

Mucopolysaccharidosis Type IX Mimicking Juvenile Idiopathic Arthritis: The Role of a Newly Identified HYAL1 Variant

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Introduction

- Juvenile Idiopathic Arthritis (JIA) is the most common type of arthritis in children under 16, presenting with symptoms such as joint effusions, restricted motion, and synovial inflammation.
- Diagnosing JIA can be challenging due to overlapping clinical features with other conditions, including rare genetic disorders like Mucopolysaccharidosis Type IX (MPS9).
- MPS9, a lysosomal storage disorder caused by a deficiency of hyaluronoglucosaminidase 1 (HYAL1), may mimic JIA with joint effusions, restricted mobility, and synovial irritation.
- Its rarity, with only four reported cases to date, contributes to misdiagnoses and delays in recognizing the underlying genetic cause.
- Goal:** Raise awareness about MPS9 as a differential diagnosis in refractory JIA cases and expand understanding of MPS9's genetic and clinical features.

Case Presentation

- Two siblings of Turkish descent, parents distantly related
- Symptom onset at age 3 and age 4
- Joint Involvement:** multiple large joints (Fig. 1A,B), joint effusions (Fig. 1C), restricted range of motion, and signs of synovial irritation
- Female sibling with fever and abdominal pain at disease onset
- Laboratory work-up: **no inflammatory parameters**, ANA-, RF-, HLA-B27-
- Initially misdiagnosed with JIA and treated with various immunosuppressive agents without clinical improvement
- Whole exome sequencing: **novel homozygous sequence variant in the HYAL1 gene** (c.676del p.Arg226ValfsTer7) in both siblings
- Variant is predicted to trigger nonsense-mediated decay and absent plasma hyaluronidase activity, consistent with **MPS9 cases**

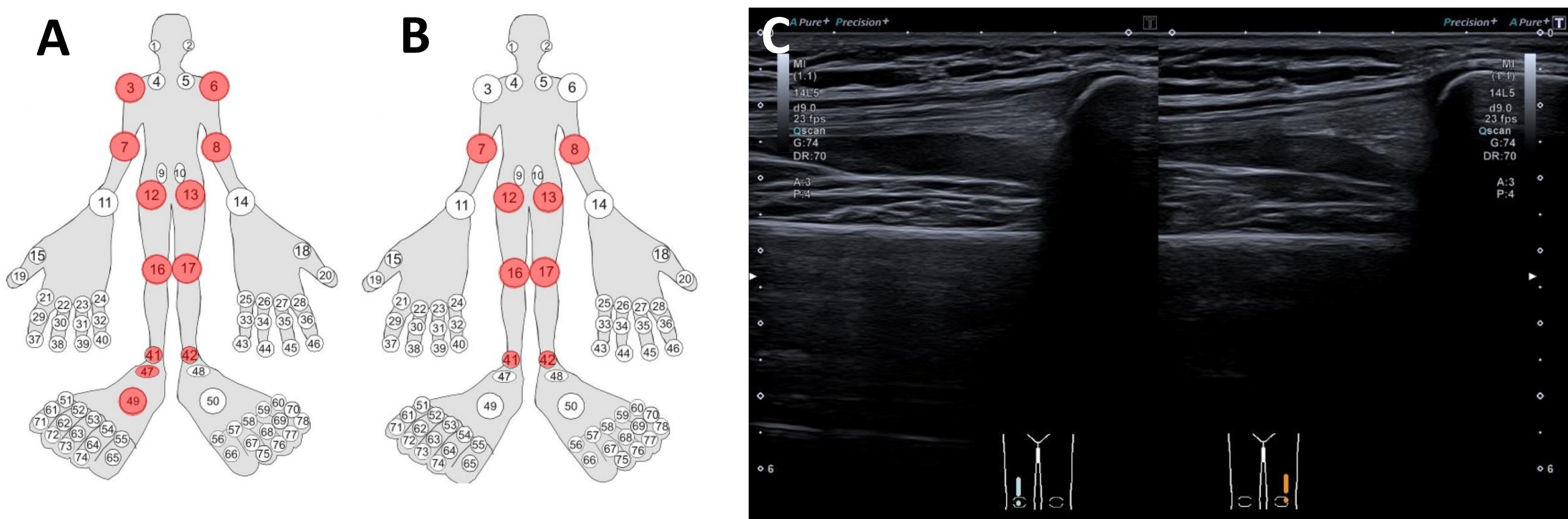


Figure 1. Joint involvement of patients. Ever affected joints of older sister (A) and younger brother (B) throughout disease is shown in red. (C) Ultrasound of both knees in female patient showing suprapatellar effusions.

