Association of interleukin-6 gene polymorphisms with hand osteoarthritis and hand osteoporosis

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Abstract

Objective: Several genes, including IL-6 encoding pro-inflammatory cytokines, are involved in development of osteoarthritis and osteoporosis. The association of radiographic hand osteoarthritis (RHOA) and osteoporosis related phenotypes (RHOP) with polymorphisms in IL-6 has been reported inconsistently. The aim of this study was to examine the association, between RHOA and RHOP and IL-6 polymorphisms in two independent samples.

Methods: Two samples: UK females, including 1440 individuals assessed for RHOA and 3470 assessed for RHOP; Chuvash pedigree including 1499 females and males were assessed for RHOP and RHOA. SNPs were genotyped in the IL-6 genomic region, and used in association analysis with RHOA and RHOP phenotypes.

Results: RHOP phenotypes showed similar heritability estimates in both samples, ranging from 34.5 ± 5.5% to 61.0 ± 2.4%. RHOA in Chuvash had substantially lower heritability estimates compared to twins (e.g. OSP scores: 11.8 ± 2.3% vs. 39.2 ± 4.1%) with much higher prevalence and considerably stronger correlation with age \( r = 0.811 \) vs. \( r = 0.505 \). RHOA in Chuvash sample may be traumatic in nature, caused by heavy and prolonged manual work related to their private farming. There were a number of statistically significant association results with both types of phenotypes. The most consistent result was obtained for JSN in both samples with SNP from the same haploblock. Their combined probability of no association was only \( p = 0.000003 \). Additionally, there were SNPs common for both RHOA and RHOP.

Conclusions: We have shown polymorphisms in IL_6 are significantly associated with RHOA and hand RHOP in two samples having different ethnicity and lifestyle. Age \times\text{environment} \times\text{genes interaction} appears as an important factor of RHOA manifestation and progression.

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1. Introduction

Osteoporosis and osteoarthritis are two major and most common musculoskeletal disorders. Although both conditions have a multifactorial nature, they develop differently, have different symptoms, and are diagnosed differently. Both conditions, however, governed to a large extent by genetic factors and involve inflammatory processes. A major contribution of genes to appearance of osteoporosis-related phenotypes, bone mass loss and others, as well as to a development and manifestation of osteoarthritis, is well established [1,2]. However, specific genetic factors and polymorphisms associated with these conditions remain poorly understood, and numerous candidate genes and genomic regions have been proposed [3–6]. The interleukin-6 gene...
(IL-6) has been proposed as a candidate gene for a variety of osteoporosis and osteoarthritids phenotypes because of its role in inflammation, but studies have reported quite contradictory results [7,8]. At least 50 single nucleotide polymorphisms (SNP) and five common haplotypes have been identified in IL-6, and have been surveyed recently [9,10]. The epidemiological data suggest that circulating IL-6 is a significant factor in bone loss [11], as well as in a development of osteoarthritis-related phenotypes [12]. However, testing the genetic association between IL-6 variants and osteoarthritis and osteoporosis phenotypes assessed on lower and upper limb bones and joints, has generated inconsistent results. While some studies found statistically significant associations [13–18] others – did not [16,19–21]. Thus, the question concerning the association between osteoarthritis – and osteoporosis-related phenotypes variations with genetic variation of IL-6 remains largely unresolved.

It should be mentioned that manifestation of radiographic hand osteoarthritis (RHOA) and osteoporosis (RHP) – related phenotypes may not be independent for several reasons. One of the RHOA characteristics is that it is associated with presence of hand osteophytes and cartilage loss [22], but the progress in RHOA is correlated with hand bone mineral density (BMD) [23]. The link between BMD and RHOA has been explained by pleiotropy, i.e. shared genetic effects [24]. The potential mechanism for this is involvement of inflammatory processes in development of both osteoarthritis and –arthritis. Osteoarthritis is characterized by chronic local inflammation of the joints involving pro-inflammatory mediators, including IL-6 that causes cartilage degradation by upregulation of catabolic factors [25]. On the other side, IL-6 is also involved in bone remodeling [9], i.e. RHOA could also be dependent on IL-6 action and genetics. Thus, testing the hypothesis that genetic variation in IL-6 variants influence RHOA and RHP is of interest and importance. In the present study we examined these associations using two independent samples.

