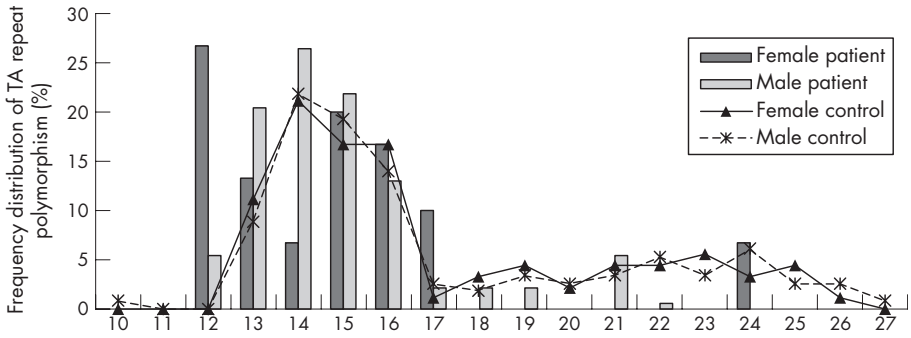

Figure 1 Frequency distribution of oestrogen receptor gene thymine–adenine (TA) repeats polymorphism in patients with gout and healthy controls.

Table 1 Mean (SD) of the oestrogen receptor gene thymine–adenine repeats and androgen receptor gene *CAG* repeats for patients with gout and healthy controls

	Women			Men		
Group	**n**	**Mean (SD)**	**p Value**	**n**	**Mean (SD)**	**p Value**
OR gene *TA* repeats						
Control	90	17.0 (3.8)	0.002	114	17.2 (4.0)	<0.001
Gout	30	14.8 (3.0)		362	14.9 (2.1)	
AR gene *CAG* repeats						
Control	84	22.0 (2.8)	0.928	55	21.4 (2.9)	0.300
Gout	30	21.9 (2.9)		181	21.9 (2.9)	

AR, androgen receptor; OR, oestrogen receptor; TA, thymine–adenine.

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Accepted 11 March 2006

REFERENCES

1 **Anton FM**, Puig JG, Ramos T, Gonzalez P, Ordas J. Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 beta (E_2) on the renal handling of urate. *Metabolism* 1986;**35**:343–8.
2 **Marinello E**, Giuseppe RS, Marcolongo R. Plasma follicle-stimulating hormone, luteinizing hormone, and sex hormones in patients with gout. *Arthritis Rheum* 1985;**28**:127–31.
3 **Yahata T**, Quan J, Tamura N, Nagata H, Kurabayashi T, Tanaka K. Association between single nucleotide polymorphisms of estrogen receptor alpha gene and efficacy of HRT on bone mineral density in post-menopausal Japanese women. *Hum Reprod* 2005;**20**:1860–6.
4 **Pollak A**, Rokach A, Blumenfeld A, Rosen LJ, Resnik L, Dresner P R. Association of oestrogen receptor alpha gene polymorphism with the angiographic extent of coronary artery disease. *Eur Heart J* 2004;**25**:240–5.
5 **Takagi H**, Ishiguro N, Iwata H, Kanamono T. Genetic association between rheumatoid arthritis and estrogen receptor microsatellite polymorphism. *J Rheumatol* 2000;**27**:1638–42.
6 **Kawasaki T**, Ushiyama T, Ueyama H, Inoue K, Mori K, Ohkubo I, *et al.* Polymorphic CAG repeats of the androgen receptor gene and rheumatoid arthritis. *Ann Rheum Dis* 1999;**58**:500–2.
7 **Mori K**, Usyiyama T, Inoue K, Hukuda S. Polymorphic CAG repeats of the androgen receptor gene in Japanese male patients with ankylosing spondylitis. *Rheumatology* 2000;**39**:530–2.
8 **Alevizaki M**, Cimponeriu AT, Garofallaki M, Sarika HL, Alevizaki CC, Papamichael C, *et al.* The androgen receptor gene CAG polymorphism is associated with the severity of coronary artery disease in men. *Clin Endocrinol* 2003;**59**:749–55.
9 **Wallace SL**, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü T-F. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977;**20**:895–900.

