

Letter to the Editor

Myeloid lineage-restricted somatic mosaicism of *NLRP3* mutations in patients with variant Schnitzler syndrome

To the Editor:

Schnitzler syndrome is an elusive autoinflammatory disorder characterized by chronic (neutrophilic) urticaria, monoclonal gammopathy, and systemic inflammation.¹ The cause is unknown, but a pathophysiologic clue has been provided by the efficacy of anti-IL-1 treatment¹ and IL-1 β inhibition in particular.² The lack of familial clustering and the late onset of the disease suggested an acquired rather than genetic nature.

Phenotypic characteristics of patients with Schnitzler syndrome, including responsiveness to anti-IL-1 therapy, are also seen in patients with cryopyrin-associated periodic syndrome (CAPS). In patients with CAPS, activating germline or somatic mutations of the *NLRP3* gene result in increased spontaneous IL-1 β production. Routine genetic screening of our patients with Schnitzler syndrome thus far did not reveal pathogenic *NLRP3* mutations.³ Here we applied next-generation sequencing technologies to further address the possibility of a genetic cause in Schnitzler syndrome.

Exome sequencing of whole blood DNA from 3 patients with Schnitzler syndrome revealed a known missense mutation in the *NLRP3* gene (c.1569C>G; p.F523L) in patient 7 in 22 (17%) of 127 reads (see Table E1 in this article's Online Repository at www.jacionline.org), which was previously reported as disease causing in 2 neonates with severe CAPS.⁴ It had been missed by previous Sanger sequencing³ but could now be confirmed as a small peak underlying the wild-type allele, potentially representing a somatic mosaicism (Fig 1, A). No further plausible candidates have been identified yet in the exome data.

Next, we performed deep targeted MiSeq resequencing of the *NLRP3* gene in whole blood DNA from 11 patients with Schnitzler syndrome, including the 3 exome-sequenced patients (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). This analysis confirmed the presence of the p.F523L mutation in patient 7 and also revealed an *NLRP3* mutation (c.1303A>G; p.K435E) in patient 8 in 27% of 930 reads, which is predicted to be pathogenic (Table 1). The mutation was confirmed by means of Sanger sequencing of whole blood DNA from patient 8 (Fig 1, B), and his 3 healthy sisters did not show this variant. Remarkably, the 2 patients who carried the *NLRP3* variants were the most severely affected patients of our cohort, and the highest percentage of *NLRP3* mutant alleles in whole blood was found in patient 8, who had the most severe phenotype. Both patients were classified as having variant (IgG κ)-type Schnitzler syndrome.

Deep MiSeq resequencing of *NLRP3* from purified granulocytes, monocytes, T lymphocytes, B lymphocytes, keratinocytes, and fibroblasts showed that the mosaicism of the identified variants in patients 7 and 8 was restricted to the granulocytes and monocytes (Table 1), hence the myeloid lineage. These 2 cell types are the predominant cells in the dermal infiltrate of lesional skin, as is the case in all patients with Schnitzler syndrome (Fig 1, C). No *NLRP3* genetic variants were found in any of the analyzed cell types derived from 2 patients with Schnitzler syndrome without *NLRP3* variants in whole blood (Table 1).

Because we have previously demonstrated that IL-1 β is a pivotal mediator of the clinical signs of Schnitzler syndrome,^{2,5} we proceeded to investigate the functional consequences of the *NLRP3* mosaic mutations on IL-1 β and IL-6 production in PBMCs (see the Methods section in this article's Online Repository at www.jacionline.org). PBMCs from patients with Schnitzler syndrome were collected during symptomatic episodes and during treatment with IL-1 receptor antagonist (IL-1Ra) or anti-IL-1 β antibodies. PBMCs of patients with *NLRP3* mosaicism produced IL-6 and IL-1 β constitutively, even during *in vivo* anti-IL-1 therapy, whereas this was not seen in the other patients with Schnitzler syndrome. Interestingly, in PBMCs of these patients, the spontaneous *in vitro* production of IL-6 and IL-1 β was completely abolished by means of *in vitro* addition of IL-1Ra (Fig 1, D). This implies a strong positive feedback loop and that IL-6 overproduction is entirely IL-1 β dependent in these patients. The excessive spontaneous *in vitro* production of IL-1 β in patients with *NLRP3* mosaicism correlates with their severe phenotype and the dramatic response to IL-1 β inhibition *in vivo*.²

Somatic mosaicism of *NLRP3* has been reported in patients with neonatal-onset CAPS (Fig 1, E).^{6,7} In patients with CAPS, there was no significant difference in mutation frequency between several leukocyte subsets and the buccal mucosa.⁷ In contrast, in our 2 patients with Schnitzler syndrome, the mosaicism was restricted to the granulocytes and monocytes. We speculate that in the patients with CAPS, the mutation occurred rather early in embryogenesis because both mesenchymal and ectodermal tissues were equally affected. In our patients the mutational event took place soon after differentiation of the myeloid precursor cells, leading to mosaicism in both granulocytes and monocytes.

