New or vanishing frontiers: LACC1-associated juvenile arthritis

Sulaiman M. Al-Mayouf a, b, *, Mada Yateem a, b, Haya Al-Dusery b, Dorota Monies b, Salma Wakil b, Manal AlShiakh b, Abdullatif AlEnazi c, Boshra Aladaileh d, Raed Alzyoud d, Brian Meyer b

a Department of Pediatric Rheumatology, Riyadh, Saudi Arabia
b King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
c King Fahad Medical City, Riyadh, Saudi Arabia
d Queen Rania Children Hospital, Amman, Jordan

ABSTRACT

Background: The classification and pathogenic basis of juvenile idiopathic arthritis (JIA) are a subject of some controversy. Essentially, JIA is an exclusion diagnosis that represents a phenotypically heterogeneous group of arthritis of unknown origin. Familial aggregation of JIA supports the concept of genetic influence in the pathogenesis of JIA.

Objective: To present the spectrum of laccase domain-containing 1 (LACC1)-associated juvenile arthritis with clinical, biochemical, and molecular genetic data of a cohort of 43 patients, including 11 previously unpublished cases.

Methods: We studied 11 patients with different categories of juvenile idiopathic arthritis from 5 consanguineous families, all from Saudi Arabia, except 2 patients who were of Jordanian ethnicity. Whole-exome sequencing was used to identify the disease-causing variant of LACC1. We also reviewed the clinical spectrum and molecular genetic data of previously published cases of LACC1-associated juvenile arthritis.

Results: This study describes 43 (29 females, 14 males) patients from consanguineous multiplex families. Most of the included patients were of Arab origin with 86% having early onset disease. The most frequent categories were systemic (19 patients) and rheumatoid factor-negative polyarticular (19 patients). Thirty-seven (86%) had progressive erosive arthritis and 10 (23.3%) had persistent limb lymphedema. None of the patients had features of macrophage activation syndrome. Genetic analysis confirmed LACC1 variant in all patients; 22 patients had common founder mutation (LACC1: c.850T>C.p.C284R), while the others showed different LACC1 variants. All patients were treated aggressively with methotrexate and sequential biologic agents. Most of them showed a poor response to treatment.

Conclusion: This report expands the pathogenic variants of LACC1 and the clinical spectrum associated with this genetic subset of juvenile arthritis. The predominance of autosomal-recessive inheritance and strong genetic evidence allowed us to propose LACC1-associated juvenile arthritis as a distinct disorder.

Article info

Article history:
Received 30 June 2020
Received in revised form 24 September 2020
Accepted 9 November 2020
Available online 12 November 2020

Keywords: Juvenile idiopathic arthritis Familial arthritis LACC1-associated juvenile arthritis Arthropathy

1. Introduction

To date, juvenile idiopathic arthritis (JIA) has largely been regarded as a polygenic disorder. The International League of...
categories regarding genetic and immunologic findings [6]. Since its first description in 2015, several clinical reports of siblings from consanguineous families with different subtypes of JIA have been linked to \textit{LACC1} variants, but there has been no comprehensive overview of the clinical spectrum and molecular genetic data [7–10].

Here, we present characteristics, including new clinical phenotypic features, laboratory, and molecular genetic findings of a large new cohort of patients with \textit{LACC1}-associated juvenile arthritis. We also review all published cases of \textit{LACC1}-associated juvenile arthritis.

2. Methods

The study cohort comprised patients with familial juvenile arthritis who underwent treatment and regular follow-up in the pediatric rheumatology clinics at King Faisal Specialist Hospital and Research Center (KFSH-RC), King Fahad Medical City, Riyadh, Saudi Arabia and Queen Rania Children Hospital, Amman, Jordan. Patients were from consanguineous families. All patients met the ILAR classification criteria for JIA. All patients were assessed for demographic features, age at first disease manifestation, clinical findings, and diagnostic evaluation. All patients underwent genetic testing.

