May 08. 2020

Regional Rare Disease Diagnostic Programs

Cecilia Poli M.D. , Ph. D
Universidad del Desarrollo-Clínica Alemana
Santiago, Chile

Global Genomic Medicine Collaborative

Outline

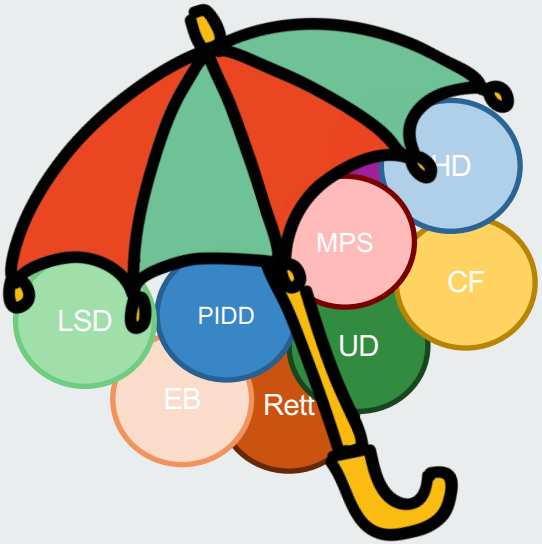
- Rare Diseases Programs in Latin America
- DECIPHERD: a multidisciplinary approach
- Immunodeficiency Cohort
- Discoveries and future directions

Rare Diseases Programs in Latin America

RD in Latin America (LA): Challenges and needs

- Newborn screening: Lack of universal NBS for metabolic diseases, primary immunodeficiencies, cystic fibrosis, spinal muscular atrophy among others. First Barrier to diagnosis.
- Diagnostic coverage: genetic testing is not covered in most of LA countries. Second barrier to diagnosis.
- Registries: include some individual or small groups of RD
- Pressing need to view RD as a larger entity to impact public policies for diagnosis and treatment.
- Patient organizations are invaluable drivers of progress in RD.
- Brazil has a Policy for the Integral Attention to Subjects with Rare Diseases, pending full implementation (Giuliani et al Orphanet JRD, 2016)

RD in Latin America (LA): Programs



- Diagnostic and treatment programs are focused on single RD (e.g. Gaucher, 22q11 microdeletion, mucopolysaccharidoses, immunodeficiencies.)
- Undiagnosed diseases need a systematic interdisciplinary approach (UDN, UDNI, NORD, etc.)
- Viewing RD as a larger entity will help assess real needs in terms of testing, coverage, and orphan drug necessities.

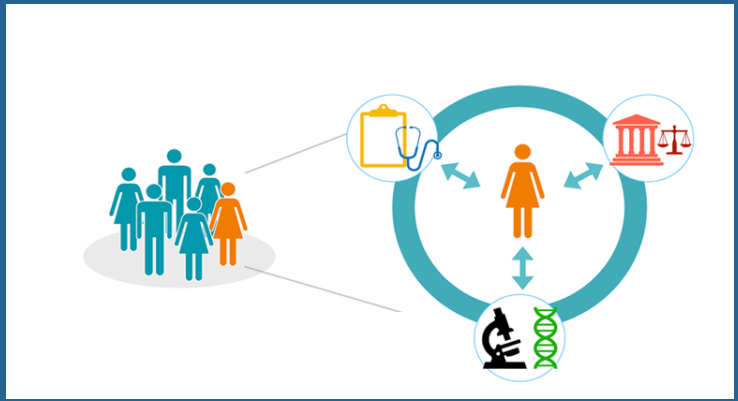
Rare Diseases in Chile

- Considering an estimated prevalence of 1/2000 and 7000 RD described, more than 1 million people can be affected by a RD in Chile.
- Diagnostic and governmental programs available for 20 RD, include screening and isolated treatments
- Lack of comprehensive coverage both for diagnosis and treatment
- NANEAS program for children offers an integrated approach for chronic management of children with complex diseases.
- Lack of integrated diagnosis and treatment programs.
- Diagnostic Odyssey is still a challenge, moreover for undiagnosed diseases.

