The Young and the HOIP-less: Two siblings with autoinflammation and combined immunodeficiency due to autosomal recessive RNF31-loss of function

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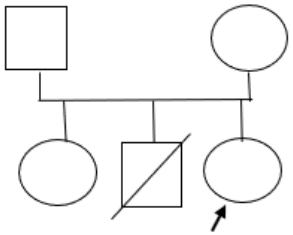
Introduction

- The linear ubiquitin chain assembly complex (LUBAC) plays crucial roles in immune NFkB signaling and cell death regulation.
- In the last five years, few patients have been described from consanguineous families.
- Phenotypes that include: myopathy, combined immune deficiency and autoinflammation.

Family History



Brother presented:

- HLH, regional BCG-itis
- Recurrent fever
- Hepatosplenomegaly
- Diarrhea
- High serum acute reactants
- Hyperleucocytosis
- Hypergamaglobulinemia

Whole Exome Sequencing Analysis

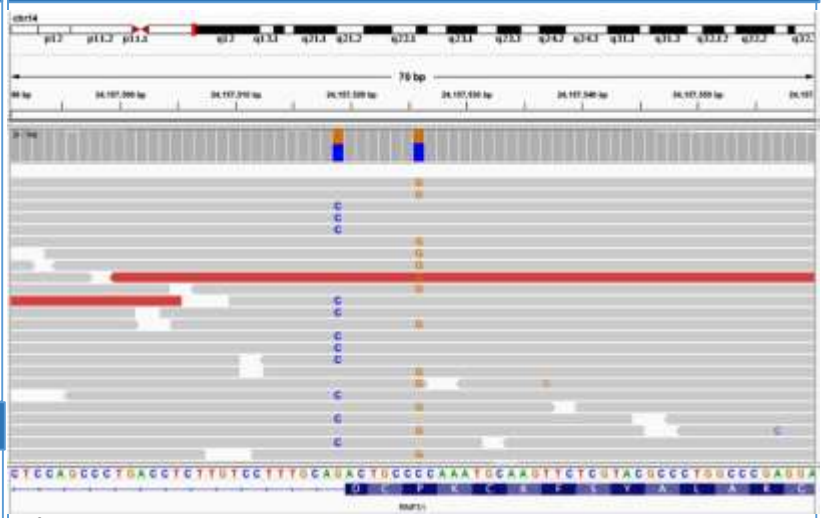


Fig. 1

Compound-heterozygous genotype in RNF31 (HOIP):

Splice-site transversion en intrón 15 (c.870-1C>G)

Missense transversion en exon 16 (c.2615C>G, p.Pro782Arg)

Case Presentation

1 month

- Suspected milk protein allergy
- Recurrent fever
- Diarrhea
- Eczema

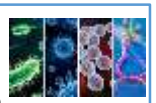
Recurrent infections:

- Gastrointestinal tract
- Respiratory tract
- Chronic hepatitis

Physical examination:

- Low weight
- Pallor
- Oral candidiasis
- Lymphadenopathies
- Hepatomegaly
- Diaper rash

Isolates:



- CMV
- *Klebsiella sp*
- *E. coli*
- *Giardia lamblia*
- *S.haemolyticus*
- *Aspergillus*

Blood tests

- Anemia
- Leukocytosis
- Neutrophilia
- Eosinophilia
- Monocytosis
- Thrombocytosis
- ↑ Serum acute reactants

Immunological tests

- IgG, IgM, IgA — High
- IgE, IgD — Normal

- LTCD3+
- LTCD8+
- LB
- NK
- LTCD4+

Others: Lymphoproliferation assays, perforin expression, DHR, serum complement, and extended metabolic screening were all normal.

Other comorbidities: Epilepsy, failure to thrive, renal tubular acidosis, exogenous Cushing syndrome, osteoporosis, and truncal obesity.
Treatament: Ig, colchicine, prednisolone, valganciclovir, trimethoprim/sulfamethoxazole and itraconazole, and levetiracetam.
HSCT was declined by her parents.

Discussion

- Part of the LUBAC complex, involved in NFkB signaling, inflammation and cell death regulation, HOIP deficiency has been described to cause a Combined/Autoinflammatory syndrome.
- Our patient and her dead brother are, to our knowledge, the third and fourth patients identified with HOIP-LOF, expanding the clinical phenotype.