

PI4KA-RELATED DISORDER

Genetic explanation of a complex phenotype between autoinflammation and autoimmunity? – A case report –

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Background:

PI4KA-related disorder is a clinically variable condition with neurological dysfunction, gastrointestinal manifestations and immunodeficiency. A 17-year-old male with a history of spastic paraplegia, developmental delay, and recurrent fever presented with systemic inflammation, polyarthritis, and autoimmune symptoms. Genetic testing identified biallelic variants in the *PI4KA* gene.

Case report:

- ✓ 1 year of life: Progressive spastic paraplegia, epilepsy and developmental delay
- ✓ 17 years: hospitalized with fever and pleuropneumonia, after discharge he presented polyarthritis, chilblain-lesions of the fingers
- ✓ Signs of systemic inflammation (CRP 120 mg/l, ferritin 500 µg/l, calprotectin 95 mg/l), lymphopenia, complement deficiency, elevated antibody profile (ANA 1:10.240, dsDNA and anti-Sm highly positive), strong interferon signature.
- ✓ Exome sequencing identified two biallelic variants of uncertain significance (VUS) in *PI4KA* encoding phosphatidylinositol 4-kinase.
- ✓ *PI4KA* synthesizes phosphatidylinositol 4-phosphate, an integral lipid of Golgi membranes required for membrane trafficking and signal transduction [1,2].
- ✓ Antibiotic and immunosuppressive therapy (prednisolone, methotrexate, anakinra) resulted only in partial improvement.
- ✓ Inflammatory markers (CRP, Ferritin) remained elevated with a fluctuated clinical picture - especially during steroid tapering.
- ✓ A therapeutic trial with JAK inhibition (baricitinib) was initiated due to clinical similarities with type I interferonopathies and systemic lupus erythematosus without success [3,4].
- ✓ Tapering of steroids became possible after switch to canakinumab combined with methotrexate.
- ✓ Our patient differs from the typical immunologically manifestations described in *PI4KA*-related disorders (hypogammaglobulinemia, B-cell deficiency) and rather presents with features of autoinflammation and autoimmunity.

PI4KA - Phosphatidylinositol (PI) 4-Kinase

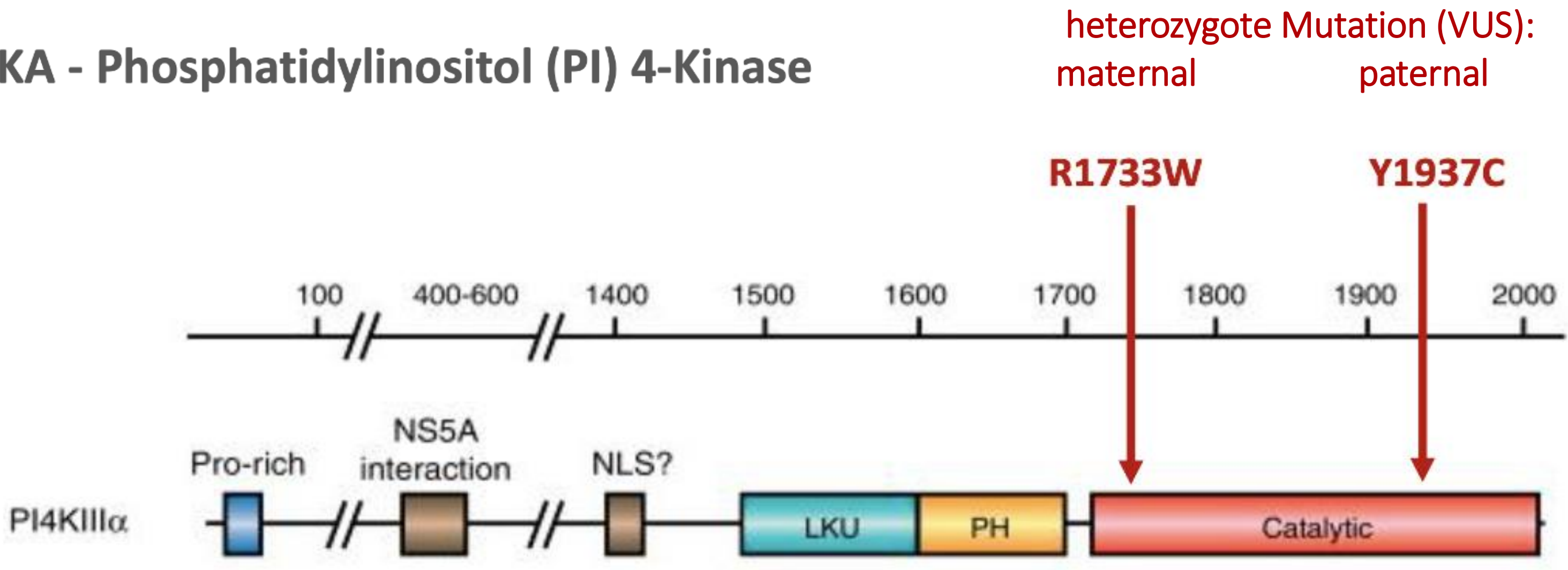


Fig. 1 Biallelic *PI4KA* mutation (chromosome 22)