2.1. Ethical considerations

The ethics committee of the Research Affairs Council at KFSH-RC approved the study protocol (RAC# 20200023). Further ethics approval for enrolling patients in the study was obtained from the participating centers as required by their institutional regulations. Full informed consent for genetic testing was obtained from parents at the time of blood extraction. The patient's enrollment was documented in the medical file according to institutional regulations.

2.2. Collection of data

We comprehensively reviewed all published cases of \textit{LACC1}-associated juvenile arthritis focusing on the spectrum of phenotypic characteristics and underlying genetic variants. All previously reported cases since 2015 were included and referenced [6–10].

3. Molecular genetic studies

3.1. Participants

A total of 5 unstudied consanguineous multiplex families with 11 patients were included in this study. All were collected through the participating centers between 2015 and 2019. All patients presented with juvenile arthritis although clinical presentation included a wide range of symptoms. DNA was extracted from peripheral blood samples using standard procedures (Flexi Gene DNA Handbook, Qiagen). Samples were quantitated spectrophotometrically and stored at –20 °C.

3.2. Whole exome sequencing and analysis

Briefly, 100 ng of each DNA was amplified in 12 separate wells using Exome Primer Pools, AmpliSeq Hifi mix (Thermo Fisher, Carlsbad, CA, USA) and 10 amplification cycles. All 12 PCR pools were combined in one well and subjected to primer digestion by incubation with FuPa reagent (Thermo Fisher, Carlsbad, CA, USA). Amplified exome targets were ligated with Ion P1 and Ion Xpress Barcode adapters. After purification, libraries were quantified using qPCR with the Ion Library Quantification Kit (Thermo Fisher, Carlsbad, CA, USA). The prepared exome library was further used for emulsion PCR on an Ion OneTouch System, and templated Ion Sphere particles were enriched using Ion OneTouch ES, both procedures following the manufacturer’s instructions (Thermo Fisher, Carlsbad, CA, USA). The template-positive Ion PI Ion Sphere particles were processed for sequencing on the Ion Proton instrument (Thermo Fisher, Carlsbad, CA, USA). Reads were mapped to UCSC hg19 (http://genome.ucsc.edu/), and variants were identified using the Saudi Human Genome Program (SHGP) pipeline [11].

4. Results

Collectively, including this study, only 43 patients (29 females, 14 males) with seven mutations of \textit{LACC1} were identified. The mean age of disease onset was 3.2 (SD± 1.8) years. Most of the patients were of Arab origin (22 Saudi, 3 Moroccan, 2 Jordanian, 2 Lebanese), 11 Turkish, and 3 were Indian. According to the ILAR classification criteria, the most frequent categories were systemic (19 patients) and rheumatoid factor (RF)-negative polyarticular (19 patients). There were two patients with RF-positive polyarticular, two patients with oligoarticular subtype, and one patient with enthesitis-related arthritis (ERA) [1]. The most common founder mutation (\textit{LACC1}:NM_001128303.2:c.850T>G;p.Cys284Arg) was identified in 51.2% (22/43) of patients. The clinical spectrum is shown in Table 1. Members of the same families generally shared an identical clinical spectrum related to a common \textit{LACC1} variants. However, high variability in the age of disease onset, clinical presentation, and disease category of arthritis was observed among siblings of 5 families (Family 8, 9, 11, 15, and 17).

The frequency of clinical and laboratory features, treatment administered, and outcomes are summarized in Table 2. Thirty-seven (86%) patients developed first disease manifestation prior to their second year, and most of the patients (93%) experienced a chronic disease course. No patient had features suggesting inflammatory bowel disease. All patients in the systemic category had fever and associated skin rash. Patients in systemic and polyarticular categories had symmetrical polyarthritis involving small and large joints. Ten (23.3%) patients with polyarticular subtype developed persistent lymphedema involving at least one extremity. Two patients (family 6) had recurrent perioral and periorbital angioedema; all work-up including C1-estrase were unremarkable. In family 7, one patient had bilateral developmental dysplasia of the hip, single kidney, with refractory hypertension but no vascular anomalies, while the other sibling had pulmonary involvement in form of plastic bronchitis. There was no clear phenotype-genotype correlation. Dual pathologies are not infrequent in highly consanguineous populations and may explain phenotypic heterogeneity observed in this family. Of note, patients with the same disease subtypes shared similar clinical and laboratory features regardless of their ethnicity.

