Inflammatory arthritis as an atypical manifestation of Coffin-Siris syndrome linked to a novel *ARID1B* variant

Sir,

Nicolaides-Baraitser syndrome and Coffin-Siris syndrome (CSS) are distinct but overlapping syndromes characterised by dysmorphic features and a varied phenotype, including corpus callosum agenesis, short stature and other features (1-3). Both are caused by heterozygous variants in genes encoding components of the BAF chromatin remodelling complex, particularly ARID1A and ARID1B (1, 2, 4). These complexes regulate transcription, cell differentiation, and DNA repair. ARID1A and ARID1B are specific to the canonical BAF (cBAF) complex and function as mutually exclusive paralogs (4, 5). Disorders related to ARID1B follow an autosomal dominant inheritance with a haploinsufficient mechanism (6).

Previously, joint abnormalities in CSS were considered dysplastic rather than inflammatory, though a recent case described inflammatory arthritis in a young boy with ARID1B-related CSS (7). Additionally, one-third of children with CSS experience recurrent infections, though no confirmed immune deficiencies have been reported (6). We present a 51-year-old male with short stature and long-standing polyarthritis. Since age 28, he experienced arthritis affecting the elbows, metacarpophalangeal and proximal interphalangeal joints, knees, and ankles, accompanied by dactylitis. He had restricted neck mobility but no axial pain, psoriasis, or gastrointestinal symptoms. During follow-up, he required multiple arthrocenteses of the left knee and later developed secondary osteoarthritis and a right elbow flexion contracture.

Laboratory tests showed persistently elevated inflammatory markers, with CRP levels of 1.73-12.30 mg/dL (normal: 0-0.5 mg/dL) and ESR of 40-67 mm/h (0-15 mm/h). Imaging, including neck X-ray, sacroiliac joint CT, and upper GI series, was unremarkable. Brain MRI confirmed corpus callosum agenesis (Fig. 1A).

Immunologic evaluation revealed a reduced regulatory T-cell (Treg) count (Figs. 1B, 1C), and a T-cell receptor Vβ clone single clone expansion (Fig. 1D). Humoral immunity assessment showed increased IgM (709.40 mg/dL; normal: 40-230 mg/dL) with normal IgG and IgA. Specific IgG testing confirmed past vaccine responses except for pertussis and hepatitis A/B. ELISA cytokine profiling demonstrated elevated pro-inflammatory IL-6 (10.2 pg/mL; normal: 0-10 pg/mL) and IL-1β (9.7 pg/mL; normal: 0-5 pg/mL). The patient was treated with corticosteroids, methotrexate, tocilizumab, and infliximab but showed no significant improvement due to poor adherence.

