"CAH-X" due to homozygous deletions of CYP21A2 and TNXB exon 35 in a newborn from the 17 OHP screening

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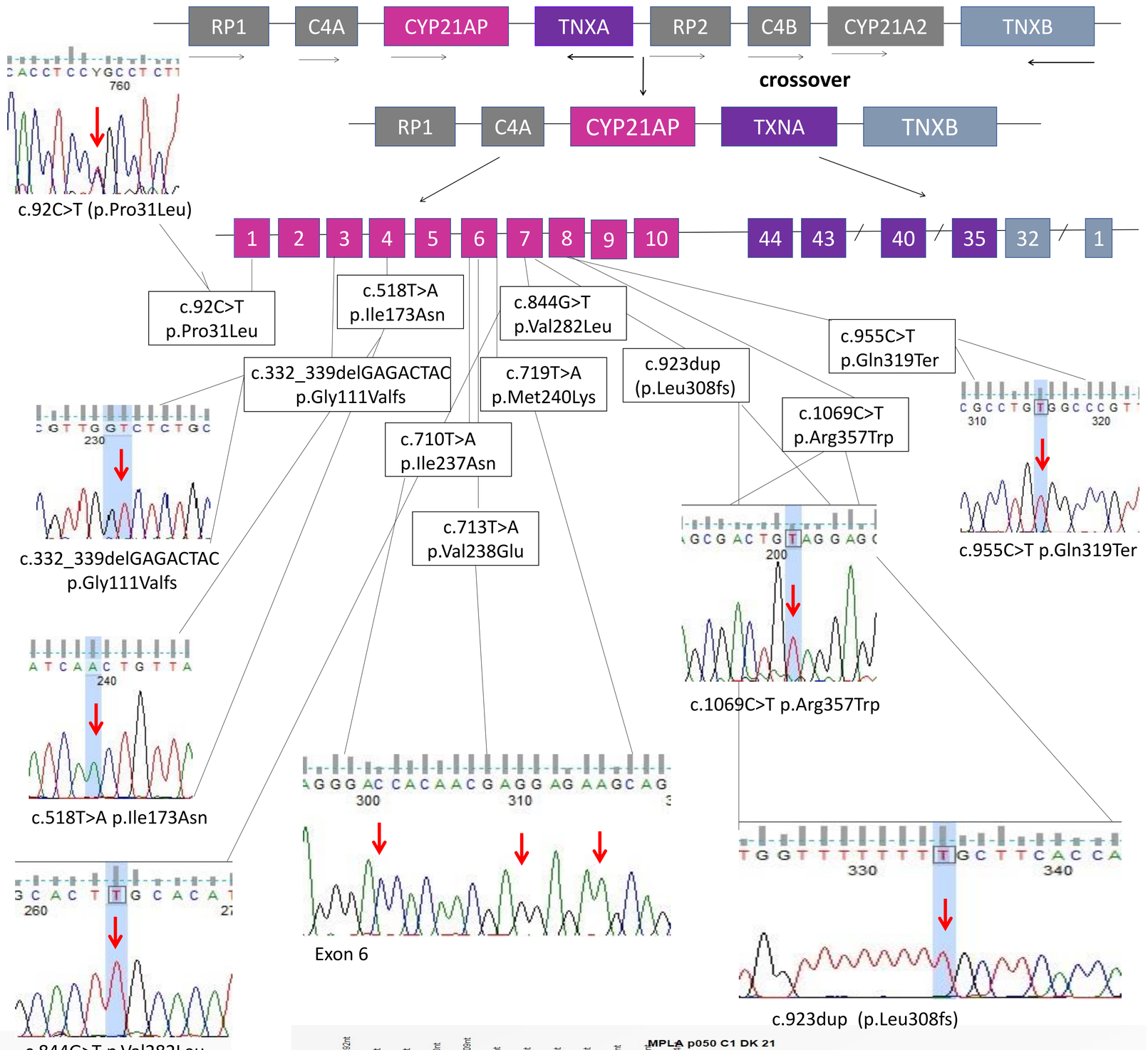
Introduction: The CYP21A2 and the TNXB genes are highly homologous with their corresponding pseudogenes (CYP21A1P and TNXA), leading to frequent homologous recombination (fig1). The TNXB includes 43 exons, the mRNA encodes tenascin-X (TNX), an extracellular matrix (ECM) glycoprotein that is highly expressed in connective tissue. Congenital adrenal hyperplasia (CAH) patients with a "contiguous gene syndrome" comprising a deletion of both genes- CYP21A2 and TNXB have been described. Chimeric genes generated by large gene deletion or gene conversion events, account for 20%–30% of the common CYP21A2 pathogenic variants in CAH patients. Nine CYP21A2/CYP21A1P (CH-1 to CH-9) and one TNXA/TNXB chimera have been described. TNXA/TNXB CH-1 resulted in a contiguous CYP21A2 and TNXB deletion. TNXA/TNXB CH-1 is characterized by a 120-bp deletion crossing exon 35 and intron 35 carried over from the TNXA pseudogene.

