Inborn Errors of Immunity: Discovery of novel variants and genes involved in their development

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Introduction

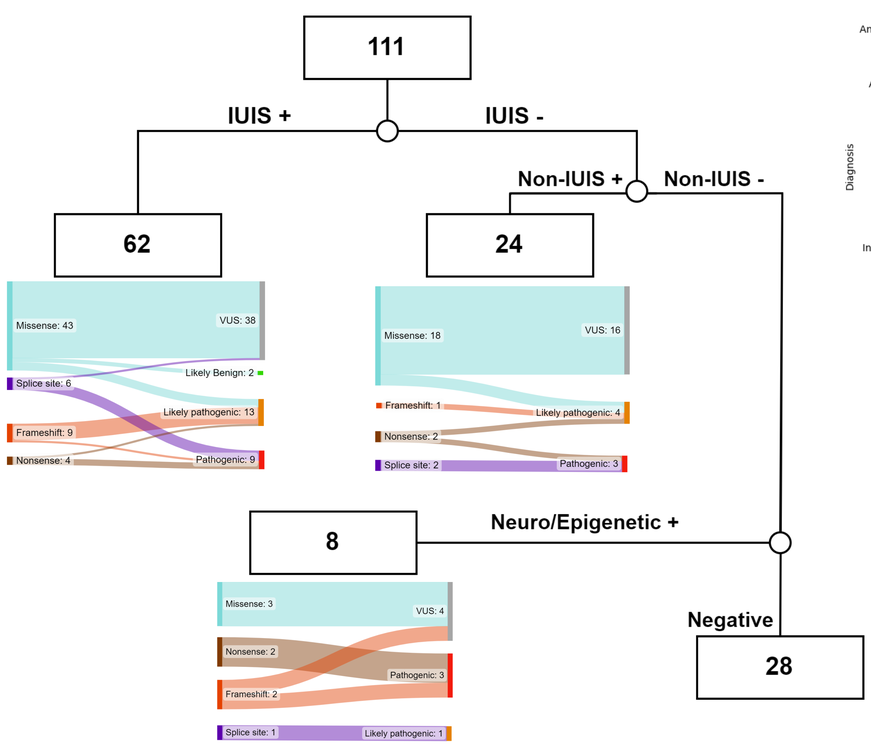
Patients with Inborn Errors of Immunity have monogenic defects that lead to immune system dysregulation phenotypes. Advances in molecular genetics and the use of next-generation sequencing, have led to the identification of an increasing number of IEI associated genes, although molecular diagnosis is complex.

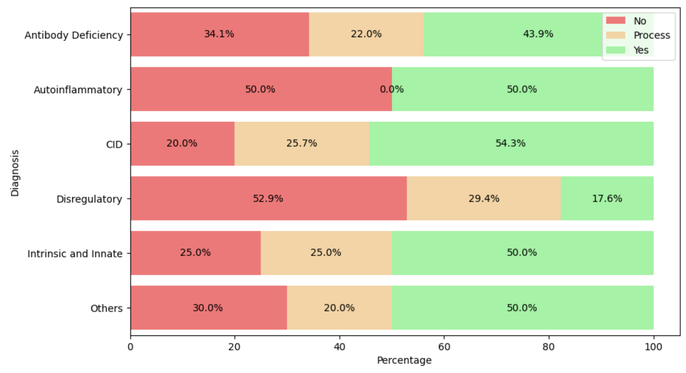
The overall objective of this study is to improve the genetic diagnosis of patients with IEI through comprehensive analysis of exome data performed by our laboratory.

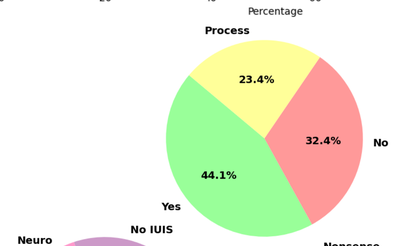
In collaboration with AINCA, we conducted massive sequencing on 111 index cases of Argentine patients with IEI and neurological manifestations.

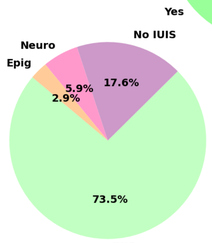
Bioinformatic analysis of the exome data was performed (fastQ processing, variant prioritization, and association with clinical phenotype).

