Periostin gene variants are associated with disease course and severity in juvenile idiopathic arthritis

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Abstract

Objective

This study aimed to identify polymorphic variants of the Periostin gene associated with disease severity and clinical course in children with juvenile idiopathic arthritis.

Methods

DNA genotyping of 7 single-nucleotide polymorphisms within the periostin gene was performed in 117 patients and their parents and in 102 control samples. Our patients were divided in the following 4 disease categories: 1) persistent oligoarthritis; 2) extended oligoarthritis; 3) polyarthritis; 4) systemic arthritis. Quantitative association analysis was performed in order to test for association between the 7 genetic variants and 18 selected clinical traits.

Results

A harmful association was observed between the minor allele of rs17197936 and 2 clinical traits, count of joints with active arthritis and count of joints with pain on motion/tenderness, in patients with extended oligoarthritis. Furthermore, the haplotype represented by the minor allele variants of rs3829364, rs6750 and rs9547951 showed an unfavourable association with the above 2 traits plus the following 3 in the whole patient group: juvenile arthritis damage index articular score, childhood health assessment questionnaire score and disease duration.

Conclusion

These associations suggest that the variants involved can be regarded as genetic factors influencing some phenotypic aspects of juvenile idiopathic arthritis. Genotyping of this gene may represent a useful tool to identify patients who are at greatest risk of experiencing a poorer long-term outcome.

Key words

periostin, juvenile idiopathic arthritis, genotype-phenotype association

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children and an important cause of short-term and long-term disability (1). It is a heterogeneous condition, which is classified into different subtypes on clinical grounds. Based on the current International League of Associations for Rheumatology (ILAR) classification, 7 subtypes, named disease categories, are identified (2). The most common of these categories in Western population are the following: oligoarthritis, which is defined as an arthritis that affects 4 or fewer joints during the first 6 months of disease and is then sub-classified in persistent oligoarthritis, in which the disease remains confined to 4 or fewer joints throughout the whole disease course, and extended oligoarthritis, in which arthritis extends to more than 4 joints after the first 6 months of disease; polyarthritis, which is defined as an arthritis that affects 5 or more joints, and is sub-classified as rheumatoid factor (RF)-positive or RF-negative, depending on the presence or absence of RF; systemic arthritis, which is characterised by the association of arthritis with particular extra-articular features, including high-spiking intermittent fever, skin rash, hepatosplenomegaly, generalised lymphoadenopathy, and serositis. JIA is characterised by prolonged synovial inflammation that may lead to permanent alterations in joint structures. However, the cause of the chronic inflammatory processes targeting the synovium in JIA is not yet known.

Periostin (POSTN) is a multifunctional, 90-kDa, secreted extracellular matrix (ECM) protein originally identified in bone and implicated in regulating adhesion and differentiation of osteoblasts. Periostin also contributes in tumour angiogenesis, metastatisation, and cell migration (3). Periostin can also regulate type1 collagen expression in fibroblasts (4), and in airway epithelial cells and promotes fibrillogenesis and epithelial to mesenchymal transition (EMT) in asthmatic subjects (5). The POSTN gene is expressed in several normal adult tissues, with the highest expression in connective tissues such as bone, skin, periodontal ligament and heart valves (6, 7). Periostin was found highly upregulated in patients with atherosclerotic and rheumatic valvular heart disease (VHD). The cardiac valvular complex and cartilage are both avascular tissues and resistant to vascular invasion in virtue of their matrix composition and of the generation of antiangiogenic factors, such as troponin-1, chondromodulin-1 and of tissue inhibitors of metalloproteinases (TIMP) by articular chondrocytes (8).

Periostin interacts with ECM components such as integrins $\alpha v\beta 3$ and $\alpha v\beta 5$ (9) and matrix metalloproteinases (MMPs): MMP-2, MMP-9, and MMP-13, this latter plays a critical role in degenerative bone diseases, such as osteoarthritis and rheumatoid arthritis (10). The cartilage and tendons express chondromodulin I and tenomodulin, respectively (11), their disruption results in angiogenesis and destruction of the joints leading to arthritis (12).