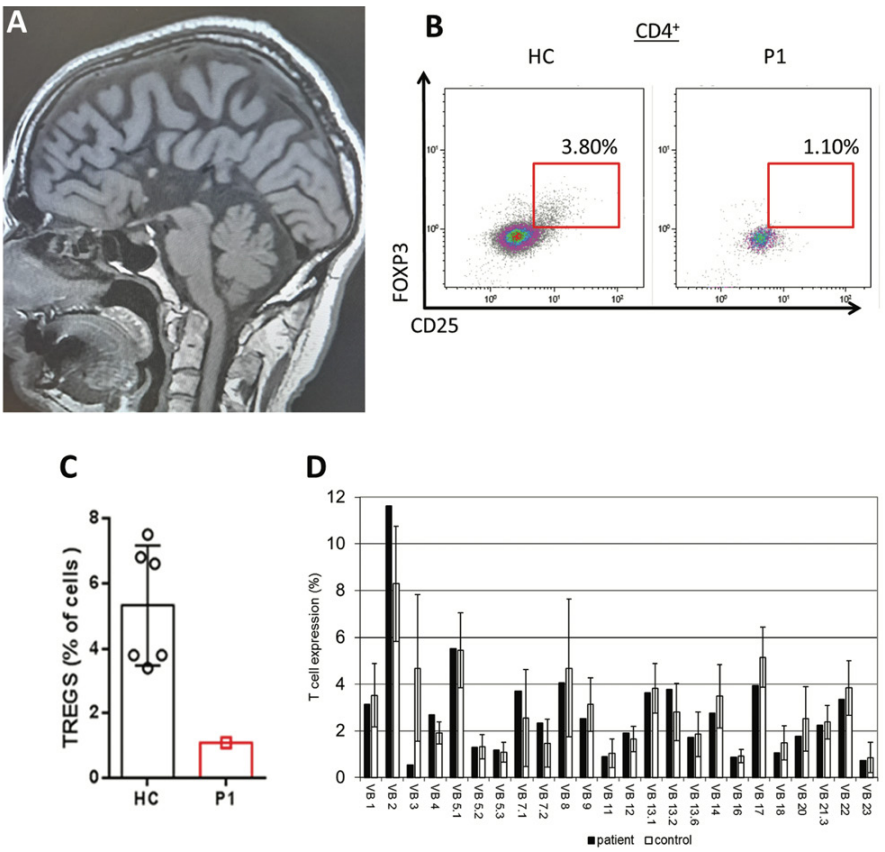

Fig. 1. Clinical and immunological characteristics of the patient.
A. Head magnetic resonance imaging (MRI) scan showing agenesis of the corpus callosum.
B. Peripheral blood mononuclear cells (PBMCs) were isolated from the patient and a healthy control, stained for CD4 and CD25, and followed by intra-nuclear staining for FOXP3. A flow cytometry density plot depicts the percentage of CD4+ CD25+ regulatory T cells (Tregs) in the patient and the healthy control.
C. Comparison of Treg percentages (as measured above) between the patient and six healthy controls.
D. T-cell receptor (TCR) V-beta repertoire analysis by flow cytometry of the patient and a pool of healthy controls. Notably, a single Vβ2 clone expansion is observed in the patient.

Given the findings of corpus callosum agenesis and chronic inflammatory arthritis, exome sequencing identified a novel heterozygous *ARID1B* variant (c.3826G>T, p.Glu1276Ter, exon 13; Fig. 2A). Parental testing was unavailable, leaving its *de novo* status uncertain. This nonsense mutation, classified as likely pathogenic, introduces a premature stop codon at position 1276, leading to a truncated ARID1B protein lacking the BAF250_C domain, critical for BAF complex integrity (Fig. 2B, C) (8-11). BAF complexes regulate gene expression and are essential for maintaining FOXP3$^+$ Tregs, which suppress excessive immune responses. The cBAF complex modulates TGF-β expression, with *ARID1A* variants impairing TGF-β signalling and reducing Tregs formation (13, 14). Loss-of-function *ARID1A* variants upregulate inflammatory genes, including IL-1β, IL-6, interferon-γ, chemokines, and IFN-stimulated genes, leading to enhanced chemotaxis, pyroptosis, and innate immune activation. ARID1B loss-of-function likely mirrors these effects by impairing TGF-β expression, reducing Tregs induction, and promoting inflammation (4). Unlike ARID1A, which primarily influences pBAF and ncBAF complexes, ARID1B's immunoregulatory role remains less defined (15).

ARID1A also influences germinal centre B-cell differentiation and antibody affinity maturation. ARID1A-deficient cells exhibit elevated surface IgM/IgD expression and efficient class-switching to IgG1 but generate lower-affinity IgM and IgG1 antibodies (4). While ARID1A has been extensively studied, ARID1B's precise contributions remain unclear.

In conclusion, our patient presented with chronic inflammatory arthritis, reduced Tregs, elevated IL-6 and IL-1β, persistently increased CRP and ESR, elevated IgM, and T-cell clonal expansion. Thus, our report highlights CSS as a plausible primary immune regulatory disorder. Further studies are necessary to elucidate ARID1B's role within the BAF complex and its impact on immune homeostasis.

This study was approved by Hadassah's institutional review board (No. 0059-24-HMO). The patient signed an informed consent for publication of this study.