Autoinflammation

- ✓ Pleuropneumonia
- ✓ Serositis (pleuritis, pericardial effusion)
- ✓ Transient Exanthema in fever, chilblain-like lesions of the fingers
- ✓ Polyarthritis (multiple fingers, wrist)
- ✓ Fatigue and fever
- ✓ Lab findings: mild anemia, leucopenia with lymphopenia
CRP up to 100 mg/l (in relapses 60 - 120 mg/l)
Ferritin 400 - 500 µg/l
Calprotectin i.p. max 95 mg/l (<2.7)

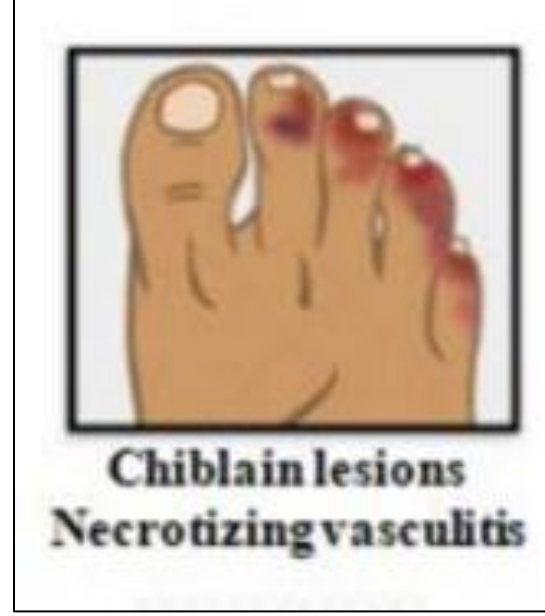
Autoimmunity

- ✓ ANA 1:10.240 (homogenous, fine-speckled)
- ✓ dsDNA high positiv (FIA and IIF)
- ✓ Smith-AB high positiv
- ✓ Nukleosomes high positiv (>200 U/ml)
- ✓ Complement deficiency low C3

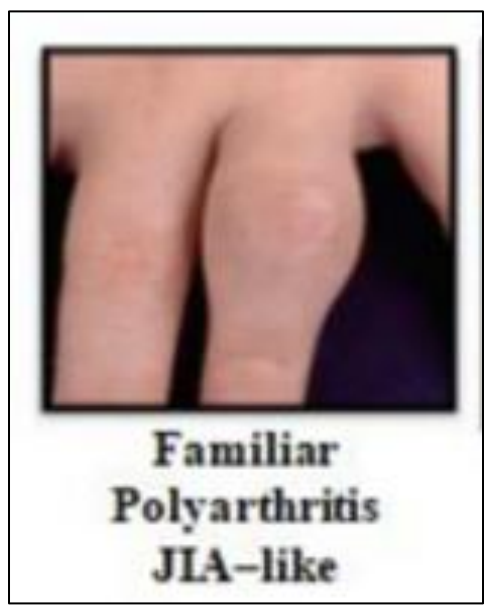
EULAR/ACR criteria for SLE: 25 points

Neurology

- ✓ Progressive spastic paraparesis and epilepsy (after 1st year of life)
- ✓ Developmental delay, intellectual disability
- ✓ MRI: generalized hypomyelination, hypoplasia of the corpus callosum
- ✓ Very strong interferon signature