Periostin regulates collagen fibrillogenesis and collagen cross-linking and is essential to the biomechanical properties of fibrous connective tissues (13). Periostin expression and secretion can be induced by several factors and cytokines, including TGF-β, IL-4 and IL-13, in wound-site healing processes, in fibroblasts of periosteum, in synovial membranes and connective tissues, particularly those subject to high levels of mechanical loading (14). In virtue of its function, periostin is a candidate player in the pathogenesis of joint diseases, such as rheumatoid arthritis (RA), osteoarthritis (OA) and, possibly, JIA (15). Because of its role in extracellular matrix organisation, epithelial-mesenchymal interactions, development and wound repair of connective tissue, and angiogenesis, we considered POSTN as a good candidate for a gene association study in JIA.

Methods

Study design and patient selection

Peripheral blood samples were collected from 117 JIA patients and their parents (96 patients with both parents tested and 21 patients with only one parent tested) and 102 unrelated control subjects. We analysed the patient samples both as a whole and subdivided in

Table I. Number of JIA patients stratified by subtype and clinical characteristics analysed.

JIA subtypes	Number	Percentage
1 Oligoarthritis persistent	45	38.4
2 Oligoarthritis extended	30	25.6
3 Polyarthritis	32	27.3
4 Systemic arthritis	10	8.54
	n=117	

	Clinical traits	Definition
1	ANA	Antinuclear antibody
2	Tender joint count (TJC)	Number of joints with pain on motion/tenderness
3	Swollen joint count (SJC)	Number joints with swelling
4	Restricted joint count (RJC)	Number of joints with limited range of motion
5	Active joint count (AJC)	Number of joints with active disease
6	Steinbrocker	Steinbrocker functional class
7	MD-disabil	Physician global assessment of patient's disability
8	PAR disabil	Parent global assessment of patient's disability
9	ESR	Erythrocyte sedimentation rate, mm/h
10	Stiffness	Duration of morning stiffness, minutes
11	MD global	Physician Visual Analogue Scale
12	CHAQ	Childhood Health Assessment Questionnaire score
13	PAR glob	Parent global assessment of patient's well-being
14	PAR Pain	Parent assessment of patient's pain
15	CRP	C-reactive protein, mg/d
16	Dis dur	Disease duration, years
17	JADI-E	Juvenile Arthritis Damage Index (JADI) Extra-articular score
18	JADI-A	JADI Articular score

the following 4 subtypes according to the ILAR classification and characterised by increasing disease severity: 1) oligoarthritis persistent; 2) oligoarthritis extended; 3) polyarthritis; 4) systemic arthritis; furthermore, eighteen selected clinical traits were considered for the study (Table I). All consecutive patients were included who were seen as inpatients or outpatients between September, 2002 and December, 2006 at the paediatric rheumatology units of the Istituto G. Gaslini of Genova, Italy and the Fondazione Policlinico S. Matteo of Pavia, Italy, and met the following entry criteria: 1) diagnosis of JIA by the 2001 revised ILAR criteria); 2) disease duration of at least 5 years; 3) informed consent to participate in the study, provided by the patient or a parent/guardian, as applicable. All patients first seen before the publication of ILAR criteria for JIA were re-classified using such criteria.

Clinical assessment

At the time of the study visit, the following information was obtained for each patient by reviewing clinical charts: sex, age at disease onset, ILAR category, disease duration (Dis dur) and age at study visit, and previous therapies with second-line drugs, biologic agents, systemic corticosteroids, and intra articular corticosteroids.