All patients in the systemic category had leukocytosis, thrombocytosis, and elevated inflammatory markers, while patients with other subtypes had normal leucocyte and platelet counts with elevated inflammatory markers. None of the patients had features suggesting macrophage activation syndrome. Imaging studies revealed erosive arthritic changes. All patients had progressive moderate-to-severe disease and required treatment with a systemic corticosteroid and methotrexate. Forty patients received sequential treatment with multiple biologic agents, including anti-tumor necrosis factor (anti-TNF), anti-interleukin-1 (anti-IL1) (anti-IL-6), rituximab, and abatacept. Few patients required treatment with more than three sequential biologic agents. Most of the patients had a poor to partial response, but four patients showed a good response to the corticosteroid, methotrexate, and anti-TNF and anti-IL-6 agents.
Remarkably, family history of JIA was not considered in the classification criteria [13]. Like other autoimmune and autoinflammatory disorders, the interactions of epigenetic and environmental factors contribute to and influence the susceptibility to disease and its manifestation [4,14]. Familial aggregation of JIA supports the concept of genetic influence in the pathogenesis of JIA and is probably associated with refractory disease [15,16]. Interestingly, an increased risk for JIA was observed among first-degree relatives of patients with JIA [17]. LACC1-associated juvenile arthritis is an autosomal recessive disorder, characterized by inflammatory arthritis. LACC1-associated juvenile arthritis was identified by a combination of homozygosity mapping and whole exome sequencing [6]. LACC1-associated juvenile arthritis is a rare condition. Unfortunately, the frequency of this disorder worldwide is unknown. This report represents the largest published series of LACC1-associated juvenile arthritis. Consanguineous marriage represents an increased risk for rare diseases such as LACC1-associated juvenile arthritis. This study included 40 affected individuals from unrelated consanguineous Arab and Turkish families, which makes it relatively frequent in these ethnicities.

Our new patients and the previously published case series expand the clinical spectrum and the pathogenic variants of LACC1-associated juvenile arthritis. Obviously, it is not limited to systemic subtype as recognized previously, but it is in line with JIA categories. Furthermore, Rabionet et al. performed targeted LACC1 gene sequencing studies in patients with sporadic systemic and RF-negative polyarticular JIA, which revealed no pathogenic LACC1 gene variants [9]. These findings support the causative role of LACC1 gene variants in familial juvenile arthritis. Typically, patients with LACC1-associated juvenile arthritis presented with early onset disease, chronic disease course, and high inflammatory markers with variable phenotypes. Interestingly, a significant number of patients with LACC1-associated juvenile arthritis have been identified with new disease causing variants. However, on the basis of the available data, we could not find clear genotype-phenotype correlations. Our data showed guarded therapeutic responses to intensive treatment.

5. Discussion

The classification and pathogenic basis of JIA are a subject of controversy. Essentially, JIA is an exclusion diagnosis that represents a phenotypically heterogeneous group of arthritis of unknown origin [12]. ILAR criteria for JIA is mainly based on clinical features. Remarkably, family history of JIA was not considered in the classification criteria [13].

### Table 1

Demographics of patients with LACC1-associated juvenile arthritis.