Encina et al, Orphanet JRD 2019

DECIPHERD

An interdisciplinary research approach to rare and undiagnosed diseases (RUD)



Decoding Complex Inherited Phenotypes of Rare Disorders

- Provide an interdisciplinary approach to patients with RUD

  - Multidisciplinary clinical assessment

  - Unbiased genomic sequencing for diagnosis and discovery
  - Comprehensive bioinformatics, interdisciplinary variant interpretation

  - Mechanistic discovery and therapeutic target identification

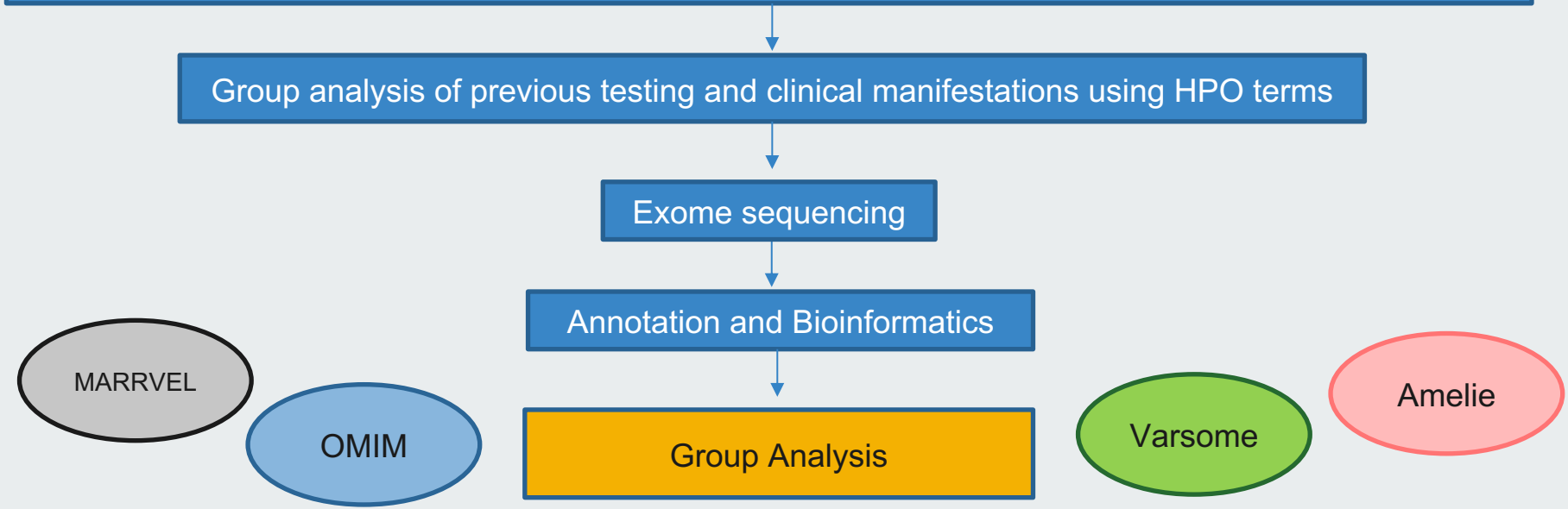
  - Promote public policies and regulatory aspects for RD.