The following clinical assessments were made by the attending paediatric rheumatologist: physician's global assessment of disease activity (MD global) on a 10-cm visual analogue scale (VAS) (0 = no activity; 10 = maximum activity) and disability (MD disabil) on a 1 to 6 categorical scale (1 = no disability; 6 = severe disability); swollen joint count (SJC); tender joint count (TJC); restricted joint count (RJC); active joint count (AJC) (16). The attending physician also assigned the Steinbrocker's functional classification (17). A parent of each patient (the mother, whenever possible) was asked to make a global assessment of the child's well-being (PAR glob) on a 10-cm VAS (0 = very good; 10 = very poor) and disability (PAR disabil) on a 1 to 6 categorical scale (1 = no disability; 6 = severe disability), to rate the intensity of the child's pain (PAR pain) on a 10-cm VAS (0 = no pain; 10 = very severe pain), to evaluate the presence and duration of morning stiffness (Stiffness), and to complete the Italian version of the CHAQ (0 = best; 3 = worst) (18). For purposes of the analysis, the CHAQ score was divided into 4 categories: 0 = no disability; >0 and ≤0.5 = mild disability; >0.5 and ≤1.5 = moderate disability; and >1.5 = severe disability (19). The laboratory assessment of JIA activity included the erythrocyte sedimentation rate (ESR), determined with the Westergren method, and the C-reactive protein (CRP), determined with nephelometry. Patients were classified as having inactive disease if they had no joints with active arthritis, no systemic manifestations attributable to JIA, normal acute phase reactants, and an MD global indicating no disease activity (20). The amount of articular and extraarticular damage was assessed by the attending paediatric rheumatologist through the Juvenile Arthritis Damage Index (JADI) (21). Briefly, this index is composed by two parts, one devoted to the assessment of articular damage (JADI-A) and one devoted to the assessment of extraarticular damage (JADI-E). In the JADI-A, 36 joints or joint groups are assessed for the presence of damage and the damage observed in each joint is scored on a 3-point scale (0 = no damage; 1 = partial damage; 2 = severe damage, ankylosis, or prosthesis). In individual joints, contractures and other joint deformities are scored only when they are completely explained by prior damage, are not due to currently active arthritis, and are present for at least 6 months. The maximum total score is 72. The JADI-E includes 13 items in 5 different organ/systems. Extraarticular damage is defined as persistent change in anatomy, physiology, pathology, or function, which may occur since the disease presentation, may result from previous disease activity, or its treatment, and is present for at least 6 months. Each item is scored as 0 or 1 if damage is absent or present, respectively. Due to the relevant impact of ocular damage on the child health, in each eye a score of 2 is given in case the patient has had ocular surgery and a score of 3 in case the patient has developed legal blindness. The maximum total score is 17. Patients were defined as being antinuclear antibody (ANA) positive if they had at least 2 positive results on indirect immunofluorescence at a titer of ≥1:160, as previously reported (22).

Genotyping

We selected seven tag SNPs (Table II)

of the POSTN gene [chromosome position: 13q13.3; length: 36.09 kb; Reference Sequence: NM_006475; sequence position in chr. 13: 38136719-38172981; 23 exons], using data from the HapMap Genome Browser regarding the European population and the pairwise r^2 tagger method from Haploview software (23) using the following selection criteria: r^2 ≥0.8 and MAF ≥0.08. All subjects were genotyped for these SNPs using newly designed primers for Polymerase Chain Reaction (PCR), target sequence amplification was performed in a volume of 10 µl using 25ng of DNA extracted from whole blood. The PCR conditions were the followings: a first denaturing step at 96°C for 7 minutes (using Taq Gold DNA polymerase by Applied Biosystems, Life Technology, Monza-Italy) followed by 35 amplification cycles of denaturing at 94°C for 45 seconds, annealing between 57°C and 60°C (according to the nucleotide content of the primers) for 35 seconds and extension at 72°C for 45 seconds. The PCR products were then purified by vacuum using microplates for DNA purification and following the manufacturer's instructions (Millipore S.p.A., Vimodrone (Mi) Italy). Direct sequencing reactions were performed using Big Dye sequencing kit and the manufacturer's instructions (Applied Biosystems). The sequencing reactions were run on a 16 capillary sequencing apparatus (3130xl Genetic Analyzer, Applied Biosystems) and then analysed using the Sequencer 4.7 program (Gene Codes Corporation, Ann Arbor, MI 48108 USA).

Results

Genotype frequencies and statistical analysis

The allele and genotype frequencies (Table II) obtained from our control population were similar to those reported in the literature (Hap-Map and National Center for Biotechnology Information (NCBI) genome browsers). All markers were tested for the Hardy-Weinberg Equilibrium (HWE) in both control and patient populations and none of them showed significant deviation from HWE (p>0.001).