The myeloid-confined *NLRP3* mosaicism, late age of onset, lack of family history, and (transient) gammopathy differentiate these 2 patients with Schnitzler syndrome from the known spectrum of patients with CAPS. However, because the name CAPS implies association with *NLRP3* mutations, we propose that patients with Schnitzler syndrome and *NLRP3* mosaicism should be added to the spectrum of CAPS as "Schnitzler syndrome-variant CAPS."

The 2 patients with *NLRP3* mosaicism had the most severe clinical phenotype of our patient group, and in both of them, an unquantifiably low IgG κ paraprotein level was previously found, although levels are currently undetectable. The latter fact might be a mere coincidence, or perhaps these 2 patients are part of a specific subgroup with *NLRP3* mosaicism, transient paraproteinemia, and a severe phenotype. If disease severity is determined by the proportion of cells carrying a mutation, the frequency in the other patients might have been too low to allow detection. Alternatively, (mosaicism of) mutations in other genes of the NLRP3-IL-1 β pathway could be involved in the pathophysiology of Schnitzler syndrome.²

Previously, a p.V198M variant in *NLRP3* has been detected in 2 patients with Schnitzler syndrome, but both had unaffected family members carrying this variant.^{8,9} The population allele frequency of this variant is about 0.5%, and at present, the pathophysiologic significance of this variant remains to be determined.

Most of the known CAPS-associated mutations are localized in the NACHT domain of exon 3 of the *NLRP3* gene, as are the