| Reference | Patient no. | Gender | Disease type | Gene mutations |
|-----------|-------------|--------|--------------|----------------|
| Family 1  | 4           | F      | Systemic     | LACC1: c.850T > C, p.C284R |
| Family 2  | 3           | F      | Systemic     | LACC1: c.850T > C, p.C284R |
| Family 3  | 1           | M      | Systemic     | LACC1: c.850T > C, p.C284R |
| Family 4  | 2           | F      | Systemic     | LACC1: c.850T > C, p.C284R |
| Family 5  | 2           | F      | Systemic     | LACC1: c.850T > C, p.C284R |
| Family 6  | 1           | M      | Poly (RF)    | LACC1: c.850T > C, p.C284R |
| Family 7  | 2           | F      | Poly (RF)    | LACC1: c.850T > C, p.C284R |
| Family 8  | 1           | M      | Poly (RF)    | LACC1: c.850T > C, p.C284R |
| Family 9  | 1           | F      | Poly (RF)    | LACC1: c.850T > C, p.C284R |
| Family 10 | 2           | M      | Systemic     | LACC1: c.827delC, p.T276Kfs*2 |
| Family 11 | 1           | F      | Systemic     | LACC1: c.827delC, p.T276Kfs*2 |
| Family 12 | 2           | F      | Poly (RF)    | LACC1: c.3G > A, p.G0 |
| Family 13 | 3           | M      | Poly (RF)    | LACC1: c.3G > A, p.G0 |
| Family 14 | 2           | M      | Systemic     | LACC1: c.3G > A, p.G0 |
| Family 15 | 1           | M      | ERA          | LACC1: Homo c.760A > G, p. Ile254Val/Hetero c.1109G > A, p. C370T |
| Family 16 | 1           | M      | Poly (RF)    | LACC1: Homo c.760A > G, p. Ile254Val/Hetero c.1109G > A, p. C370T |
| Family 17 | 2           | F      | Poly (RF)    | LACC1: c.128delG, p. Ile330del |
| Family 18 | 2           | F      | Poly (RF)    | LACC1: c.128delG, p. Ile330del |

* Family 1–5 (Ref No. 6), family 11 (Ref No. 7), family 12–15 (Ref No. 8), family 16 (Ref No. 9), family 17 (Ref No. 10) M = male, F = female, Poly = polyarticular, RF = rheumatoid factor, Oligo = oligoarticular, ERA = enthesitis-related arthritis.

### Table 2

The frequency of clinical and laboratory features and treatment.

| Features                              | Frequency | Percentage (%) |
|---------------------------------------|-----------|----------------|
| Consanguinity                         | 40/43     | 93             |
| Age at onset (≤2 years)                | 37/43     | 86             |
| Fever                                 | 22/43     | 51.2           |
| Skin rash                             | 16/43     | 37.2           |
| Joint involvement:                    | 43/43     | 100            |
| Large                                 | 31/43     | 72.1           |
| Small                                 | 2/43      | 4.6            |
| Erosive arthritis                     | 37/43     | 86             |
| Hepatosplenomegaly                    | 8/43      | 18.6           |
| Lymphadenopathy                       | 7/43      | 16.3           |
| Disease course (Chronic)              | 40/43     | 93             |
| Pencartidias                          | 3/43      | 6.9            |
| Limb lymphedema                       | 10/43     | 23.3           |
| Leukocytosis                          | 23/43     | 53.5           |
| ESR (normal < 15 mm/h)                | 37/43     | 86             |
| RF                                    | 7/30      | 23.3           |
| ANA                                   | 8/27      | 29.6           |
| Treatment:                            | 43/43     | 100            |
| Methotrexate                          | 40/43     | 93             |
| Biologic agents (multiple, sequential)| 26/43     | 60.5           |
| Response:                             | 13/43     | 30.2           |
| Partial                               | 4/43      | 9.3            |
| Complete                              |           |                |

ESR = erythrocyte sedimentation rate, RF = rheumatoid factor, ANA = antinuclear antibody.
Our findings have limitations and accordingly results should be interpreted carefully. Part of the data was retrospectively collected. There are variations in management modalities based on the availability of medications and resources.

In summary, LACC1-associated juvenile arthritis is a rare disorder with a wide clinical spectrum. This report is intended to increase the awareness of health care providers about these diseases. Our data suggest that patients with early onset of chronic inflammatory arthritis and a positive family history should be genetically screened for pathogenic LACC1 variants. We believe that conducting the test might help in diagnosis and counselling. It might also help in predicting the treatment response and outcome. Furthermore, the predominance of autosomal-recessive inheritance and strong genetic evidence allowed us to propose LACC1-associated juvenile arthritis as a distinct disorder to differentiate it from non-Mendelian juvenile arthritis of unknown cause “juvenile idiopathic arthritis”.

