P2 - 90 - B

NEONATAL DIABETES IN TWO SIBLINGS WITH FOXP3 VARIANT

COLOMBI CAROLINA*, TORNESE VIRGINIA*, POTT GODOY CLARA**, PEÑA SONIA***, DE FRANCO ELISA****, GUNTSCHE ZELMIRA*

*Endocrinology and Metabolism Department, Notti Hospital, Mendoza, Argentina.

**Molecular Biology Department, Notti Hospital, Mendoza, Argentina.

***Alergy and Inmunology Department, Notti Hospital, Mendoza, Argentina.

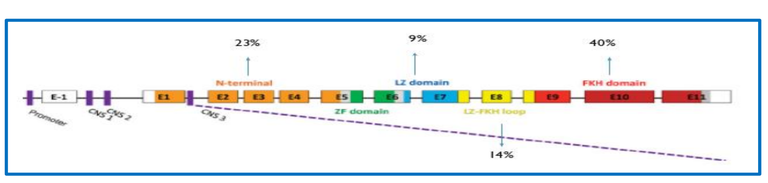
****Molecular Genetics Laboratory, University of Exeter, UK.

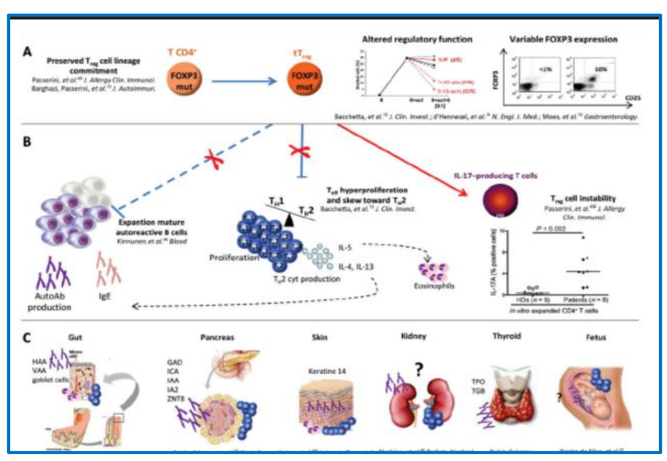
Hospital Pediátrico Dr. Humberto J. Notti - Mendoza - Argentina

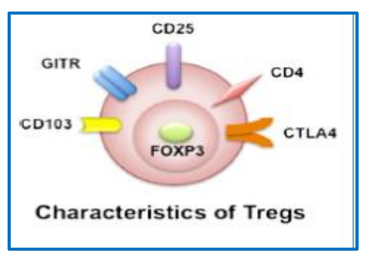
Background: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by loss-of-function mutations in the gene encoding the forkhead box P3 (FOXP3) transcription factor. This factor plays a key role in the differentiation and function of CD4+ CD25+ natural regulatory T cells, which are essential for the establishment and maintenance of natural tolerance.

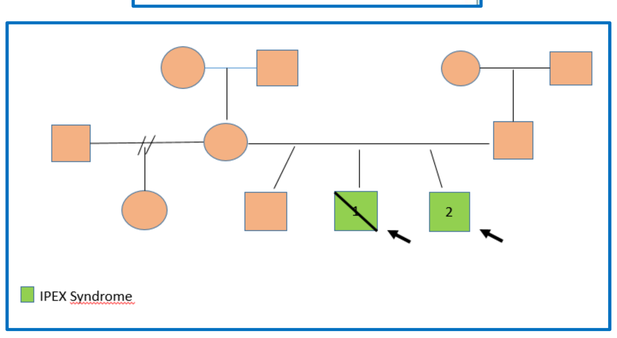
Objective: To describe clinical, biochemical and genetic characteristics in two siblings with neonatal diabetes and a novel FOXP3 variant.

Method: Genomic DNAs were extracted from peripheral blood leukocytes from both patients and their parents with informed consent for genetic studies. Sanger sequencing was performed.









