Letter to the Editor (Case report)

Rheumatology Advances in Practice 2022;00:1–2
https://doi.org/10.1093/rap/rkac018
Advance access publication 21 March 2022

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Dear Editor, Deficiencies of early components of the classical complement pathway are associated with an increased risk of SLE. There is a hierarchy of disease susceptibility and severity according to the position of the deficient protein in the classical complement pathway. SLE penetrance in C1q deficiency is 90%, and patients generally present with severe disease, whereas only 10–20% of C2-deficient patients develop SLE, with a disease severity comparable to sporadic SLE [1, 2]. C1q inhibits type I IFN (T1IFN) release, and its deficiency is associated with upregulated T1IFN signalling [3, 4]. Increased T1IFN signalling in C1q deficiency is proposed to explain the association with SLE [3]. It is unknown whether T1IFN signalling is also increased in other, more common early complement deficiencies, such as C2 deficiency (estimated prevalence in European population 1 in 20 000) [2]. We identified only one C2-deficient patient in the literature for whom T1IFN signalling was assessed [4]. In the present report, we investigate the association between C2 deficiency, T1IFN signalling and autoimmunity in a kindred with C2 deficiency and primary SS (pSS). The UZ/KU Leuven ethics committee approved this study (S52653).

The index patient was born to consanguineous parents of Moroccan descent (Fig. 1A

feature of type I interferonopathies, but occurs in only <10% of paediatric pSS patients [5, 7].

In this kindred, both C2-deficient sisters harbour autoantibodies and high T1IFN signalling. High T1IFN signalling has been reported in patients with C1q deficiency and in one C2-deficient patient, and early complement deficiency is being considered as a cause of autoimmune interferonopathy [3, 4, 7]. The link between early complement deficiency and T1IFN signalling is still under investigation and might involve uncleared neutrophil extracellular traps serving as a source of interferogenic autoantigens, thus fuelling a T1IFN amplification loop [7, 8]. Consequently, patients with early complement deficiency and signs of autoimmunity might benefit from therapies that inhibit T1IFN signalling (e.g. HCQ and Janus kinase inhibitors) [9]. Our findings further support the observation that female sex is associated with increased T1IFN signalling, potentially contributing to the susceptibility of females to autoimmunity, also in the context of C2 deficiency [10].

Together, we provide evidence for an association between C2 deficiency, autoimmunity and high T1IFN signalling. C2-deficient patients are potentially at risk of developing secondary autoimmune interferonopathies, including pSS, and might benefit from therapies targeting T1IFN signalling.

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C.W., A.L. and S.H.-B. conceptualized and supervised the study. C.W. and L.D.S. collected clinical data. E.V.N. and N.S.S.T. performed wet lab experiments. M.W. and E.V.N. performed genetic analysis. M.W. and F.S. drafted the manuscript. All authors were involved in revising the manuscript critically for important intellectual content, and all authors approved the final version to be published.Patient consent: All study participants provided written informed consent.

Funding:

Disclosure statement: The authors have declared no conflicts of interest.

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All data are available upon request via contacting the authors Mathijs Willemsen and Carine Wouters.

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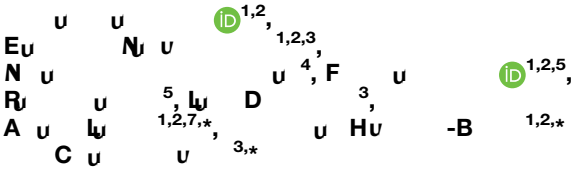
Supplementary data are available at Rheumatology Advances in Practice online.



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Accepted 23 February 2022
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1 Omarjee O, Picard C, Frachette C et al. Monogenic lupus: dissecting heterogeneity. Autoimmun Rev 2019;18:102361.

2 Jönsson G, Sjöholm AG, Truedsson L et al. Rheumatological manifestations, organ damage and autoimmunity in hereditary C2 deficiency. Rheumatology (Oxford) 2007;46:1133–9.

3 Wolf C, Brück N, Koss S et al. Janus kinase inhibition in complement component 1 deficiency. J Allergy Clin Immunol 2020;146:1439–42.e5.

4 Rice GI, Melki I, Frémond ML et al. Assessment of type I interferon signaling in pediatric inflammatory disease. J Clin Immunol 2017;37:123–32.

5 Basiaga ML, Stern SM, Mehta JJ et al.; Childhood Arthritis and Rheumatology Research Alliance and the International Childhood Sjögren Syndrome Workgroup. Childhood Sjögren syndrome: features of an international cohort and application of the 2016 ACR/EULAR classification criteria. Rheumatology (Oxford) 2021;60:3144–55.

6 Levy D, Craig T, Keith PK et al. Co-occurrence between C1 esterase inhibitor deficiency and autoimmune disease: a systematic literature review. Allergy Asthma Clin Immunol 2020;16:41.

7 Kim H, Sanchez GA, Goldbach-Mansky R. Insights from