Hyperimmunoglobulinaemia D syndrome in India: report of two siblings with a novel mutation

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Ann Rheum Dis 2006;**65**:1674–1676. doi: 10.1136/ard.2006.054494

Hyperimmunoglobulinaemia D syndrome (HIDS) is an autosomal recessive auto-inflammatory syndrome caused by mutation in the mevalonate kinase (MVK) gene.[1] It presents with febrile episodes starting in infancy with increased serum immunoglobulin (Ig)D levels.[2] It is mostly described in people of Dutch or North European descent.[3] Isolated cases have been reported from Turkey,[4]

Abbreviations: HIDS, hyperimmunoglobulinaemia D syndrome; MVK, mevalonate kinase

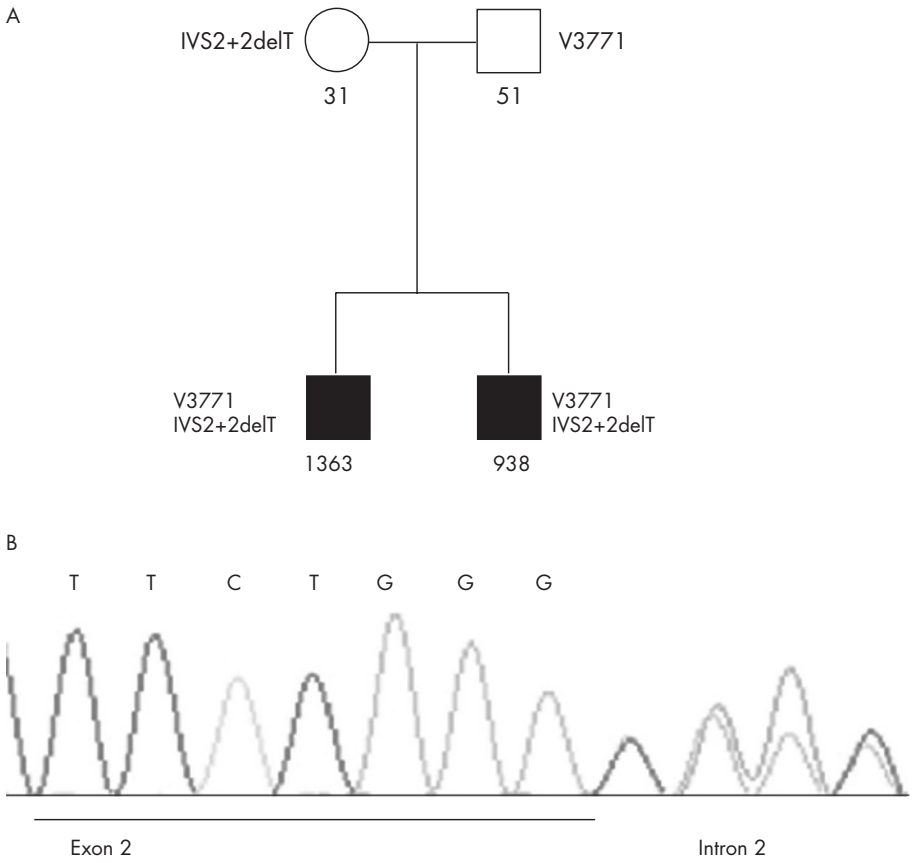

Figure 1 (A) depicts the family tree of hyperimmunoglobulinaemia D syndrome. Females are indicated by circles and males by squares. Solid symbols denote affected members. The mevalonate kinase (MVK) mutations are listed on the left and right sides of the members. Note that the parents are heterozygotic for MVK mutations whereas both siblings are compound heterozygotic for V377I and IVS2+2 delT. The IgD serum concentrations are listed below the members. The serum concentrations of the affected siblings are grossly increased (normal <100 IU/ml), whereas those of the nonaffected father and mother are normal. (B) shows the electrospherogram with sequence identification of the deletion of a T nucleotide in intron 2. This mutation, IVS2+2 delT, is predicted to affect correct splicing of the exon, resulting in a shift of the reading frame.

Japan[5] and Qatar.[6] No case of HIDS has been reported from South Asia.

