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Familial Clustering of Juvenile Psoriatic Arthritis Associated with a Hemizygous *FOXP3* Mutation

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Abstract

Purpose of Review We describe the clinical and genetic findings in four patients from a single family who presented with refractory psoriatic arthritis and were hemizygous in the forkhead box protein 3 (*FOXP3*) gene (c.1222G>A).

Recent Findings We report four siblings with hemizygous mutation in the *FOXP3* gene (c.1222G>A) who presented with type 1 diabetes mellitus and psoriatic arthritis poorly responsive to treatment. Our findings expand the phenotype spectrum of *FOXP3* mutations.

Summary Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome is a rare disorder caused by mutations in *FOXP3* gene, which lead to early onset of constellation of autoimmune manifestations. This report highlights the influence of immune dysregulation in juvenile arthritis.

Keywords Juvenile arthritis · Psoriatic arthritis · Diabetes mellitus · Immune dysregulation · IPEX · Hemizygous *FOXP3*

Introduction

Juvenile idiopathic arthritis (JIA) is an autoimmune disease comprises a phenotypically heterogeneous group of disease subtypes including psoriatic arthritis which is characterized by the presence of arthritis and psoriasis or strong family history of psoriasis, which makes it distinct from other JIA subtypes [1]. It is widely accepted that autoimmune diseases are polygenic conditions of unknown etiology. However, a spectrum of autoimmune manifestations is linked to immune dysregulation disorders characterized by heterogeneous genetic defects, which illustrate the intersection of autoimmunity and immune dysregulation [2–4]. Affected individuals may exhibit overlap manifestations of the constellation of autoimmune diseases. Immune dysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) syndrome is a rare inherited disorder caused by defects in the forkhead box protein 3 (*FOXP3*) gene. Typically, IPEX patients present in the first year of life with intractable diarrhea, dermatitis, and type I diabetes mellitus (IDDM) [5–7•]. However, many atypical presentations have recently been reported, suggesting that IPEX incidence might be underestimated [5, 8]. This work shows the heterogeneity of phenotypic features of *FOXP3* gene mutation. Here, we describe the clinical and genetic findings in four patients from a single Jordanian family who presented with refractory psoriatic arthritis and IDDM and were hemizygous in the *FOXP3* gene (c.1222G>A).

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Methods

This study describes a case series of Arab patients with psoriatic arthritis and IDDM who underwent treatment and regular follow-up in the pediatric immunology and rheumatology clinics at Queen Rania Children Hospital, Amman, Jordan. Data were collected from the hospital medical records for demographic data, age at onset, clinical and laboratory findings, and response to treatment.

DNA was extracted from peripheral blood samples using standard procedures (Flexi Gene DNA Handbook, Qiagen). Samples were quantitated spectrophotometrically and stored at −20 °C. Molecular analysis using whole exome sequencing was performed on the index as described before [9••].

All family members were Sanger sequenced for *FOXP3*:NM_014009.3:c.1222G>A using a BigDye Terminator kit (Applied Biosystems, Foster City, CA) and run on an ABI 3730xl automated sequencer (Applied Biosystems, Foster City, CA). SeqScape v.2.6 software (Applied Biosystems, Foster City, CA) was used to align sequence data against the relevant reference.

Ethical Considerations

The data was part of a study conducted under the Declaration of Helsinki and approved by the Ethics committee of the Research Affairs Council (RAC) at KFSH-RC (RAC# 2020023). All the collected data resulted from routine medical assessment. All data were collected anonymously, and the confidentiality of the patients was protected. Informed consent for genetic testing as part of patient care was obtained from the parents at the time of blood extraction.

Results

Four patients were from a first-degree consanguineous Jordanian family; they were born with normal antenatal history, and the parents and one sibling were healthy. The family pedigree is illustrated in Fig. 1. The mean ± SD age at enrollment was 15.3 ± 2.9 (range 12 and 19 years), two patients had early onset disease, and the age at disease onset was 23.5 ± 32.4 months. Interestingly, none had enteropathy. All patients had arthritis affecting small and large joints; three of them had characteristic psoriasis. Additionally, three patients had IDDM. All had elevated erythrocyte sedimentation rate. All patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular and systemic glucocorticoids, and sequential conventional synthetic and biologic disease-modifying anti-rheumatic drugs (DMARDs). All included patients met the International League of Association for Rheumatology (ILAR) classification criteria for JIA, specifically psoriatic arthritis [1]. Here, we present the detailed clinical data of the index case and summarized the clinical presentation and laboratory investigations of all patients in Tables 1 and 2.