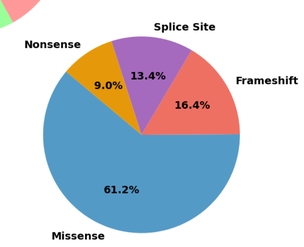
Results











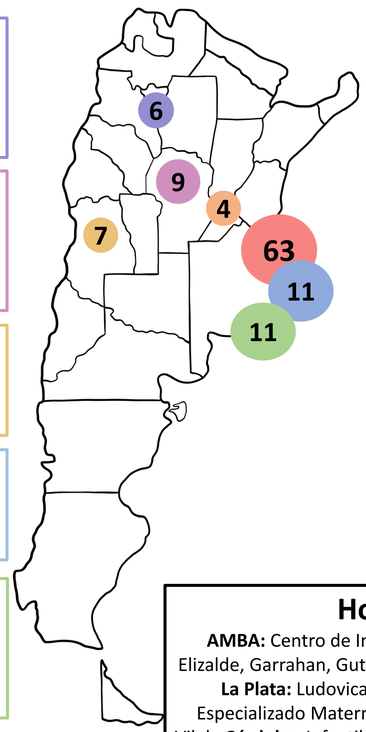
Tucumán
TNFRSF13B, PTCH1, NEK4, NLRP3, MSH2, TFEB, STXBP3, TFRC

Córdoba
RUNX1, MECP2, IKBKB, GATA2, ATAD3A, TBX1, MST1, RELA

Mendoza
SOS1, DNMT3A, NBN, AICDA, UNC119

La Plata
JAK3, CREBBP, NFE2L2, RFXANK, ASXL3

Mar del Plata
STAT3, CARMIL2, IFIH1, NLRP1, TNFRSF13B, RET, MAN2B2



Rosario
TNFRSF13B, CREBBP, RAG1, TLR3, MRE11

AMBA
NBEA, CD96, MAGT1, BCL11B, LRBA, AFF2, TNFRSF13B, CFTR, NOTCH2, MRE11, IKZF2, TCF3, IL2RG, IKZF2, MED13L, IL7R, CHD7, BLM, NLRC4, ADAMTS13, CD40LG, JAK1, STXBP2, ERBIN, PROC, ANKRD11, PIK3CD, SIAE, IL10RA, SATB1, ARHGAP31, TCF3, ATP1A1, CREBBP

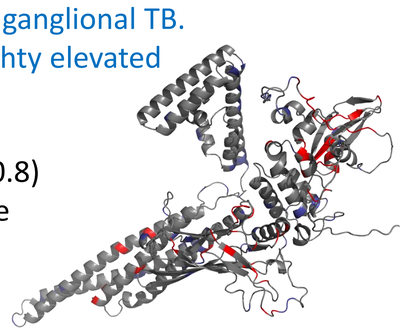
Hospitals
AMBA: Centro de Inmunología Clínica, Durand, Elizalde, Garrahan, Gutiérrez, Italiano, Muñiz, Posadas **La Plata:** Ludovica **Mar del Plata:** Interzonal Especializado Materno Infantil **Santa Fe:** de Niños Vilela **Córdoba:** Infantil Municipal y de Niños Santísima Trinidad **Mendoza:** Notti, Fleming **Tucumán:** del Niño Jesús

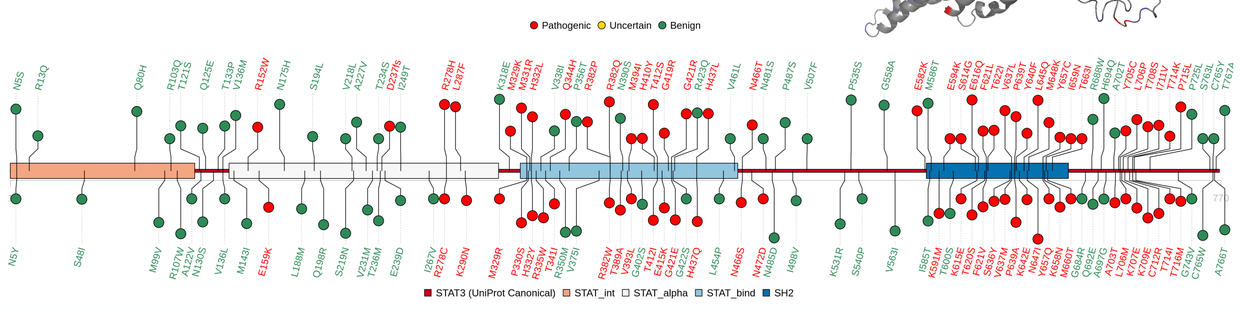
Clinic Case I (MDP01)

Gene	Chromosomic Position	Variant (Type)	Predictor	ACMG	Classification	Frequency
STAT3	17:42337858 C>G	Splice Site (FrameShift)	AL 0.99 -1bp AG 0.47 -10 bp	PVS1 PM2_Supp	Likely Pathogenic (0.949)	--

MH: 13 y.o. Female. Disseminated, cavitated and ganglional TB.
TH17 0.32% Lymphopenia T CD8>CD4. Ig-E slighty elevated