DECIPHERD

Patients

1. Congenital anomalies with or without neurologic manifestations
2. Undiagnosed primary immunodeficiencies
3. Other RD of suspected Mendelian inheritance

No genetic underlying explanation after routine testing (specific panels, CMA, MLPA, karyotype)



DECIPHERD group 2019

2019-2020

- ≈ 60 families evaluated in collaboration with Baylor College of Medicine (Dr. J. Lupski)
- Incorporation of other national collaborating centers
- Added 4 new scientists
- Incorporated trainees to in different aspects of work and discussions
- Supported international training of team members

DECIPHERD

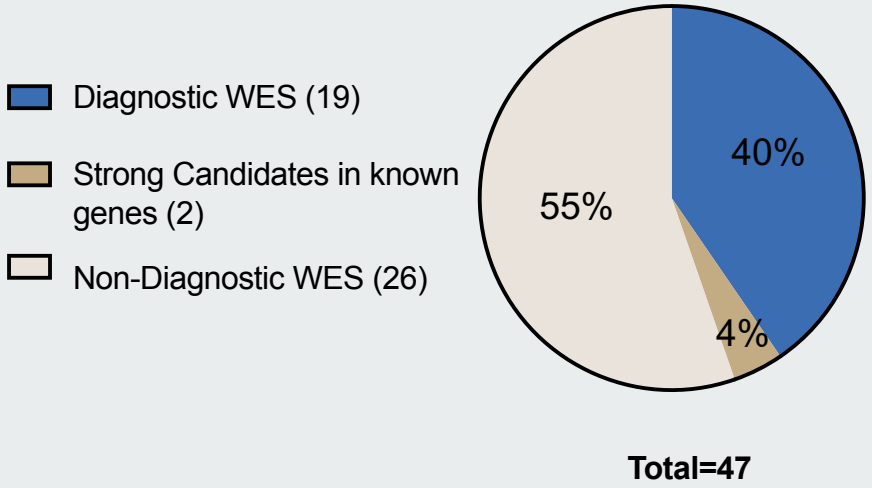
Challenges in a cohort with limited resources

- Clinical Exome (≈ 6,000 disease-associated genes) vs Whole exome (≈ 20,000 genes)
    - First 5 patients sequences with both approaches only 2/5 were diagnosed with CES, 3/5 had a diagnosis by WES.
    - Decided WES for patients with no suspected diagnoses or negative panel testing
- In-house annotation vs commercial software, both perform well for research purposes.
- Family trios vs proband testing: Proband testing as initial approach , parental DNA is saved for future testing.

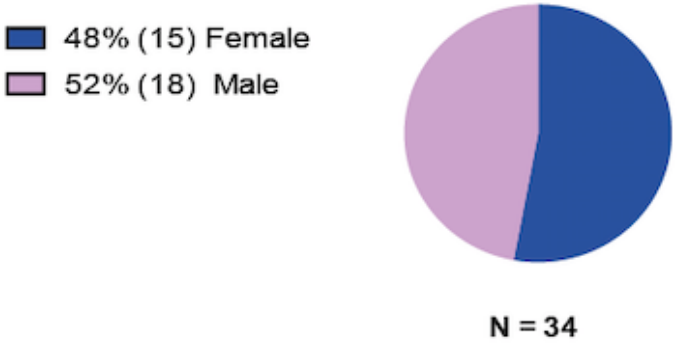
DECIPHERD Cohort

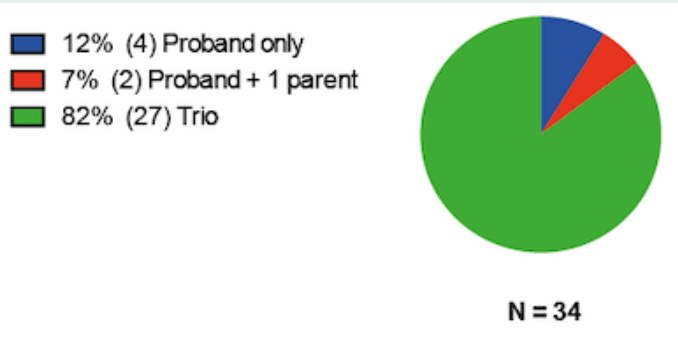
1. **Congenital Anomalies and ID: 24** WES in international labs
   Dg. 40% (19/47) in known genes
   2/47 Gene candidates