Statistical analysis of genotype data was performed using Plink software, version 1.07-dos, using Wald association test and linear regression analysis with additive model in order to test for the additive effect of allele dosage (24).

Table II. Selected POSTN SNPs.

Position of the SNPs in the POSTN gene, MAF and HWE in our control polulation.						
SNPs	bp position	Gene location	A2/A1	H-M MAF	Our MAF	HWE (P)
rs17197936	-2976	5' near gene	A/G	0.093	0.088	0.56
rs17197908	-2881	5' near gene	C/A	0.15	0.22	1.00
rs2957208	-2824	5' near gene	C/T	0.32	0.36	0.83
rs17056196	-2781	5' near gene	G/A	0.13	0.17	0.16
rs3829364	-1670	5' near gene	A/G	0.14	0.15	0.69
rs6750	36032	Exon 23 UTR	G/C	0.13	0.16	0.46
rs9547951	36182	3' near gene.	G/T	0.36	0.36	1.00

SNP: nomenclature as from NCBI and Hap-Map genome browsers; bp position: distance of the SNP (in base-pairs) from the first base of the coding sequence; Gene location: position of the SNP with regard to direction of transcription; A2: major allele; A1: minor allele; H-M MAF: minor allele frequency from Hap-Map European population; our MAF: minor allele frequency in our control population; HWE (P): *p*-values obtained from the Hardy–Weinberg Equilibrium test performed by Plink software; UTR: Untranslated Region.

Single marker quantitative trait association analysis

Wald association test and linear regression analysis were performed in order to find a significant association of the considered minor allele SNP variants (independent or predictor variables) with the considered 18 clinical traits (dependent or response variables) which describe the clinical course and disease severity in JIA patients. In Table III, we show the value of the regression coefficient BETA, its 95% CI, the standard error (SE), the coefficient of t-statistics (STAT), and the values of R^2 and adjusted R^2, these latter represent the fraction of variation of our dependent variable that is predicted by our independent variable calculated in our sample (R^2) and adjusted in the population (adj R^2), respectively. Furthermore, besides the asymptotic *p*-value for t-statistic, we used two levels of permutation procedure to obtain two empirical significance values, EMP1 and EMP2, in order to correct for both pointwise estimates of individual SNP significance and multiple testing, respectively. A total of 100,000 permutations were performed in each test. When permitted by the software, the asymptotic *p*-values were submitted to seven different algorithms to obtain genomic-control (GC) corrected *p*-values and other corrections for multiple comparisons. The results from this analysis showed that the minor allele G of SNP rs17197936 was significantly associated with increased values of two clinical traits, AJC and TJC, in patients belonging to class 2 (oligoarthritis extended), meaning that, under the influence of this allele, an increased number of joints are involved in the disease. A strong statistical significance was maintained after all 7 correction procedures. We confirmed the above described association using a further test called Family-based association test for Quantitative traits (QFAM) (available in Plink software), which is based on linear regression of phenotype on genotype, but includes a special permutation procedure that corrects for family structure. Again, a significant association was obtained between the minor allele G of rs17197936 and the AJC and TJC clinical traits in class 2 patients. The association remained significant after all adjustments for genomic control and multiple testing. Figure 1 provides a graphic representation of the significant results obtained from this single marker association analysis.

Haplotype-based quantitative trait association analysis

Linear regression was used for this haplotype analysis, the same parameters as for single markers and two levels of permutation procedure were reported. The results of this test showed significant association of five clinical traits (AJC, TJC, CHAQ, JADI-A and Dis dur) with the haplotype formed by the minor alleles of the following three SNPs: rs3829364, rs6750, rs9547951, in all ILAR categories of patients ana-

Table III. Single marker quantitative trait association analysis.