Index Case

A 19-year-old male presented at the age of 7 months with bilateral knee arthritis. There was no evidence of constitutional symptoms, eye or gastrointestinal manifestations. He was labeled as oligoarticular JIA. He was managed initially with NSAIDs and intra-articular glucocorticoids and short course of glucocorticoids but with partial improvement; thus, methotrexate was initiated. Few months later, he developed skin rash consistent with psoriasis. Accordingly, his diagnosis was modified to psoriatic arthritis. Interestingly, he had distant relatives from the maternal side with psoriasis. At the age of 10 years, he developed IDDM. Because the response was not optimal, as he experienced progressive arthritis and frequent cutaneous relapses, sequential conventional synthetic and biologic DMARDs were added. Unfortunately, remission was not achieved. He developed significant limitations of motion in multiple joints with contractures associated with guarded functional capacity. Imaging studies showed erosive arthritic changes with significant damage, mainly in the wrist and hip joints.

Further immunological assessment using flow cytometry showed normal CD4+, CD8+, and CD19+ cells percentage and coins in all patients. However, patient no.1 had absent NK cells. Unfortunately, flow cytometry analysis of Treg cells (CD4+CD25+FOXP3+ population) was not available in our institution.

Molecular Genetic Findings Whole exome sequencing of the index revealed a hemizygous mutation:*FOXP3*:NM_014009.3:c.1222G>A: p.V408M. The mutation was confirmed through bidirectional

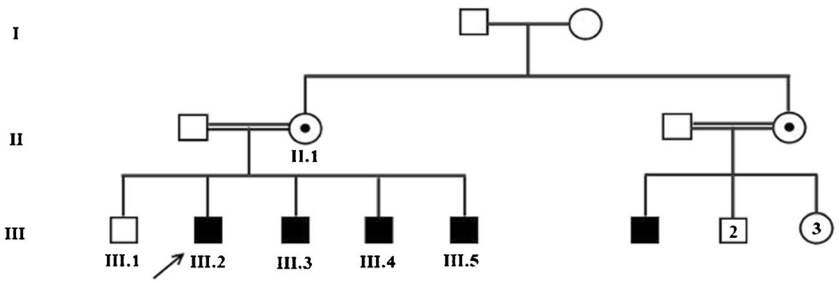

Fig. 1 Pedigree of a consanguineous family of four patients with psoriatic arthritis. All affected subjects (solid symbols)

Table 1 Summarized the clinical findings of four siblings with *FOXP3* mutation

	Patient I	Patient II	Patient III	Patient IV
Current age, years	19	14	16	12
Age at onset, months	7	72	60	9
Enteropathy	No	No	No	No
DM type I	Yes	Yes	Yes	No
Arthritis	Yes	Yes	Yes	Yes
Affected joints	Hips, knees, elbows, wrists	Knees	PIPs, MCPs, knees	PIPs, MCPs, elbows, knees
Psoriasis/nail pitting	Yes	No	Yes	Yes
Constitutional symptoms	No	No	No	No
Thyroid disease	No	No	No	No
Recurrent infection	No	No	No	No
Eye manifestations	No	No	No	No
Short stature	Yes	No	No	Yes
Medications	Corticosteroid, methotrexate, cyclosporine, infliximab, etanercept, adalimumab, etanercept, leflunomide	Corticosteroid, methotrexate, etanercept, adalimumab	Corticosteroid, methotrexate, leflunomide, cyclosporine, infliximab, etanercept, adalimumab, secukinumab, leflunomide	Corticosteroid, methotrexate, leflunomide, cyclosporine secukinumab

DM diabetes mellitus, *PIPs* proximal interphalangeal joints, *MCPs* metacarpophalangeal joints

Table 2 Summarized the laboratory findings of four siblings with *FOXP3* mutation