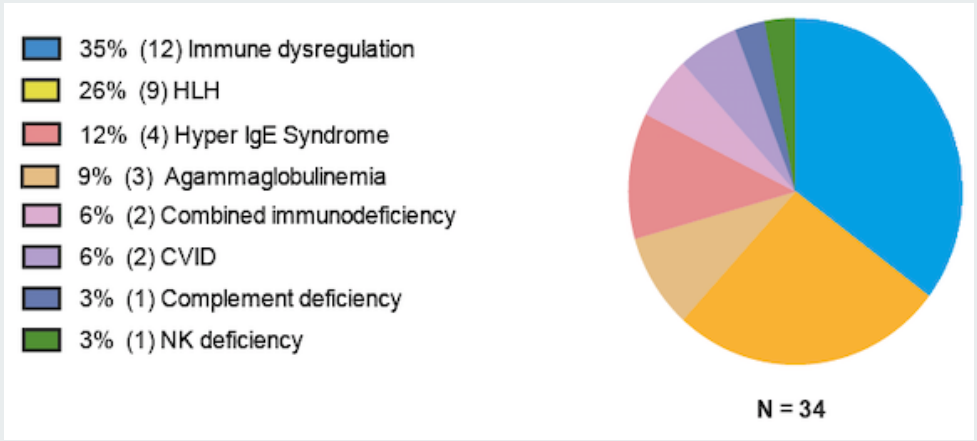
2. Inborn Errors of Immunity (PIDD)
   34 Families Trio WES analysis
(Collaboration Baylor College of Medicine).
   Dg. In known genes 20% (7/34)