Results Patient 1:

- Male, born at term, birth weight 3,050 kg.
- Neonatal diabetes. DKA at 1 month old.
- Glycemia 5,11 g/L. HbA1c 4%. C-peptide 0,1 ng/mL. Anti-insulin Antibodies 13,4 U/mL. Ig E 7710 IU/mL.
- Treatment: NPH and aspartic. Variable glycemic control.
- Severe enteropathy was confirmed by endoscopy and biopsy. Parenteral nutrition. IPEX syndrome was suspected based on neonatal diabetes, enteropathy and eczema.
- Multiple infectious diseases associated with autoimmune cytopenias.
- Died cachectic at 6 months old because of sepsis after 5 months at hospital.
- Sequence analysis confirmed he was hemizygous for a **novel FOXP3 frameshift variant** resulting in loss of the stop codon, p.(Thr428fs). Evidence up to that moment suggested that the variant was likely pathogenic, consistent with IPEX syndrome. His mother is heterozygous for the mentioned variant, being a carrier.

Results Patient 2:

- Male, born at term, birth weight 1,720 kg.
- Neonatal diabetes. Given his older brother record, patient 2's glycemia was controlled since birth.
- Glycemia 2,5 g/L on first day of life. HbA1c 4%. C-peptide 0,1 ng/mL. GADA 11,1 U/mL. IgE 2,3 IU/mL.
- Treatment: lispro administered by insulin pump. Variable glycemic control.
- Hydrolyzed formula since birth, hospital discharge at 43 days of life. No persistent enteral symptoms.
- Adecuate weight gain.
- His genetic testing showed patient 1's same variant.
- He successfully received bone marrow transplant at 3 months old.

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	Inheritance	HGVS description	Location: GRCh37 (hg19)	Classification
FOXP3	Hemizygous	Maternal	NM_014009.3: c.1282dup p.(Thr428fs)	ChrX:g.49107809dup	Likely pathogenic

Test methodology

Sanger sequencing of *FOXP3* exon 12 and the flanking intronic regions to test for the familial variant (NM_014009.3).

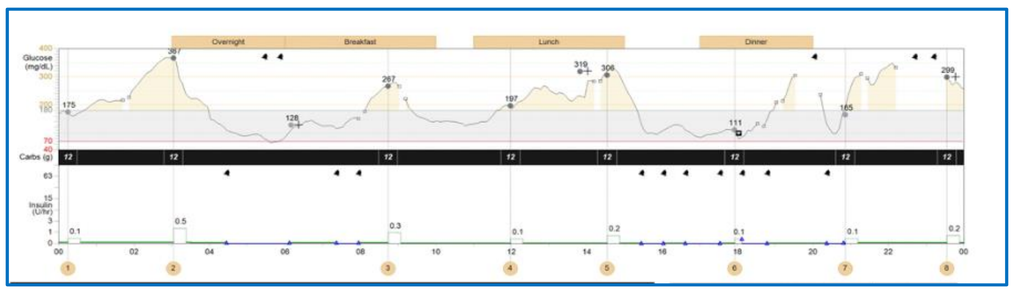
Test methodology

Analysis of all coding regions and exon/intron boundaries of the *FOXP3* gene (NM_014009.3) by Sanger sequencing.

Result:	Hemizygous likely disease-causing variant identified
Variant details:	Gene : *FOXP3* Location : Exon 12 DNA Description : c.1282dup Protein Description : p.(Thr428fs) Consequence : Stop Loss

Interpretation

[redacted] is hemizygous for a *FOXP3* stop loss variant, p.(Thr428fs). Current evidence suggests that this variant is likely to be pathogenic (see Appendix 1) and this result is consistent with a diagnosis of IPEX syndrome.



Conclusion: Distinctive manifestations have been described in two siblings with neonatal diabetes as first diagnosis with a novel variant in FOXP3's Sanger sequence. Their mother is the carrier of the X-linked mutation.

References:

- ACMG guidelines. Richards et al. 2015. Genet Med.
- Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. Hattersley et al. 2009. Diabetes Care.
- Long term follow up of patients with IPEX syndrome after different therapeutic strategies. Bacchetta et al. 2018. J Allergy Clin Immunol.