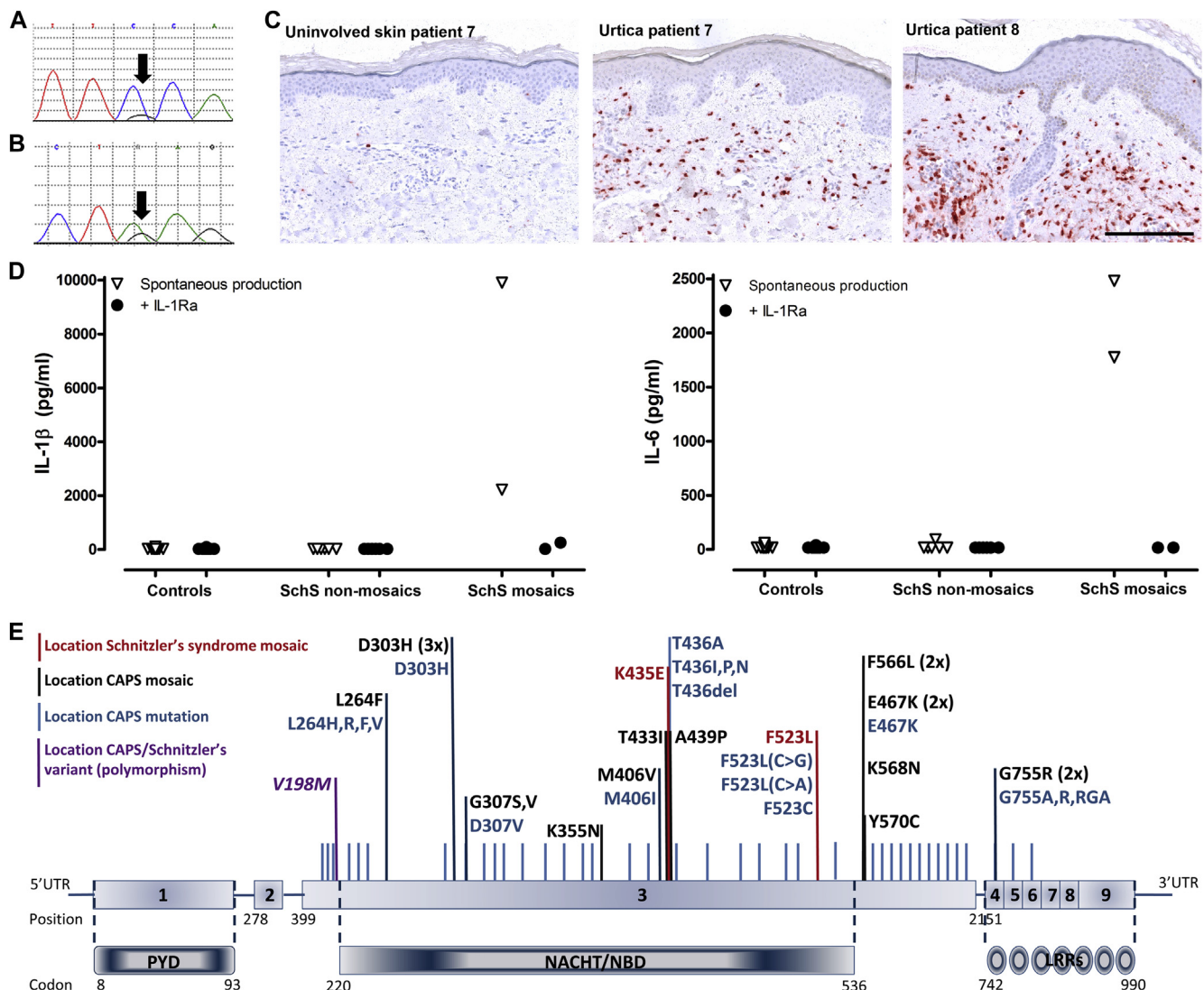


FIG 1. **A**, Sanger sequencing in patient 7. The chromatogram shows the *NLRP3* variant c.1569C>G (p.F523L), as well as the wild-type allele. **B**, Sanger sequencing in patient 8. The chromatogram shows the *NLRP3* variant c.1303A>G (p.K435E), as well as the wild-type allele. **C**, Neutrophils and monocytes in lesional skin of patients with Schnitzler syndrome. Immunohistochemical staining of skin sections with anti-myeloperoxidase, which is predominantly present in neutrophils and, to a lesser extent, in monocytes, is shown. The panels show the uninvolved skin of patient 7 and the lesional skin of patients 7 and 8. *Bar length* = 100 μ m. **D**, Spontaneous *in vitro* production of IL-1 β and IL-6 in PBMCs with *NLRP3* mosaicism. PBMCs from patients with Schnitzler syndrome without (*SchS non-mosaics*) and with (*SchS mosaics*) *NLRP3* mosaicism sampled during anti-IL-1 β treatment and PBMCs from healthy control subjects were cultured for 24 hours either in the presence of IL-1Ra or not. Supernatant IL-1 β and IL-6 levels were measured by means of ELISA. **E**, Positions of known and mosaicism-related mutations in the *NLRP3* gene in patients with CAPS and those with Schnitzler syndrome. *LRR*, Leucine-rich repeats; *PYD*, pyrin domain; *NACHT* domain; *UTR*, untranslated region.

mutations of patients with chronic infantile neurological, cutaneous and articular syndrome (CINCA)/neonatal-onset multisystem inflammatory disease (NOMID) with *NLRP3* mosaicism. The V198M variant found in patients with CAPS and 2 patients with Schnitzler syndrome but also healthy control subjects is localized in exon 3, although not in the NACHT domain. The p.F523L mutation found in patient 7 was previously described in 2 severely affected patients with NOMID/CINCA. The p.K435E variant found in patient 8 is novel but localized in close proximity to known CAPS mutations, and the effect of the

resulting amino acid change is predicted to affect protein functioning (Fig 1, E).^{6,7,10}

In conclusion, we found somatic mosaicism of *NLRP3* mutations exclusively in the myeloid lineage in 2 patients with variant Schnitzler syndrome. To our knowledge, this is the first report on somatic mosaicism confined to the myeloid lineage in a patient with a nonmalignant disorder. Our identification of myeloid lineage-restricted somatic mosaicism of *NLRP3* as the cause of Schnitzler syndrome–variant CAPS is not merely a step forward in our understanding of this particular disease but also highlights

TABLE I. Mutation analysis of 2 patients with somatic mosaicism of *NLRP3* variants

	Patient 7	Patient 8
<i>NLRP3</i> genetic variant	c.1569C>G	c.1303A>G
<i>NLRP3</i> amino acid change	p.F523L	p.K435E
Percentage of variant reads in exome sequencing, whole blood	17%	NA
Percentage of variant reads in MiSeq resequencing, whole blood	8%	27%
Percentage of variant reads in MiSeq resequencing, granulocytes	13%	32%
Percentage of variant reads in MiSeq resequencing, monocytes	6.5%	29%
Percentage of variant reads in MiSeq resequencing, T lymphocytes	ND	ND
Percentage of variant reads in MiSeq resequencing, B lymphocytes	ND	ND
Percentage of variant reads in MiSeq resequencing, keratinocytes	ND	ND
Percentage of variant reads in MiSeq resequencing, fibroblasts	ND	ND
Pathogenicity: prediction or known association	NOMID/CINCA	Possibly damaging*

Percentages of *NLRP3* mutants in different cell subsets from patients 7 and 8.