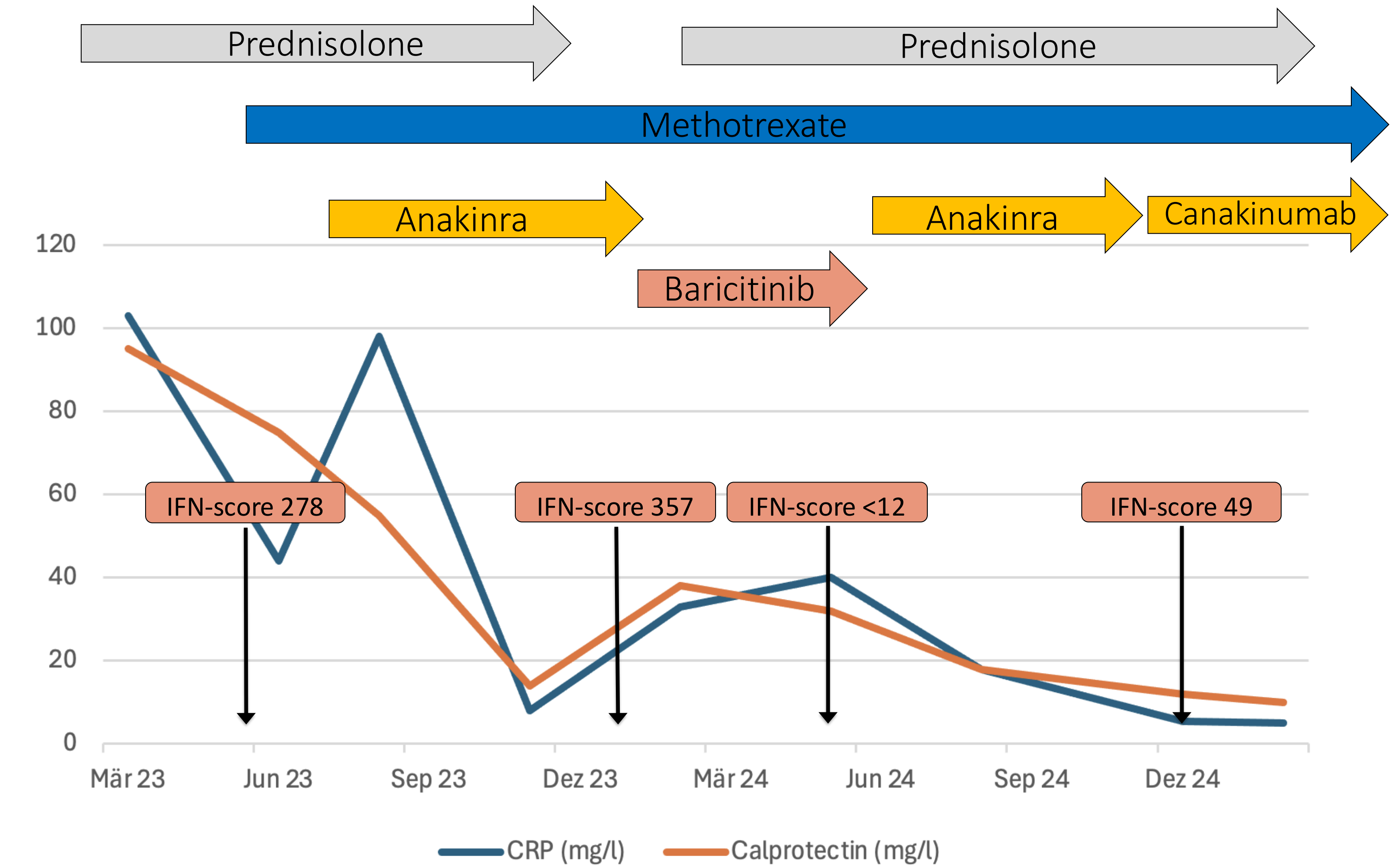


+



+

multiple SLE like-autoantibodies
diseases specific features



PI4KA-RELATED DISORDER

NEUROLOGICAL

- ✓ Manifestation 1st year
- ✓ Spastic paraparesis
- ✓ Epilepsy
- ✓ Developmental delay
- ✓ Ataxia, nystagmus
- ✓ MRI: hypomyelinating leukodystrophy

GASTROINTESTINAL:

- Chronic inflammatory bowel disease
- Multiple intestinal atresias

IMMUNOLOGICAL

- B-cell deficiency
- Hypogammaglobulinemia
- Recurrent infections
- ✓ Autoinflammation
- ✓ Autoimmunity, JIA
- hypothyroidism

✓ Criterias fulfilled by our patient

Conclusion:

This case highlights the importance of genetic testing in diagnosing rare complex disorders like *PI4KA*-related conditions. The identification of biallelic *PI4KA* variants provides a potential genetic explanation for the patient’s multi-systemic disease. Further functional analysis is necessary to determine the causality *PI4KA* VUS in disease pathogenesis and to derive improved treatment strategies.

Literatur

[1] Saettini F, Guerra F et al. Biallelic *PI4KA* Mutations Disrupt B-Cell Metabolism and Cause B-Cell Lymphopenia and Hypogammaglobulinemia. J Clin Immunol. 2025. [2] Salter CG, Cai Y et al. Biallelic *PI4KA* variants cause neurological, intestinal and immunological disease. Brain. 2021. [3] d’Angelo D, Di Filippo P et al. Type I Interferonopathies in Children: An Overview. Front Pediatr. 2021. [4] Aringer M, Costenbader K et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019.