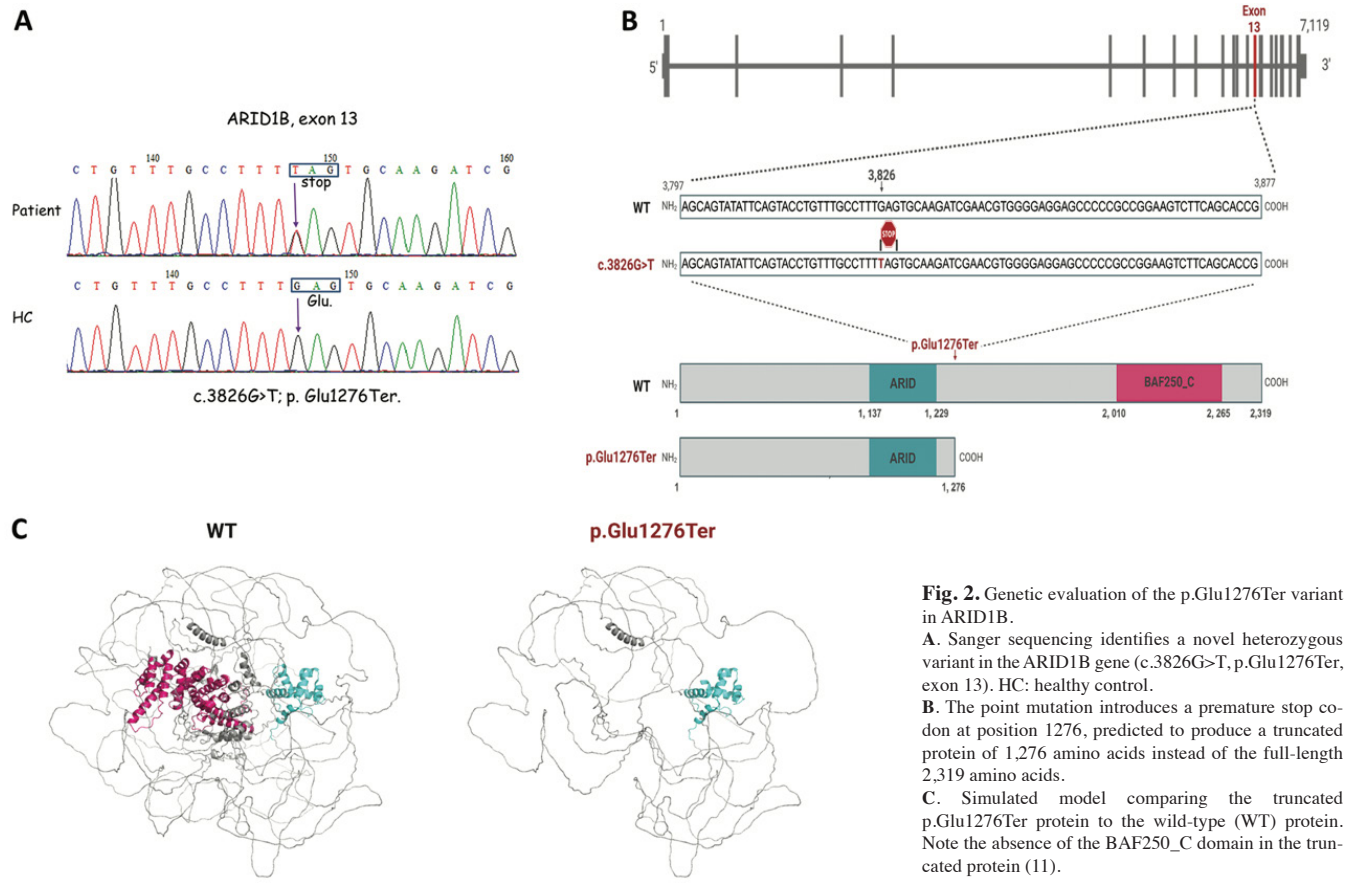

Fig. 2. Genetic evaluation of the p.Glu1276Ter variant in ARID1B.
A. Sanger sequencing identifies a novel heterozygous variant in the ARID1B gene (c.3826G>T, p.Glu1276Ter, exon 13). HC: healthy control.
B. The point mutation introduces a premature stop codon at position 1276, predicted to produce a truncated protein of 1,276 amino acids instead of the full-length 2,319 amino acids.
C. Simulated model comparing the truncated p.Glu1276Ter protein to the wild-type (WT) protein. Note the absence of the BAF250_C domain in the truncated protein (11).

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Competing interests: none declared.

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