NA, Not assessed; ND, not detectable (<2% of the threshold value for reliable detection).

*Predicted to be possibly damaging by using the SIFT, Align GVGD, and PolyPhen-2 tools.

the possibility that several other late-onset sporadic diseases might have a genetic basis.

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METHODS

Ethics statement

This study complies with the guidelines of the Declaration of Helsinki, and informed consent was obtained from patients.

Patients and sample collection

DNA was isolated from whole blood from 11 clinically characterized patients with classical (IgM) or variant (IgG) Schnitzler syndrome (Table E2). None of the patients had affected family members. From 2 patients showing mosaicism in whole blood (patients 7 and 8) and 2 patients without mosaicism (patients 9 and 10), leukocyte subsets were isolated by using Ficoll gradient. Subsequently, fluorescence-activated cell sorting was performed based on cell size (granulocytes) and CD14 (monocytes), CD3 (T lymphocytes), and CD19 (B lymphocytes) levels, followed by DNA isolation. Skin biopsy specimens were taken from lesional and uninvolved skin from patients 7 and 8 for immunohistochemical staining and isolation of keratinocytes and fibroblasts; these were cultured, as previously described,^{E1} followed by DNA isolation. For functional studies, PBMCs were isolated from 8 patients with Schnitzler syndrome (patients 1-8) and 8 age- and sex-matched control subjects.

Whole-exome sequencing

Total blood DNA from patients 1, 2, and 7 was analyzed by means of whole-exome sequencing, which was performed on a 5500XL sequencing platform (Life Technologies, Carlsbad, Calif). The exomes of the probands were enriched according to the manufacturer's protocol by using the SureSelect Human All Exon v2 XT Kit (50 Mb; Agilent Technologies, Santa Clara, Calif). LifeScope software version 2.1 (Life Technologies) was used to map color-space reads along the hg19 reference genome assembly. The DiBayes algorithm, with high-stringency calling, was used for single nucleotide variant calling, and the small Indel Tool was used to detect small insertions and deletions. Whole-exome sequencing data were filtered, as described previously.^{E2}

Sanger sequencing of the *NLRP3* gene

Exon-specific primers were used to amplify all coding exons, including the flanking regions of the *NLRP3* gene (NM_001243133.1), followed by Sanger sequencing. Each exon was amplified in duplicate and Sanger sequenced by using BigDye Terminator version 1.1 (Applied Biosystems, Foster City, Calif). Sequence Pilot software (JSI Medical Systems, Kippenheim, Germany) was used for analysis of sequence data.

Targeted deep resequencing of the *NLRP3* gene (MiSeq)

For deep targeted resequencing of the *NLRP3* gene, library preparations were performed with the TruSeq library preparation protocol, according to the manufacturer's instructions, followed by MiSeq sequencing with the MiSeq Reagent Kit v2 (500 cycles; Illumina, San Diego, Calif). Numbers of reads included all allele counts per position after Burrows-Wheeler Aligner (BWA) mapping.

Immunohistochemical staining of skin sections

Sections of paraffin-embedded lesional and uninvolved skin of patients 7 and 8 were stained with mouse anti-human myeloperoxidase (R&D Systems, Minneapolis, Minn) as a marker for neutrophils and monocytes, according to standard protocols.

Functional studies

PBMCs from 8 patients with Schnitzler syndrome (patients 1-8) with active disease or in remission during treatment with anakinra (IL-1Ra) or canakinumab (anti-IL-1 β antibody)^{E3} and from 8 age- and sex-matched healthy control subjects were isolated. Cells from patient and control subjects were cultured for 24 hours in the presence of no stimulus or anakinra (10 μ g/mL). Cytokine concentrations in the cell supernatants were measured by means of ELISA (IL-1 β , R&D Systems; IL-6, Sanquin, Amsterdam, The Netherlands).