2. Material and methods

2.1. Samples

1. TwinsUK register. The present study is based on 1440 individuals, assessed for RHOA, and 3470 individuals assessed for bone mineral density at ultradistal radius and ulna (BMD UR & BMD_UU, respectively). The Twins UK Adult Twin Registry, described in detail elsewhere [26], now includes >12,000 volunteer participants. Twin participants in this study gave written informed consent and the St. Thomas’ Hospital research ethics committee had approved the project. The register has been collected from the general population through national media campaigns in the UK without first ascertaining the presence of any individual characteristics, diseases or traits. Collected DNA was sent for genome wide genotyping using the Illumina (San Diego, USA) 317 K and 610 K SNP arrays [27]. The age and trait description of the sample is given in Table 1 for RHOA and RHP phenotypes separately. As the cohort is overwhelmingly of North European ancestry (98%), participants of other ethnicities were not included in the current study.

2. The Chuvash. This sample includes Caucasian individuals (descendants of Bulgar tribes) and has been described elsewhere [28]. The sample consists of 269 nuclear families, including 782 men and 717 women, with age range 17–90 years. All individuals in the sample were assessed for RHOA and for several RHP phenotypes. The pedigrees were collected randomly, and included individuals having no chronic infection, nor metabolic or bone-related diseases. All subjects who agreed to participate in the study signed an informed consent form and the Tel Aviv University ethics committee had approved the project. Of 1499 individuals 1100 individuals were genotyped for 4 SNPs in IL-6 genome region.

2.2. RHOA and BS related phenotypes

(A) The RHOA was assessed using similar methodology in both samples, by plain posterior–anterior radiographs, taken from both hands of each study participant. The films from twins were not read as pairs. The radiographic features of hand OA, including the presence of osteophytes (OSP), joint space narrowing (JSN) and Kellgren/Lawrence grades, were scored for each of the 14 joints on both hands. OSP and JSN were separately evaluated and graded from 0 to 3 for increasing severity using a standardized atlas. The summary K/L grade for each joint and in total was evaluated from 0 to 4 following the original atlas [29].

(B) RHP phenotypes. In TwinsUK measurements of BMD UR and BMD_UU, located proximal to the radial and ulnar end plates correspondingly were assessed using Hologic QDR-2000 DXA scanner as detailed in [30].

In the Chuvash sample, standard plain radiographs of both hands were taken in the postero-anterior position from each participating individual. The detailed description of the procedure is given elsewhere [31]. Measurements on digitalized radiographs were carried out by means of UTHSCSA Image Tool Version 3.0 for Windows software package (http://ddsdx.uthscsa.edu/dig-itdesc.html) using the scripts written by I. Malkin specifically for this purpose. The measurements included bone mineral density of the total bone (BMD_T) and its compact compartment (BMD_C), and bone surface area (B_AREA). The corresponding measurements were taken from the radiographic images of the second to fourth fingers on each of the metacarpal bone, proximal and middle phalanges, 18 bones in total [32]. In addition, we measured the metacarpal cortical index (MCI = CWT/D), representing the ratio of the cortical bone wall compact layer thickness (CWT) to bone total diameter (D) on 6 metacarpal bones [33].

2.3. SNP selection

2.3.1. TwinsUK

The genotype data were based on genome-wide genotyping scans performed in this cohort previously using the Illumina (San Diego, USA) 317 K and 610 K SNP arrays, with a call rate of genotype ≥ 98%. Using the published data, the International HapMap and UCSC browsers, the IL-6 region was identified and positioned between 22,727,147 and 22,732,002 bp on chromosome 7q21. Fifteen genotyped SNPs were available in this region and close to it (22,702,977–22,754,799 bp), in our sample. These SNPs covered the entire IL-6 locus and some markers were also located approximately 24Kbps up- and 23Kbps down-stream of the structural gene. All SNPs were at Hardy–Weinberg equilibrium p > 0.05 and with minor allele frequency (MAF) ranging between 0.11 and 0.47 (Table S1, Supplementary material).

