parental genetic testing identified an identical nucleotide mis-sense substitution in the mother, but not in the father.

Improved clinical symptoms after inhibition of interleukin 1 (IL 1) activity by anakinra was reported in all of the cryopyrin-associated autoinflammatory syndromes, although treatment failure has also been reported.¹⁻⁴ Therapy with IL 1 antagonism was begun in our patient at 9 years and a clinical response was reported within days. On taking Anakinra (~0.90 mg/kg/day) his energy level improved, his rash appeared less frequently and his arthritis and conjunctivitis were resolved. His erythrocyte sedimentation rate, white cell count and platelet count all improved (table 1). The patient's family temporarily reduced the dose of anakinra to 0.30 mg/kg/day, and he again experienced clinical and laboratory evidence of disease flare, indicating a dose-dependent response (table 1).

In all, 60 different dominantly inherited missense mutations within exon three of CIAS1 have been associated with the three heterogeneous cryopyrin-associated autoinflammatory syndromes.⁵⁻⁶ Previous patients described with characteristics of both familial cold-induced autoinflammatory syndrome and Muckle-Wells syndrome have had other unique cryopyrin mutations that were distinct from the new mutation described here.¹⁻⁷ It is interesting to note that two other mutations that would cause different amino acid substitutions at this site (Thr436Ile; Thr436Asn) were reported in patients with chronic infantile neurological cutaneous articular syndrome.⁸ These findings would suggest that specific amino acid substitutions at this site are solely responsible for the clinical phenotype. However, phenotypic heterogeneity, including incomplete penetrance among family members, has been described among individuals carrying identical mutations.⁷⁻⁹⁻¹⁰ Thus there is probably an effect of additional modifier genes or environmental factors in the phenotypic expression of the cryopyrin-associated autoinflammatory syndromes.⁸

ACKNOWLEDGEMENTS

Helpful input and comments from Dr John Carey are appreciated.

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Competing interests: None.

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Accepted 18 February 2007

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DNA microarray analysis of labial salivary glands of patients with Sjögren's syndrome

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Ann Rheum Dis 2007;**66**:844-845. doi: 10.1136/ard.2006.063370

Sjögren's syndrome (SS) is a chronic autoimmune disease characterised by dry eyes, dry mouth and focal lymphocytic infiltration in lacrimal and salivary glands. The infiltrating lymphocytes are mainly CD4 α/β T cells,¹ especially T helper 1 (Th1) type T cells, because they produce both interferon (IFN) γ and interleukin 2.²⁻³ To understand the pathogenesis of SS, several molecules in labial salivary glands (LSGs) have been screened by microarray analysis in human SS. Hjelmervik *et al*⁴ and Gottenberg *et al*⁵ reported that the upregulated genes in SS salivary glands were IFN-inducible genes, such as IFN-stimulated transcription factor 3, IFN-regulatory factor 1 and B cell-activation factor of the TNF family. However, there is little or no information on the essential genes involved in the generation of sialoadenitis in

patients with SS. We screened abnormally expressed genes in LSGs of patients with SS using cDNA microarray technology to elucidate the SS susceptibility genes.

The cDNA array was performed using total RNA from LSGs of three patients with primary SS and from three healthy subjects (control) with a DNA chip including 775 genes (JGS, Tokyo, Japan). The DNA chip contained immunoglobulins, human leucocyte antigens (HLAs), complements, T cell receptors (TCRs), IFN-inducible proteins, cytokines, transcriptional factors and other autoimmune disease-related genes. Abnormally

Abbreviations: HLA, human leucocyte antigen; SS, Sjögren's syndrome; IFN, interferon; LSG, labial salivary gland; Th1, T helper cell; TCR, T cell receptor

Table 1 Genes expressed in labial salivary glands of patients with Sjögren's syndrome (SS)

Gene name	SS/HS
Upregulated genes	
Immunoglobulin (Ig)	
Ig heavy constant $\gamma 3$	8.40*
Ig γ chain; Ig rearranged γ chain, V-J-C region	2.99
Ig κ variable 1D8	3.25
Rearranged Ig mRNA for μ heavy chain enhancer and constant region	2.23
Human leucocyte antigen (HLA)	
Human MHC HLA class I cell surface antigen (HLA-B 5102) mRNA	6.56*
HLA-F	3.31*
HLA-DR $\beta 1$	6.22*
HLA-DP light chain	3.01*
RING6 (HLA class II α chain-like product)	2.41*
MHC class II DQ	2.35*
MHC class II DR	7.28*
Complement	
Complement C3	3.96*
T cell receptor (TCR)	
TCR β chain (T cell receptor β chain)	2.11*
Interferon (IFN)-inducible genes	
IP-30 (IFN γ -inducible protein)	2.17*
I-5111 (IFN γ -inducible gene)	2.25
IP-10 (IFN γ -inducible chemokine)	2.31
IFN α / β -inducible p44	2.1*
IFN α -inducible protein 27	2.19*
Stat50 mRNA	2.04*
Thymosin β	
Thymosin $\beta 4$	2.03*
Thymosin $\beta 10$	2.12*
Transcription factor	
STAT1 α	2.88*
STAT1 β	2.07*
I κ B	2.02*
Downregulated genes	
LIM protein (cystein-rich protein 3)	0.44

MHC, major histocompatibility complex.

The average of patients with SS healthy subjects based on cDNA array fluorescent data healthy subjects (n=3, each). The Mann-Whitney U test was used to compare the control and SS groups.

*p<0.05.

expressed genes in SS LSG represented those with expression level over twofold or below 0.5-fold of that of LSGs of the controls. The Mann-Whitney U test was used for statistical analysis. p Values <0.05 were considered significant.

A total of 24 upregulated genes were identified in LSGs (table 1). These included immunoglobulins, HLAs, complements, TCRs, IFN-inducible proteins, thymosin β and transcriptional factors. We also identified one single downregulated gene, LIM protein. Among the abnormally expressed genes in SS LSG, expression level 19 was significantly higher than in the controls. These included thymosin $\beta 4$ and thymosin $\beta 10$, the regulators of apoptosis activity and inflammation-related genes such as HLA-DR and TCR β . Upregulation of HLA, complements, TCRs and immunoglobulins should be due to the infiltration of T cells and B cells in LSGs from patients with SS. Interestingly, many IFN γ -inducible genes, such as IP10, STAT1 α and STAT1 β , were highly expressed in SS, and our previous study reported

that STAT1 could function as a key molecule in the pathogenesis of SS.⁶ These findings suggest that Th1 cells and Th1 type cytokines function as destructive factors in the generation of sialoadenitis in LSGs of patients with SS. Thymosin β has anti-apoptotic activity,⁷ suggesting that it may function as a protective factor against salivary gland destruction in patients with SS.

Recent studies reported the presence of germinal centre-like structures in the salivary glands of patients with SS, and that the germinal centre formed by infiltrating mononuclear cells (B cells, T cells and others) produces autoantibodies and exhibits apoptosis.^{8,9} In this study, the significant upregulation of 10 genes—for example, IgHC γ , HLA class I, HLA class II, C3 and TCR β —might be due to mononuclear infiltrates and might be responsible for the formation of a germinal centre, in LSGs of patients with SS.

In conclusion, cDNA microarray analysis demonstrated upregulation of IFN γ -related genes in LSGs of patients with SS, indicating that Th1 cells might play a crucial role in the generation of sialoadenitis in those patients.

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Accepted 21 December 2006

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