Materials and methods: DNA extraction from peripheral blood, Sanger sequencing and MLPA analysis were performed.

Case presentation: We present a newborn with extremely severe and complex phenotype, with lethal outcome despite early and monitored hormonal substitution. He was born after 3rd pregnancy, at term, with BW 3100g, BL 50 cm, HC 34 cm, by vaginal delivery. Severe bradycardia and bradypnea lead 8 hours later to intubation. Early hypoglycemia, hyponatremia and hyperkalemia were present as well, therefore methylprednisolone was instituted early. Screening was taken on d 3, the extremely elevated 17 OHP results **(>324 nmol/l)** were reported immediately, 9-alfa fludrocortisone was added at d 9 to the GCS and fluid therapy. The patient was transferred to a tertiary neonatology center at d 10 with weight loss (9.7%), respiratory insufficiency, reduced muscle tonus and activity, severe hyperpigmentation, descended testis, elevated CRP, direct hyperbilirubinemia (316 mcmol/l, dBili 228), negative in the TORCH and hepatitis screen, with opened fetal communications, small left/right shunt, aneurism fossa ovale, left sided severe hydronephrosis and enlarged adrenals, no signs of atresia of the extrahepatic bile duct system. Hypocholic stools and dark urine were present during the entire period. The further clinical course was not typical for a newborn with classical CAH on GCS, MCS and fluid therapy.