	Patient I	Patient II	Patient III	Patient IV
WBC (4.0–11.0 $\times 10^3$/uL)	14.6	7.2	11.8	13.7
Neutrophils (2–7 $\times 10^3$/uL)	11.8	4.8	6.6	10.4
Eosinophils (0.04–0.45 $\times 10^3$/uL)	379	680	259	822
Plat (140–450 $\times 10^3$/uL)	543	321	297	657
CRP (positive < 5 mg/dL)	6	Negative	Negative	8
ESR (≤15mm/hr)	38	60	15	91
Immunoglobulin levels				
IgG (723–1685 mg/dL)	1230	1656	1097	1054
IgM (62–277 mg/dL)	117	216	221	304
IgA (69–382 mg/dL)	122	317	102	178
TSH(0.45–4.5 IU/mL)	2.4	4.8	2.21	3.38
Free T4 (0.93–1.60 ng/dL)	1.5	1.55	1.21	1.13
$HbA1_C$ (4.9–6.2%)	8.7	9.2	7.7	4.9
TtG	Negative	Negative	Negative	Negative
ANA	Negative	Negative	1:80	Negative
RF	Negative	Negative	Negative	Negative
HLA-B27	Negative	Negative	Negative	Negative

WBC white cell count, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *TSH* thyroid stimulating hormone, *$HbA1_C$* hemoglobin $A1_C$, *TtG* Anti-tissue transglutaminase, *ANA* antinuclear antibody, *RF* rheumatoid factor, *HLA-B27* human leukocyte antigen B27

Sanger sequencing and segregated with the disease in the family (Fig. 2).

Discussion

Immune dysregulation syndromes are a group of hereditary illnesses characterized by a wide spectrum of inflammatory and autoimmune clinical phenotypes because of distinct genetic defects in immune regulatory pathways [10, 11]. Despite the paucity of these conditions, they are a growing subset of diseases and increasingly have gained attention and reported worldwide [4, 12, 13]. The frequency of autoimmunity was high among patients with immune dysregulation. IPEX has become a model of monogenic autoimmunity [14, 15••]. It is worth mentioning that the immune homeostasis necessitates intact regulatory T (Treg) cells that act to suppress the immune response and maintain self-immunologic tolerance. Of note, *FOXP3* is an essential factor with a great impact on the maturation and functional stability of Treg cells. Thus, *FOXP3* mutation can result in immune dysregulation status [6•, 16]. Typically, patients affected by IPEX syndrome experienced a triad of early onset of enteropathy and endocrinopathy and dermatitis; and it can be fatal [16]. However, many patients might present with mild disease and less frequent associated autoimmune manifestations such as autoimmune cytopenia, hepatitis, and nephropathy [7•, 14, 15••]. Here, we described four siblings presented with psoriatic arthritis and IDDM; the disease course was complicated with progressive arthritis with partial response to different DMARDs. Interestingly, none of them had evidence of enteropathy, which is a classic finding of IPEX. All patients shared hemizygous mutation in the *FOXP3* gene (c.1222G>A). Noticeably, the spectrum of genetically mediated immune dysregulation syndromes associated with arthritis is expanding, and the list of genes associated with juvenile arthritis has been steadily growing. However, the available data is a bit inconsistent [3, 17–20]. The exact etiopathogenesis of JIA is not well-defined. Moreover, the ILAR classification criteria for JIA are based on clinical features. Our patients have met the ILAR classification criteria for JIA. Despite that, familial aggregation of similar disease and the possibility of *FOXP3* gene contribution to their phenotype make it difficult to classify them as JIA. Notably, lack of functional data for the role of *FOXP3* in JIA necessitates that the mutation identified may not be a causative.

The rarity of IPEX syndrome may lead to delayed diagnosis and hence delayed the proper management. IPEX patients are usually treated with immunosuppressive drugs with inconstant success. Of note, our patients were initially managed with arthritis targeted; they received sequential conventional synthetic and biologic