2.3.2. Chuvash sample

Using Nucleon BACC Genomic DNA Extraction Kits (Amersham International plc, UK), DNA was prepared from peripheral blood lymphocytes by standard techniques, according to the manufacturer’s protocol. The selected four SNPs were genotyped in 1090 individuals by KBiosciences (Hertfordshire, UK) using their proprietary competitive allele-specific PCR (KASPar) method (the details are available at the company’s website (www.kbioscience.co.uk/chemistry/index.html)). The genotyped SNPs were mapped at region 22,724,028–22,746,443, and were all at
Many of the examined phenotypes were strongly correlated, so to diminish the number of multiple tests and data redundancy, separate measurements were combined into more general variables. In twins, RHOA phenotypes, K/L, OSP and JSN on each of the 14 joints were first each standardized (z-transformation) separately and then were combined for all joints together. Thus we obtained general scores for K/L, OSP and JSN for each individual, which were further used in our genetic analysis. BMD_UU, and BMD_UR are only females. There was a considerable difference in RHOA phenotypes showed significant negative correlations with age, ranging between \( r = 0.136 \) (B_AREA) and \( r = 0.192 \) (BMD_UR), \( p < 0.001 \) in twins; and \( r = 0.519 \) (MCI), \( r = 0.819 \) to \( r = 0.453 \) (K/L) in Chuvash and \( p < 0.0001 \), in Chuvash (Fig. 2). Interestingly, unadjusted Hardy–Weinberg equilibrium \( p > 0.05 \), MAF ranging between the 0.32 and 0.47 (Table S1).

Different arrays of SNPs in were available in two studied samples. However, selected SNPs located close to each other were in high linkage disequilibrium (LD) (Fig. 1).

### 2.4. Statistical and genetic analysis

Basic descriptive statistics were obtained using SPSS package version 19 (SPSS Inc., Chicago, IL, USA). The quantitative genetic analysis including association analysis was carried out using MAN-package (Malkin and Ginsburg, 2011, MAN, Tel-Aviv University, Israel). MAN takes into account family structure of the sample, including both members of each pair of MZ and DZ twins and unrelated singletons, as well as parent-offspring, and spouse, etc. In variance component analysis it estimates the effect of the covariates simultaneously (e.g. age, sex, BMI), as well as contribution of the major components of familial variation. According to quantitative genetic theory [34], the total phenotypic variation may be decomposed into a number of major components of variation: \( V_A \) – reflects contribution of the additive genetic factors, \( V_C \) – common environment affecting the relatives sharing the same household, and the remaining unexplained variance, defined as \( V_E \). To estimate association between the selected SNP and RHOA or RHOP – related phenotypes, the corresponding best fitting and most parsimonious variance component model was modified. The SNP-specific genotypes were scored by the number of minor alleles: 0, 1 and 2 and included as covariates. A maximum likelihood ratio test (LRT) was used to compare a general model including all possible parameter estimates with a more parsimonious model, excluding potentially non-significant parameters.

### 3. Results

The basic descriptive statistics of both study samples including age, BMI, RHOA and RHOP-related phenotypes are given in Table 1. Chuvash and Twins UK were of a comparable age (47.7 ± 16.8 vs. 47.7 ± 12.5), and BMI in general, although the former were on average leaner than twins (24.0 ± 4.0 kg/m² vs. 25.3 ± 4.70 kg/m²; \( p = 0.0001 \)). This difference could be explained by the fact that Chuvash sample consists of both males and females, while twins are only females. There was a considerable difference in RHOA phenotypes, Chuvash vs. UK_twins [e.g. K/L, 21.7 ± 12.5 vs. 4.4 ± 7.5, \( p = 0.0001 \), Table 1]. The RHOP phenotypes, including BMD came from different bones and measured by different methods in the two samples, and were not therefore directly comparable. However, as expected all RHOP phenotypes showed significant negative correlations with age, ranging between \( r = -0.186 \) (BMD_UU), and \( r = -0.192 \) (BMD UR), \( p < 0.001 \) in twins; and between \( r = -0.136 \) (B_AREA) and \( r = -0.519 \) (MCI), \( p < 0.0001 \), in Chuvash. RHOA phenotypes showed significant positive correlation with age, ranging between \( r = 0.224 \) (JSN) to \( r = 0.453 \) (K/L) \( p < 0.001 \) in twins and between \( r = 0.263 \) (JSN) and \( r = 0.819 \) (K/L) \( p < 0.0001 \), in Chuvash (Fig. 2). Interestingly, unadjusted for RHOP phenotypes showed significant negative correlations with corresponding RHOP traits. The highest correlation was observed between OSP and MCI (\( r = -0.415 \)) in Chuvash and...
between OSP and BMD_U (r = 0.211) in twins. However, after adjustment for age these correlations became much lower and only marginally significant. Finally all RHOA phenotypes were also positively associated with BMI in both samples (p < 0.001).