Variant Type and Exon Distribution of Variants in HYAL1

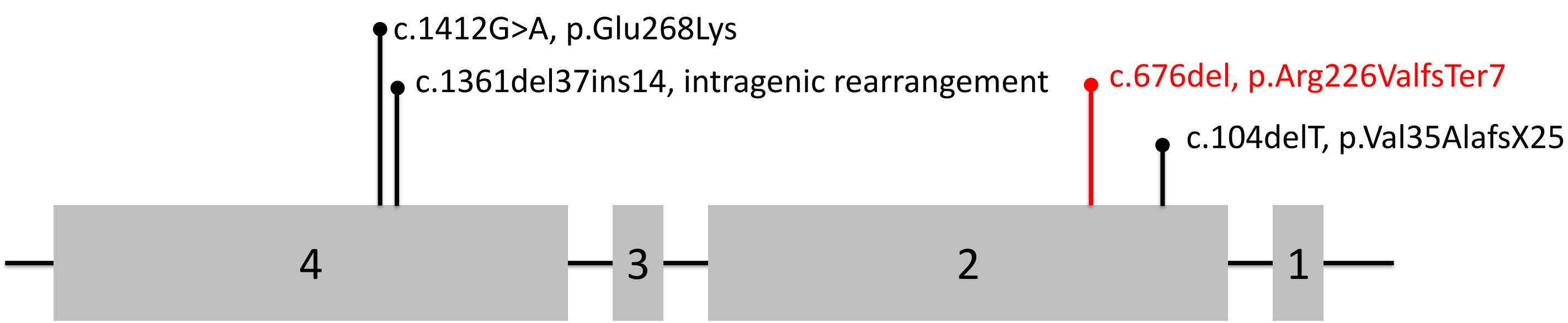


Figure 3. The HYAL1 (NM_033159.4, ENST00000395144.7) transcript is shown with numbered exons, grey boxes illustrate the coding sequence. The novel variant identified in these patients is shown in red and previously reported variants are presented in black.

Review of Reported MPS9 Cases

- To date, only **four cases** have been reported in the literature.
- Primarily affects **large and medium-sized joints**, with periarticular soft tissue changes, joint effusions, proliferative synovitis, popliteal cysts, chondral defects and, in one case, erosions.
- One patient exhibited **additional symptoms**, including short stature, fever, and dysmorphic features such as a cleft palate and bifid uvula.
- Symptom onset ranged from **6 months to 16 years**.
- Comparison to newly diagnosed cases: Although the clinical features were similar to previous MPS9 cases, our patients did not exhibit certain symptoms like proliferative synovial changes, popliteal cysts, chondral defects, dysmorphic features, or significant skeletal abnormalities.

Pedigree of the family: homozygous sequence variant in the HYAL1 gene inherited from both parents