Combined results from Wald test and linear regression analysis

clinical trait	SNP	A1	BETA	SE	L95	U95	STAT	R^2	adj R^2	P	EMP1	EMP2	NP
AJC-2	rs17197936	G	7.88	1.53	4.88	10.89	5.14	0.49	0.45	2.072e-005	0.0005	0.0007	100 000
TJC-2	rs17197936	G	7.84	1.44	5.01	10.68	5.43	0.52	0.48	9.503e-006	0.0002	0.0003	100 000

Correction of linear regression data for multiple testing

clinical trait	SNP	UNADJ	GC	BONF	HOLM	SIDAK_SS	SIDAK_SD	FDR_BH	FDR_BY
AJC -2	rs17197936	2.072e-005	0.035	0.0001	0.0001	0.0001	0.0001	0.0001	0.0003
TJC -2	rs17197936	9.503e-006	0.011	6.652e-005	6.652e-005	6.652e-005	6.652e-005	6.652e-005	0.0001

Results from the QFAM analysis

clinical trait	SNP	EMP1	NP
AJC -2	rs17197936	0.001	100 000
TJC -2	rs17197936	0.0002	100 000

Correction of QFAM data for multiple testing

clinical trait	SNP	UNADJ	GC	BONF	HOLM	SIDAK_SS	SIDAK_SD	FDR_BH	FDR_BY
AJC -2	rs17197936	0.001	0.036	0.011	0.011	0.011	0.011	0.011	0.03
TJC -2	rs17197936	0.0002	0.001	0.001	0.001	0.001	0.001	0.001	0.004

AJC-2 and TJC-2: AJC and TJC clinical traits observed in patients belonging to the category 2 (extended oligoarthritis); SNP: SNP identifier; A1: Minor allele; BETA: Regression coefficient; SE: Standard Error; L95: Lower limit of the 95% confidence interval; U95: Upper limit of the 95% confidence interval; STAT: Coefficient t-statistic; R2: Regression r-squared; adj R2: adjusted Regression r-squared in the population; P: asymptotic *p*-value for t-statistic; EMP1: Empirical *p*-value (pointwise); EMP2: Empirical *p*-value corrected for multiple tests; NP: number of permutations performed; UNADJ: Unadjusted *p*-value; GC: Genomic-control corrected *p*-values; BONF: Bonferroni single-step adjusted *p*-values; HOLM: Holm (1979) step-down adjusted *p*-values; SIDAK_SS: Sidak single-step adjusted *p*-values; SIDAK_SD: Sidak step-down adjusted *p*-values; FDR_BH: Benjamini & Hochberg (1995) step-up FDR control; FDR_BY: Benjamini & Yekutieli (2001) step-up FDR control.

lysed as a whole (Table IV). This haplotype was associated with increased values of number of affected joints, physical disability as measured with the CHAQ, clinical damage as assessed with the JADI-A, and disease duration. Figure 2 shows a graphic representation of the significant results obtained from this haplotype-based quantitative association analysis. No significant associations were found between the haplotype and individual ILAR categories (results not shown).

Discussion

Our study highlights the involvement of the POSTN gene in the pathogenic mechanisms of JIA, particularly those responsible for severity and progression of the disease. We found highly significant association between the minor allele variant of SNP rs17197936 and worsening of 2 clinical traits, AJC and TJC, in one of the most debilitating forms of JIA, the oligoarthritis extended, in which many joints can be damaged by disease progression. This SNP was previously described as located in a 37bp evolutionary conserved enhancer region of the mouse periostin gene, suggesting a role of this SNP in expression regulation (25). For the purpose of this analysis, we used the software named Regulatory Analysis of Variation in Enhancers (RAVEN) to investigate a possible function of this SNP (26). We found that it affects the binding site of several Transcription Factors (TFs), including AGL3, ROR alpha-2 and c-FOS, and is located in a highly conserved region. However, when we considered more than one variant in haplotype combinations, we found a significant association of a haplotype formed