A 15-year-old boy from Kerala, India, presented with history of febrile episodes lasting 3–7 days since the age of 3 months. The episodes of fever were variably associated with polyarthritis, abdominal pain, headache, vomiting, diarrhoea, pleuritic chest pain and erythematous papular rash. The episodes occurred at an interval of 1–6 months. He underwent a laparotomy at the age of 8 years, when peritoneal adhesions were detected. During the few episodes of fever, liver, spleen and lymph node enlargement, raised erythrocyte sedimentation rate and leucocytosis were found. He showed good response to non-steroidal anti-inflammatory drugs. His total serum cholesterol was 132 mg/dl. Serum IgG, IgM, IgA and IgD levels were 1465 mg/dl, 58.6 mg/dl, 1166 mg/dl and 938 IU/ml, respectively.

The 11-year-old brother of the proband had also suffered similar episodes of fever since the age of 2 months, except that he had arthritis only once. A laparotomy performed at the age of 4 years revealed peritoneal adhesions. Serum IgG, IgM, IgA and IgD levels were 1377 mg/dl, 119.1 mg/dl, 633 mg/dl and 1363 IU/ml, respectively.

The pedigree analysis was compatible with an autosomal recessive pattern of inheritance. The MVK gene analysis showed both sibs to be compound heterozygotes for V377I and IVS2+2delT. The father carried the V377I allele and the mother possessed the IVS2+2delT allele (fig 1).

The presence of recurrent episodic fever in two siblings with evidence of serositis suggested familial Mediterranean fever or HIDS. The duration of the episodes (3–7 days), prominence of diarrhoea and vomiting along with the early onset in infancy pointed to HIDS. HIDS is associated with increased concentrations of serum IgA and IgD,[7] and both our patients had increased concentrations. One patient with proven HIDS has been reported[6] from Doha (with Palestinian ancestry). Although there is a report of HIDS from Japan,[5] no MVK mutation has been reported. Our patients had increased serum IgD concentrations along with MVK mutation (ancestral 1129G>A(V377I) mutation along with a novel mutation IVS2+2delT). The presence of a mutation on both alleles of MVK confirmed the diagnosis of HIDS.

V377I mutation is seen mostly in patients of Dutch descent.[3] The Dutch East India company had a trading relationship with Kerala, India, and the present family hails from Kerala. The gene could have come along with the European traders or through a Mediterranean route with Arab traders. A recent report of a patient with HIDS from Qatar[6] with V3771 mutation and absence of any Dutch ancestry in the family supports the second view. The second mutation, IVS2+2delT, is reported for the first time. This mutation probably results in aberrant splicing and shifts the reading frame.

ACKNOWLEDGEMENTS

We thank Dr Remesh Bhasi, Consultant Rheumatologist at Malabar Institute of Medical Sciences, Kozhikode, for referring the patients to us for evaluation.

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Accepted 23 April 2006

REFERENCES

1 **Drenth JP**, Cuisset L, Grateau G, Vasseur C, van de Velde-Visser SD, de Jong JG, *et al*. Mutations in the gene encoding mevalonate kinase cause hyper-IgD and periodic fever syndrome. International Hyper-IgD Study Group. 1. *Nat Genet* 1999;**22**:178–81.
2 **Drenth JP**, Haagsma CJ, van der Meer JW. Hyperimmunoglobulinemia D and periodic fever syndrome. The clinical spectrum in a series of 50 patients. International Hyper-IgD Study Group. *Medicine (Baltimore)* 1994;**73**:133–44.
3 **Simon A**, Mariman EC, van der Meer JW, Drenth JP. A founder effect in the hyperimmunoglobulinemia D and periodic fever syndrome. *Am J Med* 2003;**114**:148–52.
4 **Topaloglu R**, Saatci U. Hyperimmunoglobulinaemia D and periodic fever mimicking familial Mediterranean fever in the Mediterranean. *Postgrad Med J* 1991;**67**:490–1.
5 **Miyagawa S**, Kitamura W, Morita K, Saishin M, Shirai T. Association of hyperimmunoglobulinaemia D syndrome with erythema elevatum diutinum. *Br J Dermatol* 1993;**128**:572–4.
6 **Hammoudeh M**. Hyperimmunoglobulinemia D syndrome in an Arab child. *Clin Rheumatol* 2005;**24**:92–4.
7 **Klasen IS**, Goertz JH, van de Wiel GA, Weemaes CM, van der Meer JW, Drenth JP. Hyper-immunoglobulin A in the hyperimmunoglobulinemia D syndrome. *Clin Diagn Lab Immunol* 2001;**8**:58–61.