Fig. 1. CAH1 diagram - CYP21A1P/CYP21A2 and TNXA/TNXB chimera genes



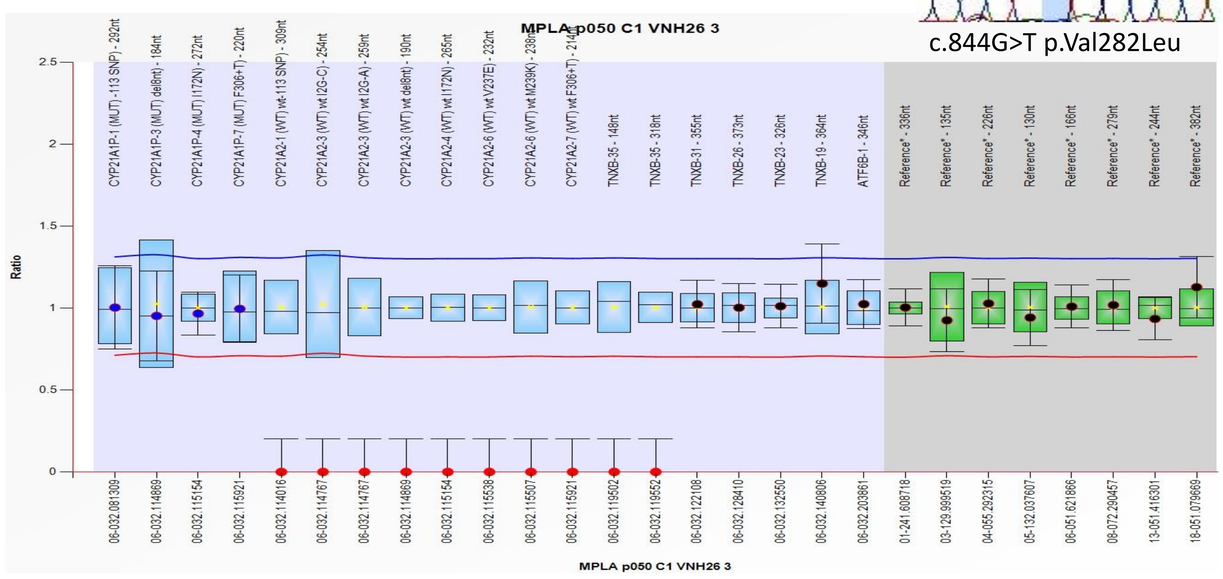


Fig. 2. Patient CAH 26 - MLPA analysis Salsa p050

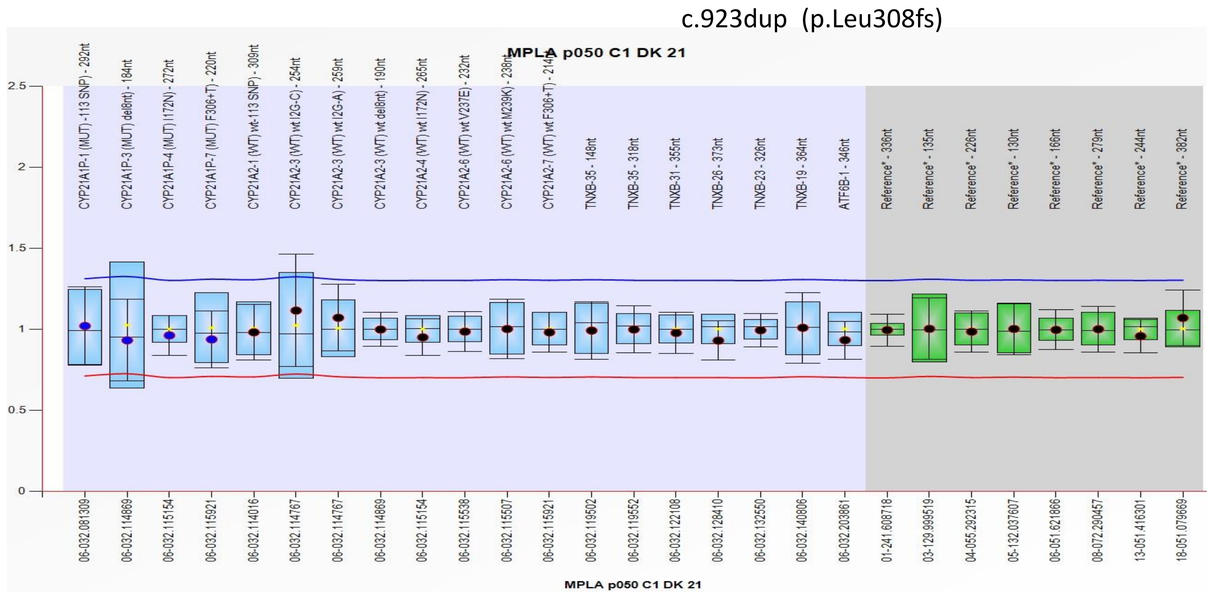


Fig. 3. Control individual- MLPA analysis Salsa p050

The results from the molecular genetic analysis revealed homozygous deletions in *CYP21A2* gene and its substitution with CYP21A1P pseudogene and chimera gene *TNXA/TNXB* at the intron - exon 35 boundary of the *TNXB* gene (fig.2,3). The skin elasticity, the hypermobility of the joints and the aneurism fossa ovale is in line with the Ehler Danlos syndrome phenotype, but due to the small age of the patient could not be further explored.

Conclusion: Our patient represents a case of TNXA/TNXB CH-1 with extremely complex phenotype and Ehler Danlos symptoms, adding to the phenotype of the contiguous CAH syndrome and additional TNXB – related diseases.

Acknowledgements: DUNK01-2/2009, NSF, Ministry of education and Science; Grant 83/2016, Medical Sciences Council, Medical University of Sofia, Adelina Krusteva.

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