Ethical statement

All authors have contributed significantly and are in agreement with the content of the manuscript. Furthermore, Ethics committee of our institution has approved the protocol for the research project. Please, note that this work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication.

We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

References

[1] Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004 Feb;31(2):390.
[2] Giancane G, Consolario A, Lanni S, Davi S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatol Ther 2016 Dec;3(2):187–207.
[3] Duffy CM, Colbert RA, Laxer RM, Chanberg BE, Bowyer SL. Nomenclature and classification in chronic childhood arthritis: time for a change? Arthritis Rheum: Off J Am Collage Rheumatol 2005 Feb;52(2):382–5.
[4] Moncrieffe H, Prahalad S, Thompson SD. Genetics of JIA: new tools bring new approaches. Curr Opin Rheumatol 2014 Sep;26(5):579.
[5] McIntosh LA, Marion MC, Sudman M, Comeau ME, Becker ML, Bohnsack JF, et al. Genome-wide association meta-analysis reveals novel juvenile idiopathic arthritis susceptibility loci. Arthritis Rheumatol 2017 Nov;69(11):2222–32.
[6] Wakil SM, Monies DM, Abouelhoda M, Al-Tassan N, Al-Dusery H, Naim EA, et al. Association of a mutation in LACC1 with a monogenic form of systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2015 Jan;67(1):288–95.
[7] Kallinich T, Thorwarth A, von Stuckrad SL, Rosen-Wolf A, Luksh H, Hundsdorfer P, et al. Juvenile arthritis caused by a novel FAMIN (LACC1) mutation in two children with systemic and extended oligoarticular course. Pediatr Rheumatol 2016 Dec;14(1):1–4.
[8] Karacan I, Urgurur S, Sahin S, Everest E, Kasapcopur O, Tolun A, Ozdogan H, Turanli ET. LACC1 gene defects in familial form of juvenile arthritis. J Rheumatol 2018 May 1;45(5):726–8.
[9] Rabionet Janssen R, Remesal A, Mensa-Vilaro A, Murias S, Alcobendas R, Gonzalez-Roca E, et al. Biallelic loss-of-function LACC1/FAMIN mutations presenting as rheumatoid factor-negative polyarticular juvenile idiopathic arthritis. Sci Rep 2019;9(2019):4579. Mar 14.
[10] Singh A, Suri D, Vignesh P, Anjani G, Jacob P, Girisha KM. LACC1 gene mutation in three sisters with polyarticular without systemic features. Ann Rheum Dis 2020 Mar;79(3):425–6.
[11] Saudi Mendeliome Group. falkuaya@ kfshrc. edu. sa. Comprehensive gene panels provide advantages over clinical exome sequencing for Mendelian diseases, Genome Biol 2015 Dec;16:1–4.
[12] Martini A, It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis 2012 Sep;71(9):1437–9.
[13] Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. J Rheumatol 2019 Feb 1;46(2):190–7.
[14] Chishtikov DA, Savost’anoj KV, Baranov AA. Genetic background of juvenile idiopathic arthritis. Autoimmunity 2014 Sep 1;47(6):351–60.
[15] Moroldo MB, Chaudhari M, Shear E, Thompson SD, Glass DN, Giannini EH. Juvenile rheumatoid arthritis affected sibpairs: extent of clinical phenotype concordance. Arthritis Rheum: Off J Am Collage Rheumatol 2004 Jun;50(6):1928–34.
[16] Al Marni M, Qari A, Al-Mayouf SM. Juvenile idiopathic arthritis in multiplex families: longitudinal follow-up. Int J Rheumatic Dis 2017 Jul;20(7):898–902.
[17] Prahalad S, O’Brien E, Fraser AM, Kerber RA, Mineau GP, Pratt D, Donaldson D, Ramshad MJ, Bohnsack J. Familial aggregation of juvenile idiopathic arthritis. Arthritis Rheum 2004 Dec;50(12):4022–7.