Table 1 BclI restriction fragment length polymorphism of human glucocorticoid receptor gene in Korean patients with RA versus healthy controls

	RA (n = 149)	Controls (n = 149)	χ^2	p Value	OR	95% CI
Genotype						
GG	77 (51.7)	86 (57.7)	2.55	0.28		
GC	63 (42.3)	59 (39.6)				
CC	9 (6.0)	4 (2.7)				
Allele						
G	217 (72.8)	231 (77.5)	1.76	0.18	0.78	0.53 to 1.13
C	81 (27.2)	67 (22.5)				

RA, rheumatoid arthritis; CI, confidence interval.

5′-AAA TTG AAG CTT AAC AAT TTT GGC-3′, and 5′-GCA GTG AAC AGT GTA CCA GAC C-3′ as primers, and BclI endonuclease (New England Bioblabs, Beverly, USA).[5]

Genotype or allele frequencies of hGR +647 G/C did not differ between patients with RA and controls (table 1) (allele frequencies of hGR G/C were 0.73/0.27 in patients and 0.78/0.22 in the controls (p = 0.18, OR = 0.78, 95% CI 0.53 to 1.13). Subgroup analysis showed no genotype or allele frequency differences between the patients with rheumatoid factor, joint erosion, or extra-articular complications and the healthy controls. When patients were stratified according to HLA-DR4 status, these results were unchanged. In conclusion, hGR +647 G/C polymorphisms probably do not play a part in the pathogenesis of RA in Korean patients.

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Tenascin-X: a candidate gene for benign joint hypermobility syndrome and hypermobility type Ehlers-Danlos syndrome?

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Joint hypermobility is a common finding, differing strongly between sexes and among races.[1] Joint hypermobility is not a disease in itself, but it can be part of heritable connective tissue disorders, such as Marfan syndrome, Ehlers-Danlos syndrome (EDS), and benign joint hypermobility syndrome (BJHS).[2] Although Marfan syndrome and most types of EDS are clinically relatively easy to distinguish by their cardinal features, it is often less easy to differentiate between the hypermobility type of EDS (HT-EDS, formerly type III) and BJHS. Recently, Grahame *et al* proposed a validated set of diagnostic criteria for BJHS[3]: the revised Brighton 1998 criteria. Its major criteria are a Beighton score of 4/9 or greater and arthralgia, but the diagnosis can also be based on the presence of minor criteria, including abnormal skin and joint (sub)luxations. HT-EDS can be identified by the Villefranche criteria; the major criteria of this classification include a Beighton score of 5/9 or greater and skin involvement.[4] Clearly, there is considerable overlap in the clinical features of BJHS and HT-EDS.

Little is known about the genetic basis of HT-EDS or BJHS. Recently, we have shown that haploinsufficiency for the extracellular matrix protein tenascin-X is associated with HT-EDS.[5] Tenascin-X is abundantly expressed in almost all connective tissues, and a 140 kDa fragment is present in

serum. The level of serum tenascin-X probably reflects the rate of tenascin-X synthesis in the connective tissues, because subjects who are heterozygous for a tenascin-X null allele express about half of the normal level in their serum.[6] Clinically, tenascin-X haploinsufficient subjects show generalised joint hypermobility, arthralgia, and about 40% of them have abnormal skin.

In this study, we investigated whether haploinsufficiency for tenascin-X also occurs in subjects who are diagnosed with BJHS. In collaboration with the Dutch BJHS patient organisation, we collected serum samples from 54 patients (53 female) diagnosed with BJHS by a medical specialist, most of whom were rheumatologists. We measured tenascin-X serum levels in these patients, and found that the mean (SD) level in the BJHS cohort group did not differ from that in the control group (97.6 (25.8)% *v* 100 (14.1)%, respectively). Of these patients, 14 (26%) had a tenascin-X serum level below the 5th centile of the controls (crude odds ratio 6.4, 95% confidence interval 2.5 to 16.3). Furthermore, four of these patients (7%, all female) had serum tenascin-X levels more than 2.5 standard deviations of control (65%) below the mean for normal subjects. Only 0.6% of subjects would be expected to have such low tenascin-X serum values based on the normal distribution, which is significantly less than the prevalence found in this BJHS group ($p<0.05$, Fisher's exact test). Interestingly, the percentage of reduced tenascin-X serum levels in BJHS is similar to the percentage we described in HT-EDS. None of the previously identified truncating tenascin-X mutations were present in any of the patients. It is likely that these patients may have other mutations of tenascin-X or they may represent the extreme in normal variation of tenascin-X expression. Only two patients were available for clinical examination. Both patients had hypermobile joints, often associated with joint subluxations, and chronic musculoskeletal pain.

We have shown that reduced tenascin-X serum levels are present in 5–10% of the patients diagnosed with BJHS or HT-EDS.[5] These findings and the considerable overlap of the clinical symptoms suggest that no meaningful distinction can be made between these conditions. Both BJHS and HT-EDS are likely to be genetically heterogeneous and, clearly, the search for candidate genes has only just begun.

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Multiple venous thrombosis in SAPHO syndrome

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A 42 year old Japanese woman presented to our clinic complaining of severe pain in her neck, both shoulders, and lumbar spine. She had had pustulosis palmaris and plantaris from age 16 and recurrent painful swelling of the clavicles, the sternoclavicular joints, and the sternum from age 25. She reported multiple visits to the doctor for similar symptoms, and she was treated with non-steroidal anti-inflammatory drugs.

On initial examination at our clinic, her lumbar and cervical spine mobility was limited considerably. She had an oedematous face and subcutaneous collateral circulation on chest and abdomen. Laboratory testing showed a white cell count of 13.5×10^9/l and a C reactive protein of 142 mg/l (normal <5). Antinuclear antibodies, antineutrophil cytoplasmic antibodies, anticardiolipin antibodies, lupus anticoagulants, and rheumatoid factors were all negative. Prothrombin time and activated partial thromboplastin time were normal. Locus B HLA typing was positive for B48 and B52. She reported that her C reactive protein level was always over 100 mg/l.

Plain radiographs disclosed marked hyperostosis in the medial aspect of both clavicles. There was narrowing and ankylosis in the apophysial joints of the cervical spine, and complete ankylosis in both sacroiliac joints. Contrast enhanced computed tomographic scans demonstrated a soft tissue mass in the upper mediastinum (fig 1A). Both subclavian veins were severely stenotic, and the superior vena cava (SVC) was almost completely occluded (fig 1B). Thrombosis was seen within the left internal jugular vein, and the right internal jugular vein could not be observed (fig 1C). Injection of contrast medium showed a network of collateral veins in the neck, chest, and abdominal wall. A diagnosis of SAPHO syndrome complicated by multiple venous thrombosis and SVC syndrome was made. Prednisolone was given at 10 mg/day, and the pain in her shoulders, neck, and lumbar spine improved. The treatment also included warfarin for anticoagulation.

DISCUSSION

Venous thrombosis complicating SAPHO syndrome is uncommon. In a series of 120 patients with this syndrome, Hayem *et al* found that only one (0.8%) patient had thrombosis of the subclavian vein.[1] We found eight well documented cases of patients with SAPHO syndrome who developed venous thrombosis.[2–8] Six of the patients had subclavian vein thrombosis,[2–6] and only one case had SVC