH1	X		X	X		1	
9	CH3			X			1	
10	CH1	X		X		X	1	
11	CH1	X		X			1	1

65 *CYP21A2* Del alleles



CH1+CH2+CH3 = 70,5%

58 patients



Conclusions

A high frequency of *TNXB* alterations was found in *CYP21A2* deletion carrier alleles in our population. MLPA and Sanger sequencing techniques resulted useful to characterize *TNXB* deletion. Accurate genotype-phenotype correlation remains to be elucidated in this cohort. Nevertheless, based on the high frequency of *TNXB* alterations in *CYP21A2* deletion carrier alleles found in this study, we recommend to evaluate *TNXB* status in these patients, warranting assessment of connective tissue dysplasia including cardiologic alterations in positive cases.