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TABLE E1. Filtering of variants found in whole-exome sequencing

	Patients		
	1	2	7
Total no. of variants	46,892	45,753	45,892
Coding+SS	18,175	17,596	17,799
Nonsynonymous	8,936	8,591	8,730
Not seen before (in house)	305	247	243
Nonsense	7	7	4
Canonical SS	9	6	10
Indels	40	29	32
Missense (phyloP>2.5)	109	87	84
Known variant (HGMD)	1 (<i>KCNQ1</i>)	0	1 (<i>NLRP3</i>)

We detected 2 known variants described in the Human Gene Mutation Database.

Patient 1 carried a variant in *KCNQ1*, which is associated with long QT syndrome.

The identified variant is considered a benign polymorphism.^{E5} In patient 7 we detected a known missense mutation in the NACHT domain of the *NLRP3* gene (c.1569C>G; p.F523L), which was previously reported as disease causing in 2 infants with NOMID/CINCA, a severe early-onset form of CAPS.^{E6}

Canonical SS, Variants located in a canonical splice site; *Coding+SS*, all variants located either in exonic regions or canonical splice sites; *Indels*, Insertions or deletions; *Known variant (HGMD)*, variants described as pathogenic in the Human Gene Mutation Database (www.hgmd.org); *Missense (phyloP >2.5)*,^{E4} highly conserved missense variants with a phyloP >2.5; *Nonsense*, nonsense variants; *Nonsynonymous*, variants leading to an amino acid change; *Not seen before (in house)*, variants that have not been detected in 672 in-house sequenced whole exomes; *Patient*, patient who has undergone whole-exome sequencing; *Total no. of variants*, all variants detected by using whole-exome sequencing.

TABLE E2. Patients' characteristics

	Patients										
	1	2	3	4	5	6	7	8	9	10	11
Sex	M	F	M	M	M	M	F	M	F	M	M
Age of onset (y)	52	64	45	43	57	58	38	50	71	43	59
Disease duration (y)	15	3,5	6	21	11	18	26	10	2	21	6
Paraprotein subtype	IgMκ and IgMλ	IgGκ	IgMκ	IgGκ	IgMκ	IgMκ	IgGκ*	IgGκ*	IgMκ	IgMκ	IgMλ
Physician's global assessment [†]	3	4	3	3	3	4	4	4	3	4	3
C-reactive protein level (mg/L)	202	147	190	16	60	250	95	333	166	164	31

Further clinical characteristics of patients 7 and 8: chronic urticaria with a dermal infiltrate of neutrophils and monocytes on histology; severe arthralgias, bone pain, intermittent fever, severe malaise, and weight loss.

*Previously, an unquantifiably low IgGκ paraprotein level was found, but levels are currently undetectable.

[†]Physician's global assessment of disease activity (PGA): PGA during symptoms was assessed by the clinician. PGA scores were as follows: 0, absent; 1, minimal; 2, mild; 3, moderate; and 4, severe.

TABLE E3. Next-generation sequencing: numbers of reads of *NLRP3* variants

	Patients										
	1	2	3	4	5	6	7	8	9	10	11
<i>NLRP3</i> genetic variant blood							c.1569C>G ^{E6}	c.1303A>G			
<i>NLRP3</i> amino acid change blood							p.F523L	p.K435E			
Percentage in exome sequencing	ND	ND	—	—	—	—	22/127	—	—	—	—
No. of reads in MiSeq sequencing whole blood	ND	ND	ND	ND	ND	ND	78/976	250/924	ND	ND	ND
MiSeq sequencing, granulocytes	—	—	—	—	—	—	2103/15249	3102/9424	ND	ND	—
MiSeq sequencing, monocytes	—	—	—	—	—	—	1304/19994	4232/14500	ND	ND	—
MiSeq sequencing, T lymphocytes	—	—	—	—	—	—	4/397	18/11814	ND	ND	—
MiSeq sequencing, B lymphocytes	—	—	—	—	—	—	17/849	59/12456	ND	ND	—
MiSeq sequencing, keratinocytes	—	—	—	—	—	—	0/882	14/10163	—	—	—
MiSeq sequencing, fibroblasts	—	—	—	—	—	—	0/563	19/11459	—	—	—
Pathogenicity: prediction* or known association							NOMID/CINCA	Possibly damaging			

—, Not assessed; ND, not detectable (<2% of the threshold value for reliable detection).

*Predicted by using the SIFT, Align GVGD, and PolyPhen-2 tools to be potentially damaging.