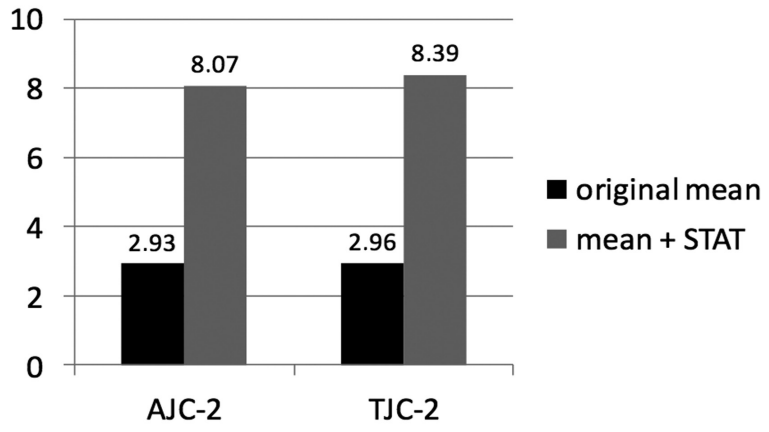

Fig. 1. Graphic representation of the significant single marker association results.
This figure shows how the mean of the quantitative values, observed for AJC-2 and TJC-2 clinical traits (left column), is expected to behave with the deleterious additive effect (STAT values from Table III) of the minor allele G of SNP rs17197936 (right column). On top of the columns the corresponding mean values. AJC-2 and TJC-2 describe the AJC and TJC clinical traits in class 2 patients with oligoarthritis extended.

Table IV. Haplotype-based quantitative trait association analysis.

Clinical traits	HAP	BETA	L95	U95	R^2	adj R^2	STAT	SE	P	EMP1	EMP2	3SNPs
AJC	GCT	127	75.72	178.27	0.21	0.19	4.92	25.8	3.91E-03	0.006	0.006	rs3829364|rs6750|rs9547951
TJC	GCT	89.46	40.35	138.56	0.13	0.11	3.62	24.7	0.0004	0.011	0.01	rs3829364|rs6750|rs9547951
CHAQ	GCT	11.66	5.02	18.29	0.12	0.1	3.49	3.34	0.0007	0.012	0.02	rs3829364|rs6750|rs9547951
JADI-A	GCT	126.7	55.74	197.65	0.12	0.1	3.54	35.7	0.0006	0.026	0.04	rs3829364|rs6750|rs9547951
Dis dur	GCT	54.91	24.31	85.5	0.12	0.1	3.56	15.4	0.0006	0.004	0.01	rs3829364|rs6750|rs9547951

Hap: alleles forming the haplotype; BETA: Regression coefficient; SE: Standard Error; STAT: Coefficient t-statistic; R2: Regression r-squared; adj R2: adjusted Regression r-squared in the population; P: asymptotic *p*-value; EMP1: Empirical *p*-value (pointwise); EMP2: empirical *p*-value obtained after the second level of permutation procedures correcting for multiple tests; 3SNPs: SNPs identifying the haplotype.

by 3 minor allele variants, rs3829364, rs6750 and rs9547951, with 5 clinical traits of the disease, AJC, TJC , CHAQ, JADI-A, and disease duration, in the entire group of patients considered as a whole. Again, this appears a harmful association leading to a more severe disease phenotype. None of these associated SNPs resides in the coding region whereby, considering their location: rs17197936 is placed in the 5' flanking region, in a cis-acting element reported as a transcriptional enhancer; rs3829364 is in the 5' end; rs6750 and rs9547951 are in the 3' end of the gene, it is tempting to speculate that these SNPs may, directly or through other strictly related variants, affect regulation of gene expression either at transcriptional or post-transcriptional level. Periostin was chosen for this association study because of its role in remodeling of tissues, which has been studied more in deep in some conditions, such as tumour angiogenic activity (27), atherosclerosis and rheumatic VHD. Interestingly, some authors (28) studied 5 of the 7 SNPs tested in our study and found that the same variant identified by us, rs17197936, was associated with the development of atherosclerosis in young individuals in a population of European Americans. Hakuno and co-authors (8) suggested that periostin plays a critical role in the progression of cardiac valve complex degeneration in VHD by inducing angiogenesis and MMP production. Another study (29) showed that MMP-2, MMP-3, periostin and TIMP are all up-regulated in the joints of mice following the destabilisation of the medial meniscus to induce osteoarthritis (OA). Not surprisingly, MMPs have been implicated in cartilage destruction and periarticular bone erosion in juvenile idiopathic arthritis. The ratios of MMP1/TIMP1 and MMP3/TIMP1 correlate significantly with disease activity in JIA and some authors suggested to use them as biomarkers for this disease (30). As in VHD, it can be hypothesised that periostin-expressing inflammatory cells infiltrate the inflamed joints leading to neovascularisation of the synovium, in which periostin-expressing fibroblasts and macrophages induce secretion of MMPs that in turn directly breakdown cartilage by altering the MMP/TIMP balance, hence causing matrix degeneration. Neoangiogenesis is known to play an important role in both RA and OA, however, is not clear whether its involvement is a consequence of inflammation or is due to other specific mechanisms (31, 32). Ashraf and Walsh (12) described the mechanism of angiogenesis occurring in osteoarthritic joints: blood vessels from the subchondral bone invade the articular cartilage altering chondrocyte function and homeostasis and leading to synovitis, articular hypoxia and pain. Angiogenic and antiangiogenic factors might both be upregulated in the osteoarthritic joint, however, vascular growth predominates, and the articular cartilage loses its resistance to vascularisation. A similar mechanism has been recently described for hip disease in systemic JIA in association with particular clinical manifestations including pain, limited range of motion, osteopenia, subchondral bone erosions of the femur and/or acetabulum, and cartilage loss leading to reduction of joint space (33). It should be taken into account that in growing children epiphyseal growth plates are still present. These structures are composed of a thin layer of cartilage located near the ends of long bones and vertebrae. In these areas, progenitor