Immunodeficiency cohort

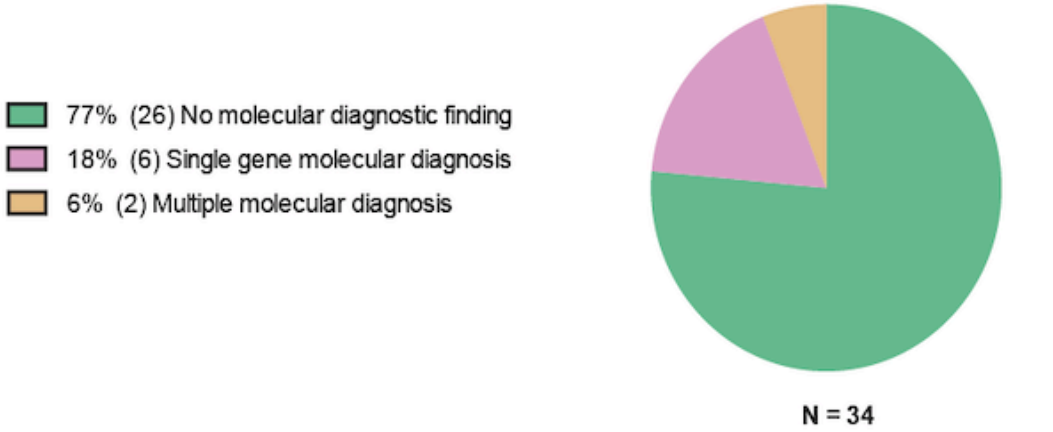






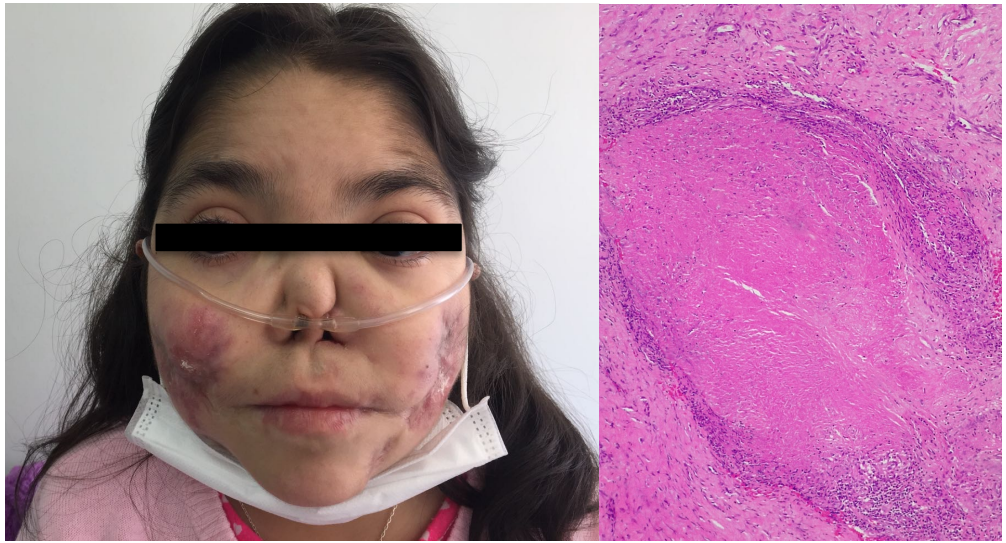
Rey-Jurado & Poli et al. Unpublished

Immunodeficiency cohort, the value of re-analysis

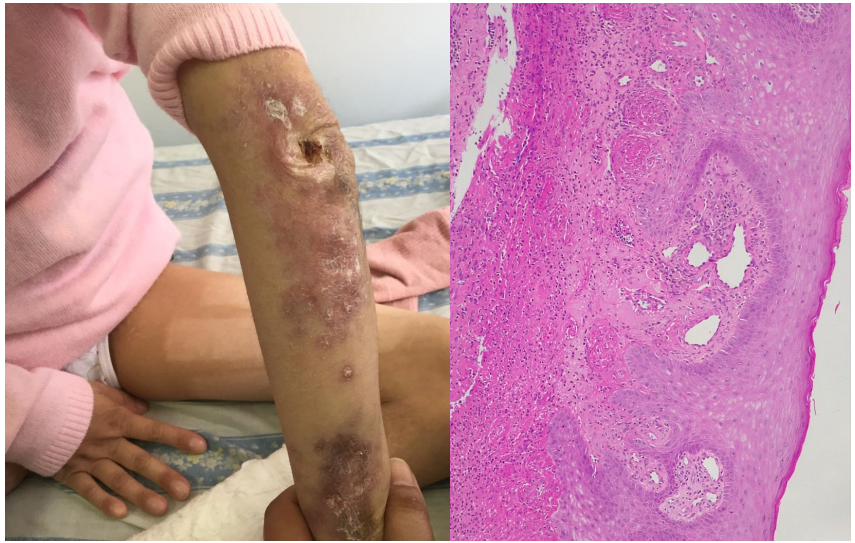


Rey-Jurado & Poli et al. Unpublished

Patient with recurrent infections and two distinct types of skin lesions



Chronic granulomatous necrotizing inflammatory process at the nose that compromised cartilage



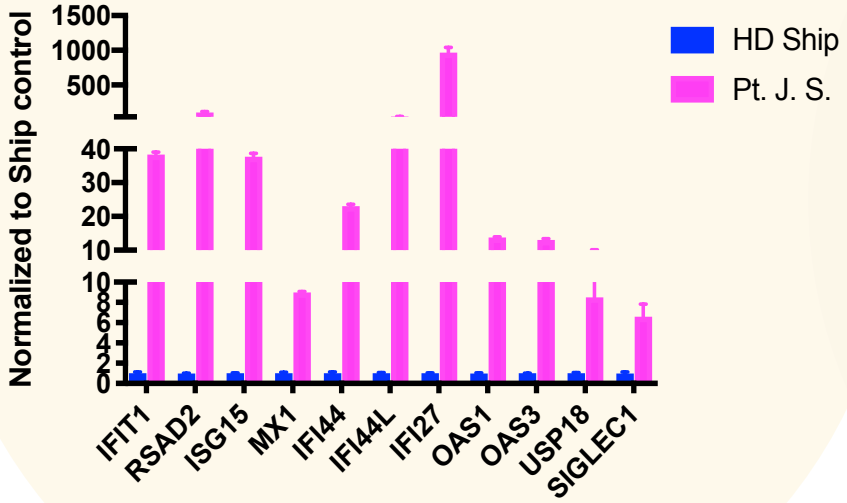
Inflammatory infiltrate with predominance of polymorphonuclear cells. Neutrophilic dermatosis