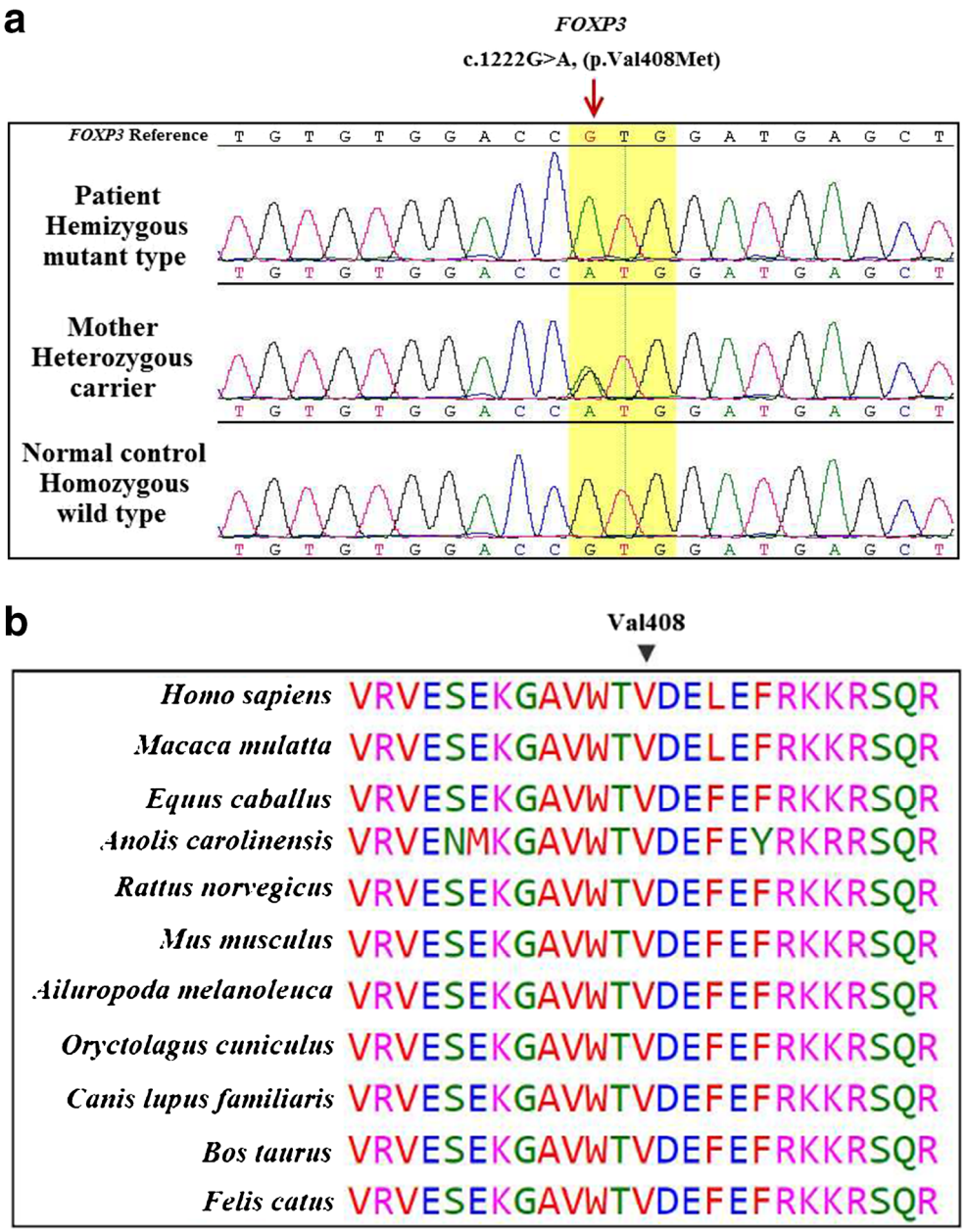

Fig. 2 **A** Sequence chromatogram showing the mutation c.1222G>A: p.V408M in *FOXP3*. **B** Evolutionary conservation of the glycine at position 1222 of *FOXP3*

DMARDs with guarded response. Off-label use of sirolimus in IPEX patients showed relevant clinical improvements [21]. However, its potential hyperglycemia may preclude its use in patients with IDDM like our patients. Recent study provided a comprehensive view of the outcomes of different therapeutic strategies of IPEX patients [22••]. The only potentially curative treatment for patients with IPEX syndrome is an allogenic hematopoietic stem cell transplant from a proper healthy donor [7, 23]. However, high risk-benefit ratio particularly in patients with mild phenotype may not justify this option.

Our study has limitations, and results should be interpreted carefully. Also, there are several gene defects that may present in IPEX-like disease forms. Nevertheless, verifying *FOXP3* mutation through bidirectional Sanger sequencing and segregated with the disease in the family indicates that *FOXP3* mutations might contribute to juvenile arthritis susceptibility. This should prompt the suspicion of an immune dysregulation in patients who present with a constellation of autoimmunity, especially in the presence of familial clustering and atypical disease course or unexpected therapeutic response to the treatment of the best available standard of practice.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Author Contribution All authors contributed to the study conception and design. Material preparation (H Maaitah, R Alzyoud, S Alansari), data collection (H Maaitah), and analysis (H AlDossari, D Monies, SM Al-Mayouf),The first draft of the manuscript was written by SM Al-Mayouf, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Ethics committee of the Research Affairs Council at KFSH-RC approved the study protocol.

Consent to Participate Informed consent for genetic testing as part of patient care was obtained from the parents at the time of blood extraction.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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