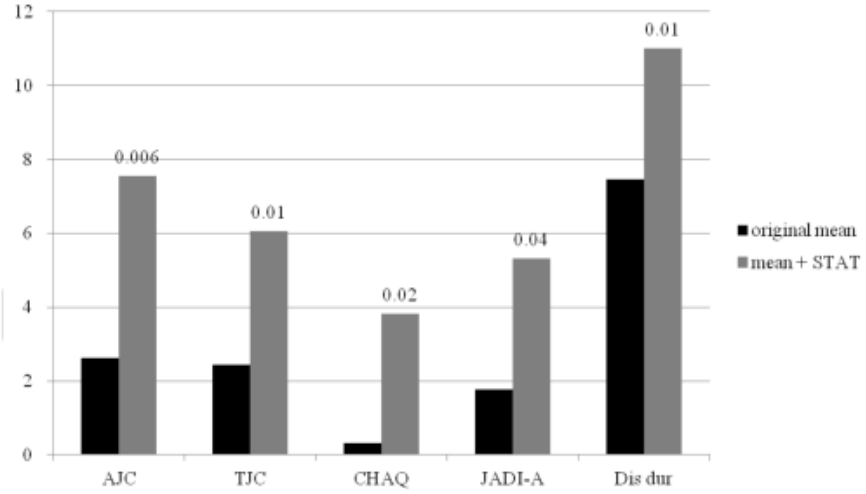

Fig. 2. Graphic representation of the significant haplotype association results.
This figure shows how the mean values observed for the five clinical traits (left columns) are expected to behave with the additive effect (STAT values from Table IV) of the associated haplotype (right columns). On top of the right columns the corresponding EMP2 values, obtained from the haplotype–based quantitative association analysis, are shown. The effect of this haplotype is to worse each of these clinical traits and consequently the overall disease severity and/or progression.

stem cells differentiate into chondrocytes, which then undergo a proliferative and differentiative phase, leading to the formation of the cartilage, which is gradually replaced by the formation of endochondral bone. It might be speculated that in JIA, inflammation could drive increased angiogenesis in the synovium, which in turn could contribute to disease progression by breaking up the osteochondral junction and could cause pain by favouring inappropriate sensory innervation of joint structures (34). Some authors have shown that a sizeable proportion of children with JIA, particularly those with the systemic category, may experience stunted growth, due to the adverse effects that pro-inflammatory cytokines and glucocorticoids might have on the growth plate of long bones (35). Notably, power or colour Doppler ultrasonography (US) often shows hyperaemia, which is assumed to result from angiogenesis, in inflamed joints of JIA patients (36, 37).

In conclusion, our study shows for the first time that polymorphic variants of the POSTN gene are significantly associated with increased severity of some clinical traits in JIA patients. Genotyping of this gene may, therefore, represent a useful tool to identify patients who are at greatest risk of experiencing a poorer long-term outcome. Functional assays are needed to investigate the potential role of periostin in the pathogenesis of structural joint changes in JIA.

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