Two novel, likely pathogenic, homozygous variants in 2 different known IEI genes

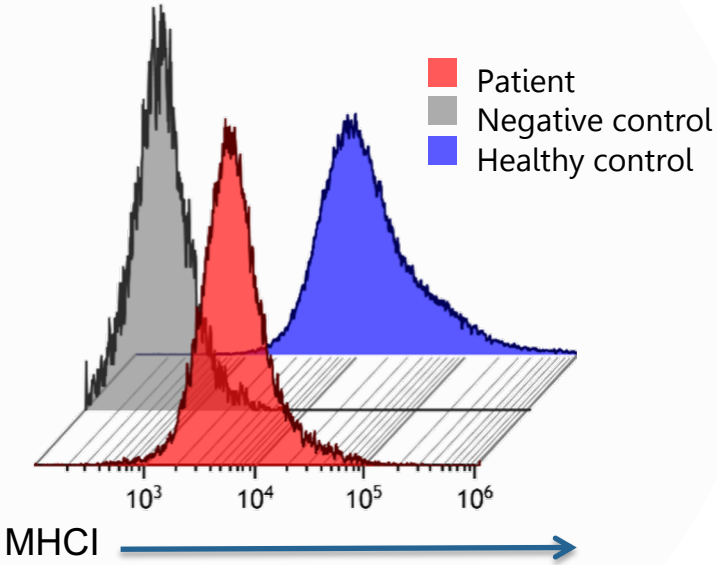
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)

Bare Lymphocyte Syndrome Type I (MHCI deficiency, necrotizing granulomas)