HLA-DRB genotyping of an Italian mummy from the 16th century with signs of rheumatoid arthritis

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Ann Rheum Dis 2006;**65**:1676–1677. doi: 10.1136/ard.2006.051490

Some paleopathological studies suggest that rheumatoid arthritis originated in the New World (among ancient Native Americans in Tennessee and neighbouring areas, 5000–500 BC); only after the discovery of America was the origin of the disease attributed to the Old World.[1] In 1996, under the floors of the San Francisco church (Arezzo, Italy), a female mummy was discovered. This 50–55-year-old woman, re-named the ''Braids Lady'', died at the end of the 16th century. Several diagnostic examinations disclosed distinctive rheumatoid arthritis skeletal deformities due to rheumatoid arthritis in her body: large erosions of the metacarpophalangeal joints of the left hand; lateral deviation of all the fingers, with a typical ''Z'' deformation of the first one; and partial overlapping and fibular deviation of the toes, but no involvement of sacroiliac articulation, a prominent symptom of ankylosing spondylitis.[2]

It is well known that several autoimmune disorders are related to highly polymorphic and codominantly expressed antigens encoded by the human leucocyte antigen (HLA) complex. The association between rheumatoid arthritis and some of the alleles of the HLA-DRB1 locus, such as DRB1*0101, DRB1*0401, DRB1*0404, DRB1*0405, DRB1*1402, and to a lesser degree DRB1*1001, has been well established. A high percentage (>90%) of people affected by this disorder possess some alleles of the DRB1*01 or DRB1*04 gene families.[3] Therefore, the purpose of this study was to define the HLA-DRB genotype of the ''Braids Lady'' and establish the presence or not of rheumatoid arthritis susceptibility genes. Molecular analysis was performed on DNA extracts of the mummy, and two different HLA typing techniques, polymerase chain reaction-sequence-specific oligonucleotides (PCR-SSO) and PCR-sequence-specific primers (PCR-SSP), were used to identify HLA-DRB alleles. The PCR-SSO analysis showed the presence of the DRB1*0101 and DRB1*1101 alleles (corresponding to DR1 and DR11 serotypes, respectively), with positivity for the DRB3 gene (phenotypically DR52). The assignment of the allele DRB1*0101 was confirmed by the results of the PCR-SSP test.

A pathogenetic hypothesis of rheumatoid arthritis that might well explain its worldwide diffusion is ''molecular mimicry'', resulting from a cross-reactive antibody response between certain microbial antigens (among which are *Proteus mirabilis* haemolysins and Epstein–Barr virus glycoprotein 110) and shared epitopes of some specific HLA-DR1, DR4 and DR14 susceptibility genes.[4–6] Additionally, HLA-DRB1 alleles and the frequency of their shared epitopes may vary between different ethnic groups. For example, DRB1*0101, DRB1*0401, and *0404–05 share the epitope Q(K/R)RAA, which is associated with rheumatoid arthritis in Mediterranean patients, including Italians;[7] DRB1*1402, 0802 and 0407, on the other hand, are absent or poorly represented in the Italian population, have a significantly higher gene frequency among Native Americans than other DRB1 alleles (Navajo and Pimans of the Gila River Indian community of Arizona, the Lakota Sioux, the Seri tribe of Northwest Mexico).[8 9] Interestingly, among patients with rheumatoid arthritis from several Native American groups, neither HLA-DR1 nor DR4 was found to be associated with specific features of rheumatoid arthritis or the severity of the disease.[10] Hence, it is more than probable that various aetiological agents could have acted on different susceptibility HLA alleles bearing shared epitopes and occurring with different frequencies within populations. Although the possession of rheumatoid arthritis risk-factor genes cannot be considered a diagnostic marker, the positive result for DRB1*0101 and the presence of rheumatoid arthritis features in the Italian mummy support the idea that this disease was present in the Old World since at least the mid-16th century.

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Abbreviations: HLA, human leucocyte antigen