Gene:
Highly conserved exon 7/24 (0.8)
Circular RNA exon candidate
pLI = 1

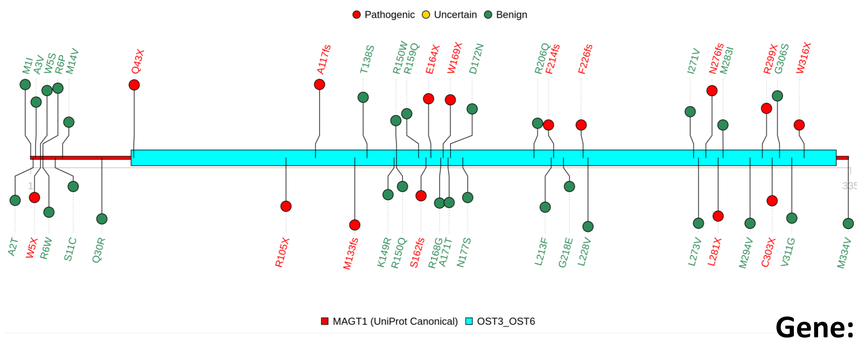


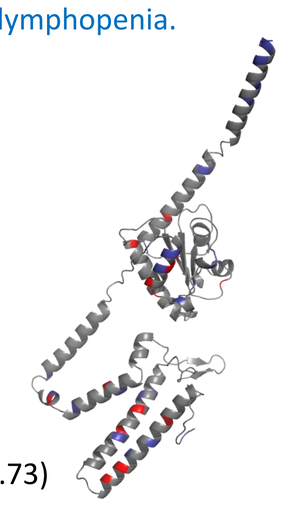


Clinic Case II (CIC03)

Gene	Chromosomic Position	Variant (Type)	ACMG	Classification	Frequency
MAGT1	X:77857419 G>GT	p.Gln189fs (FrameShift)	PVS1 PM2_Supp	Likely Pathogenic (0.949)	--

MH: 12-y.o. Male. Developmental delay, recurrent infections. HLH secondary to EBV with CNS involvement. Hypogammaglobulinemia (IgG <2DE, absent IgM), T lymphopenia.





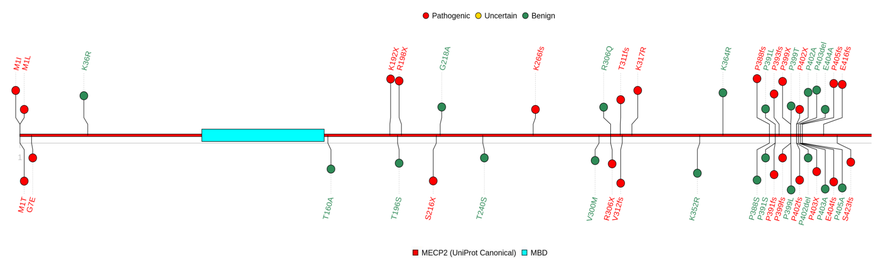
Gene:
Conservation FS (0.73)
pLI = 0.96

Clinic Case III (COR02)

Gene	Chromosomic Position	Variant (Type)	ACMG	Classification	Frequency
MECP2	X:154030627 TGGTGGGGTCCTCGGAGCTCTCGGGCTCAGGTGGAGGTGGGGGCA>T	p.Leu398fs (FrameShift)	PVS1 PM2_Supp	Likely Pathogenic (0.949)	--

MH: 3 y.o. Felmale. Mental retardation, Seizures. Erythema nodosum. Recurrent infections, lack of antibodies, lymphopenia cd8

Gene:
Conservation FS (0.76)
pLI = 0.89

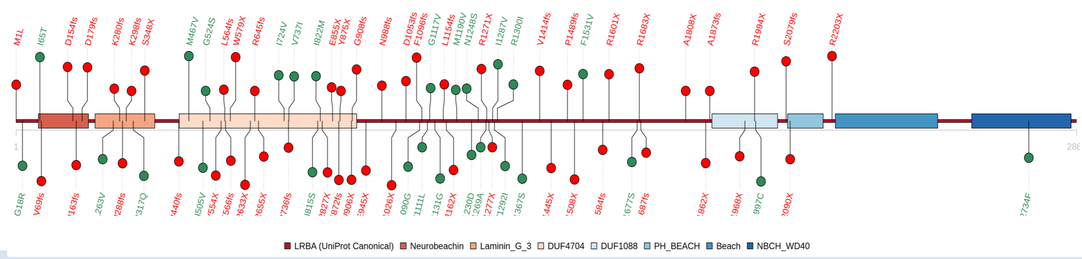


Clinic Case IV (DUR01)

Gene	Chromosomic Position	Variant (Type)	Prediction	ACMG	Classification	Frequency
LRBA	4:150761782 C>G	Splice Site	DL 1.00 (Intron retention)	PVS1 PM2_Supp	Likely Pathogenic (0.949)	--
LRBA	4:150828339 G>GA	p.Ser1671fs	Frameshift			

MH: 31 y.o. Female. Hypogammaglobulinemia, autoimmune cytopenia, sensorineural hearing loss

Gene: Inheritance model AR, pLI = 0



Conclusion

This work highlights the importance of an exhaustive analysis of candidate variants. Our findings further support the heterogeneity in monogenic defects of the immune system, emphasizing the non-redundant and fundamental functions of individual genes and proteins in the development and function of host defense.

Acknowledgments: to the patients and their families

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