Autoinflammation

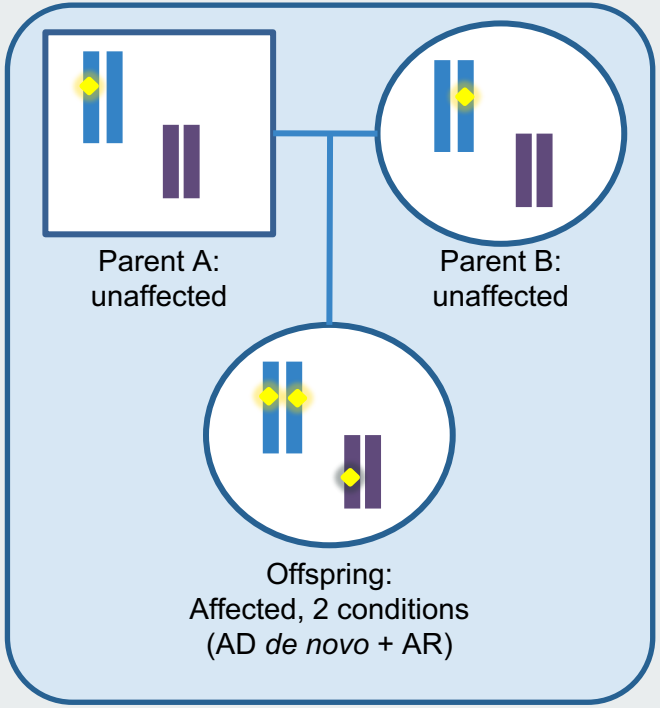


Immunodeficiency



Poli et al. Unpublished

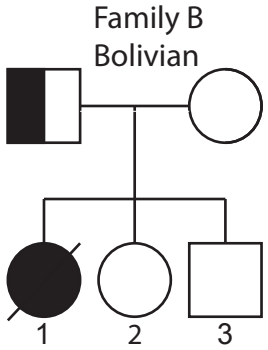
Multiple genetic diagnosis

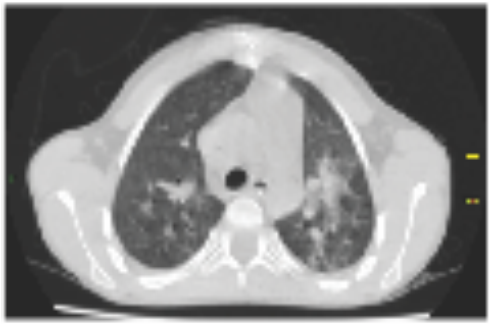


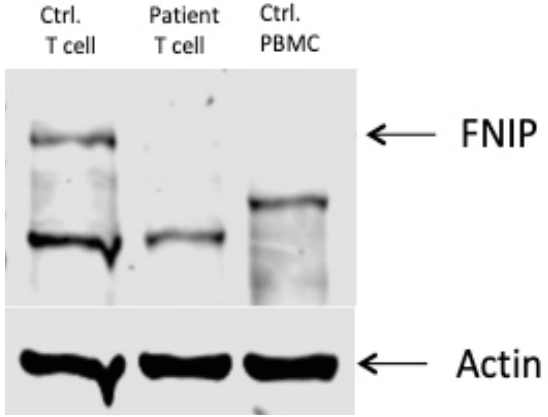
Posey et al, NEJM

Novel Gene Discovery

- Girl, inter-auricular communication (needed surgical correction) and mild hypertrophic cardiomyopathy, recurrent infections since 2 years of age, required bilateral lobectomy at 6 years of age
- Immunologic evaluation identified NO circulating B cells in periphery
- *fnip*$^{-/-}$ mouse model has heart defects and no B cells
- Exome sequencing identified a homozygous variant in *FNIP* (c.3306=1G>A)
- Genematcher helped connect with colleague in Italy and another one in the US who had two more patients with similar clinical and genetic findings.



