Absence of NLRP3 somatic mutations and VEXAS-related UBA1 mutations in a large cohort of patients with Schnitzler syndrome

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Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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LETTER

Absence of *NLRP3* somatic mutations and VEXAS-related *UBA1* mutations in a large cohort of patients with Schnitzler syndrome

Dear Editor,

Schnitzler's syndrome (SchS) is an extremely rare systemic autoinflammatory disease (SAID) characterized by a late onset of urticarial rash, recurrent fever, bone pain, arthralgia, elevated acute-phase reactants, and a monoclonal gammopathy involving IgMκ chains (classical type) and rarely IgG (variant type). To date, about 300 cases have been reported worldwide.[1] The diagnosis of SchS is currently based on a set of clinical criteria, that is, the Strasbourg diagnostic criteria.[2] It is of prime importance to establish this diagnosis given the therapeutic efficacy of interleukin-1 antagonists.[3] No genetic predisposition has been formally identified so far. Two myeloid lineage-restricted somatic *NLRP3* mutations were reported in 2015 in two SchS patients with the IgGκ variant type.[4] Nevertheless, no *NLRP3* mutation was identified in subsequent studies involving 32 SchS patients.[5,6] More recently, somatic mutations in exon 3 of *UBA1* were reported in a syndrome affecting men with adult-onset SAID and named VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic).[7] Notably, in this first VEXAS study, 20% of the patients presented multiple myeloma or monoclonal gammopathies of unknown significance (MGUS), thereby making *UBA1* a potential candidate gene for SchS.

These data prompted us to assess the contribution of *NLRP3* and *UBA1* somatic mutations, as well as of the main genes so far involved in SAID patients with cutaneous lesions in SchS pathophysiology. To this end, we screened for mutations of all these genes in the largest cohort of SchS patients constituted so far (40 unrelated cases) and at the origin of the validation of Strasbourg diagnostic criteria of SchS.[2]

We performed deep-targeted next-generation sequencing (NGS—mean sequencing depth of 943X) of 19 genes so far involved in SAIDs with cutaneous manifestations (*NLRP3*, *NLRC4*, *MEFV*, *MVK*, *TNFRSF1A*, *IL1RN*, *IL36RN*, *LPIN2*, *PSTPIP1*, *TNFAIP3*, *IL36RN*, *CARD14*, *IL10*, *IL10RA*, *IL10RB*, *NOD2*, *PLCG2*, *LYN*, and *NLRP1*), and Sanger sequencing of exon 3 of *UBA1* (NM_003334) in all patients.

None of the 40 SchS patients carried a somatic *NLRP3* mutation. Notably, the two previously reported patients with a diagnosis of SchS and an *NLRP3* mosaic mutation[4] had a transient monoclonal IgG, an observation raising the possibility of a late-onset *NLRP3*-AID diagnosis. Indeed, late-onset urticarial lesions can represent the main clinical manifestation in patients with *NLRP3* mosaic mutations.[8]

As for *UBA1*, the gene involved in VEXAS patients among whom 20% have multiple myeloma or MGUS,[7] no somatic mosaic mutation was identified in the third exon of *UBA1* in our cohort of 40 patients with SchS. These results, therefore, do not support the hypothesis of *UBA1* somatic mutations in SchS pathophysiology.

The study of 18 other genes involved in a SAID phenotype associated with cutaneous manifestations identified no somatic mosaic mutations in the 40 SchS patients. We, however, identified 33 rare heterozygous germline variations (Table S1). According to the American College of Medical Genetics recommendations used to assess their pathogenicity, 24 variations were classified as likely benign and 9 as variations of unknown significance (VUS) (i.e., 4 in *NLRP1*, 2 in *IL10RA*, 1 in *IL10RB*, 1 in *NOD2*, and 1 in *TNFRSF1A*) (Table S1). Although 4 variations were found in *NLRP1*, it is important to underline that all of them have a CADD (Combined Annotation-Dependent Depletion score, https://cadd.gs.washington.edu/) score <15, a finding that argues against their pathogenicity.

In conclusion, no somatic or germline pathogenic variations have been identified in *NLRP3*, *UBA1*, and 18 other SAID genes involved in a disease phenotype associated with cutaneous signs, in the large cohort of 40 SchS patients at the origin of the validation of Strasbourg diagnostic criteria of SchS.

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CONFLICT OF INTERESTS

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

Clinical features were collected through a standardized form. Written informed consents were obtained from all patients according to the French legislation and the principles of the Declaration of Helsinki. The study was approved by the research ethics committee from the Hôpitaux Universitaires de Strasbourg, France (N°ID RCB 2008-A01295-50).

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