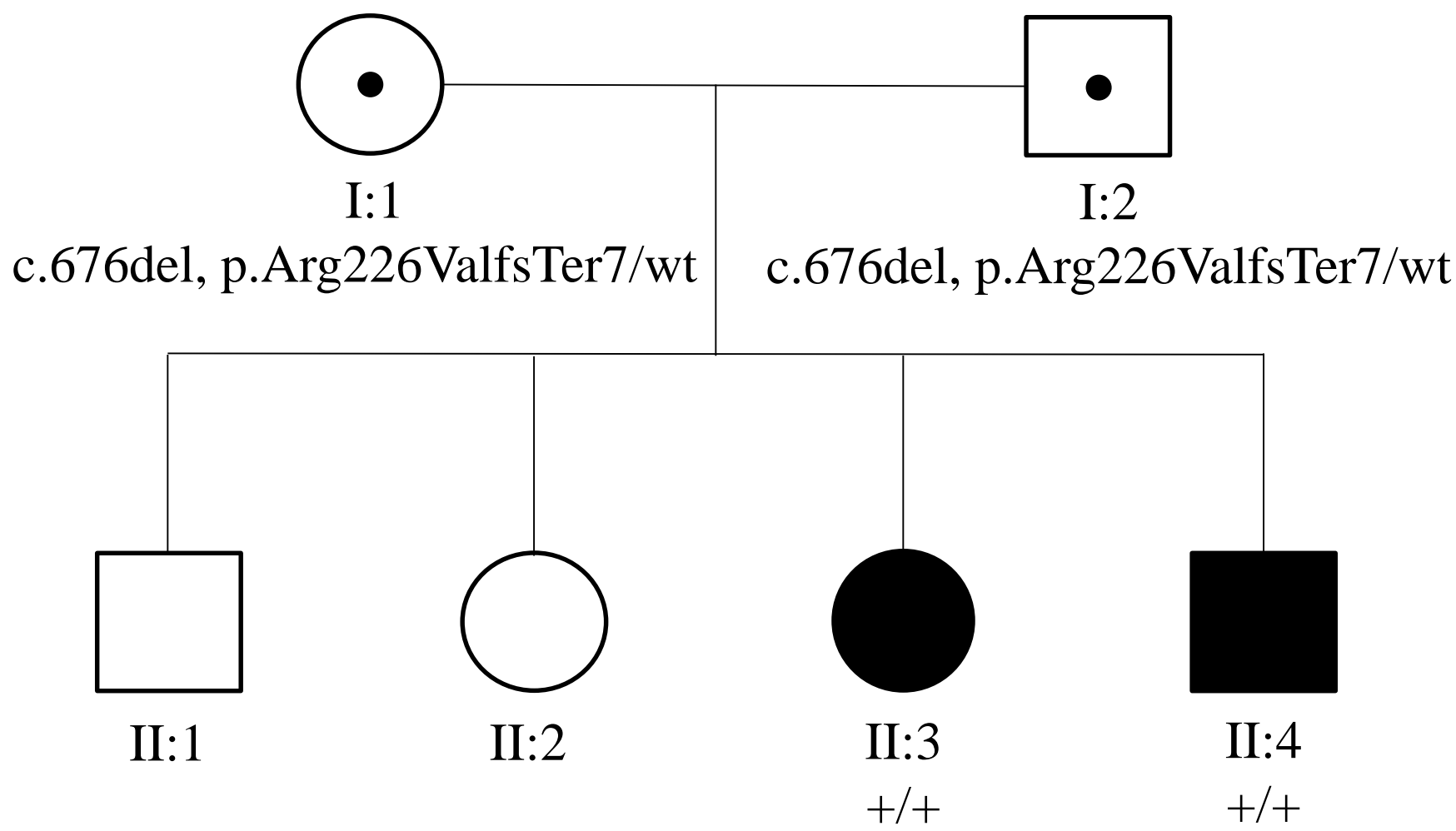


Figure 2. Black circle: affected female patient; black square: affected male patient; open square: unaffected males, open circle: unaffected female; black dots: carrier of the pathogenic variant.

Comparison of clinical features of MPS9 and JIA

Parameter	MPS9	non-systemic JIA
Age at onset of symptoms	6 m - 16 y	≤ 16 y
Family background	Middle East	all ethnic groups
Joints		
Pattern of joint involvement	peripheral joints	axial & peripheral joints
Limited range of motion	+	+/-
Effusion	+	+/-
Synovia: proliferative changes	+	+/-
Synovia: inflammatory changes	-	+/-
Laboratory findings		
Inflammatory markers elevated	-	+/-
Production of autoantibodies	-	+/-
Pathogenic variant in HYAL1	+	-
Therapy		
Response to immunotherapy	-	+

Discussion

- We report two siblings with **MPS9** who exhibited **involvement of multiple large joints**, including joint effusion and restricted range of motion.
- Their **clinical presentation resembled JIA**; however, treatment with immunosuppressive agents did not result in improvement.
- Genetic analysis revealed a **novel homozygous sequence variant in the HYAL1 gene** (c.676del p.Arg226ValfsTer7) in both siblings.
- MPS9 should be considered a **differential diagnosis for refractory JIA**, particularly in the absence of inflammatory signs and in families of Middle Eastern descent.
- Increased awareness of MPS9** among clinicians can enhance diagnostic accuracy and improve patient outcomes, underscoring the importance of genetic investigations in unexplained joint diseases.