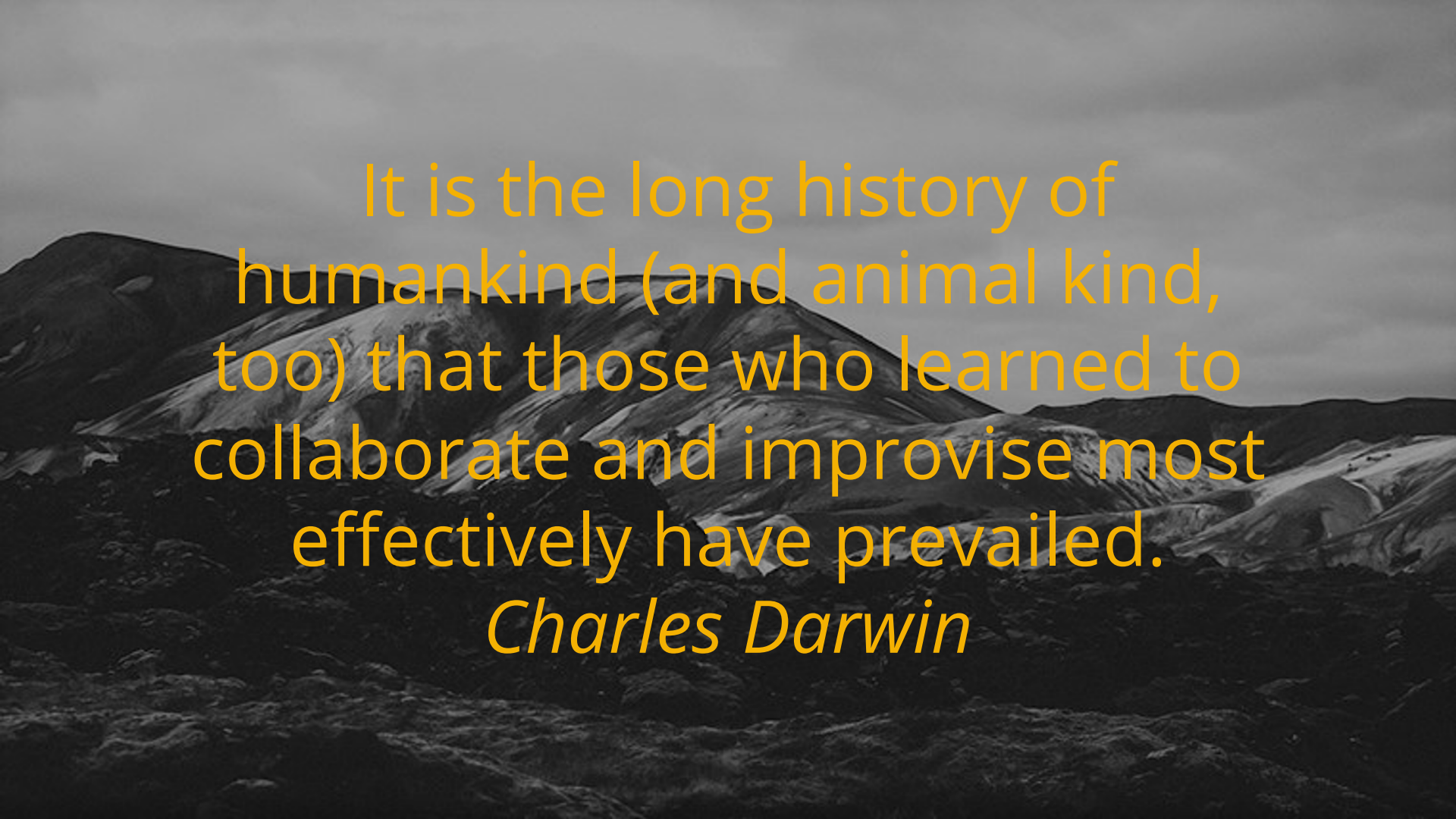




Saettini et al, submitted April 2020

Conclusions

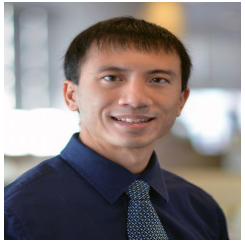
- Comprehensive programs for diagnosis and treatment of Rare diseases as a whole are greatly needed in Chile and LA
- Whole Exome sequencing and team based analysis is a powerful tool for diagnosis and discovery even in small countries with small cohorts
- Collaboration across the globe is crucial for discovery
- Functional studies are key to demonstrate pathogenicity of novel variants and genes
- Moving forward, implementation of a functional diagnostic pipeline is needed

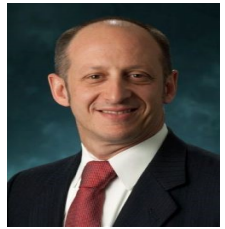

It is the long history of humankind (and animal kind, too) that those who learned to collaborate and improvise most effectively have prevailed.
Charles Darwin

Acknowledgements


James R. Lupski


Jennifer Posey


Ivan Chinn


Jordan Orange

INSTITUTO DE CIENCIAS E INNOVACIÓN EN MEDICINA
Facultad de Medicina
Clínica Alemana - Universidad del Desarrollo

DECIPHERD Team
Gabriela Repetto
Boris Rebolledo
Gonzalo Encina
Sofia Sifaqui
Luz Maria Martin
Esteban San Martin
Sara Fischer
Loreani Noguera
Ricardo Armisen
Marcelo Rojas

Program of Immunogenetics and Translational Immunology
Loreani Noguera
Emma Rey-Jurado
Flavio Carrión
Valentina Jarur
Camila Schmidt

FONDECYT
Fondo Nacional de Desarrollo Científico y Tecnológico

cpoli@udd.cl