The genotype data for each available SNP are given in Table S1 (Supplementary material). The table provides SNP location, genotype frequencies and tests for Hardy–Weinberg equilibrium, which showed no deviation from the theoretical expectations in any of the tests. The minor allele frequencies (MAF) in the selected SNPs were all >0.10. Summary results of the variance component analysis of the variables are presented in Figs. 3 and 4, with all the details provided in Tables S2 and S3 (Supplementary material). Estimates given in Figs. 3 and 4 were obtained by LRT, in the corresponding best fitting and most parsimonious models. The analyses in all instances were conducted with simultaneous adjustment of the dependent variable for age and BMI.

With respect to RHOA phenotypes, the heritability estimates explained from 10.3 ± 2.1% (JSN) to 11.8 ± 2.3% (OSP) variation in Chuvash sample, and between 39.2 ± 4.1% (OSP) to 45.8 ± 3.8% (K/L) in Twins UK. Considering RHOP phenotypes, they all showed highly significant heritability estimates. In Chuvash, the estimates varied from 34.5 ± 5.7% (BMD_C) to 59.8 ± 7.0% (B_AREA). In twins,
heritability estimates were from 59.0 ± 3.1% for (BMD_UU) to 61.0 ± 2.4% for (BMD_UR).

We tested the hypothesis that a proportion of the genetic effects on RHOA and RHOP phenotypes are attributable to SNPs in \textit{IL-6} gene. We used the best fitting and most parsimonious model for each phenotype and added the SNPs one by one as covariates. The results of these analyses are summarized in Fig. 1, with details given in Tables S4 and S5 (Supplementary material). Results were similar between the two samples despite different coverage of \textit{IL-6} and the best associated SNPs mapped to the same haploblock.

In the Chuvash sample we found that BMD_T, BMD_C and MCI were significantly associated with rs1800797 (\textit{p} = 0.007, 0.04, and 0.03 respectively). Neighboring rs2069845 and rs1829927 (Fig. 1) were associated with BMD_T and BMD_C (\textit{p} = 0.033–0.006). Of 20 tests in total, seven tests were significant at \( p < 0.05 \), which is substantially more than expected by chance. In TwinsUK there were additional SNPs (rs2056576, rs1554606 and rs10242595) which were found significantly associated with BMD_UU and BMD_UU phenotypes (\textit{p} = 0.001–0.024). Interestingly, markers rs10242595 and rs10156056 in this haploblock (22,705,287–22,760,000) were also associated with RHOA phenotypes. The association was consistently observed between all three corresponding phenotypes, K/L, OSP and JSN, and rs10156056 (\textit{p} = 0.0001–0.0002). The marker rs10242595 mapped to the same haploblock was associated with JSN (\textit{p} = 0.0002) in twins, while marker rs1546762, also from the same haploblock (\( D' = 0.83 \)) was significantly associated with JSN (\textit{p} = 0.007) in Chuvash.

### 4. Discussion

A significant contribution of genetic factors to osteo-arthritis and porosis-related phenotypes variations is well established [e.g. 35–39]. What is much less clear are the specific DNA polymorphisms causing this, in particular in osteoarthritis [40]. This study examined to what extent RHOA and hand RHOP-related phenotypes are governed by genetic factors and whether \textit{IL-6} gene polymorphisms contribute to these effects. Selection of this gene was dictated by several lines of data: involvement of inflammatory processes in the development of both osteo-arthritis and porosis [15,18,41], reported in the literature correlations between the circulating levels of \textit{IL-6}, and controversial data on \textit{IL-6} gene variants association with both these conditions [8,9,11–14]. We studied two independent samples and despite good matching in age, BMI and methodological similarity in RHOA assessment, Chuvash displayed higher prevalence of RHOA, and lower heritability estimates for K/L and OSP phenotypes in comparison to twins. The higher levels of RHOA prevalence in Chuvash is probably caused by their heavy manual work, although their ethnicity could account for some difference in genetic predisposition. The much higher correlation with age (\( r = 0.819 \) vs. \( r = 0.433 \) in Chuvash vs.
TwinsUK) may be explained at least in part by confounding by occupational exposure and suggests that higher RHOA prevalence in Chuvash is caused by environmental factors. Indeed, association of early onset of osteoarthritis with heavy labor jobs has been reported in the literature several times [e.g. 42,43] and could also well explain lower heritability (vs. strong environmental effects) compared to UK middle-class females exposed to much lower levels of hand trauma.

We found that putative genetic factors made a significant contribution to both RHOA and RHOP phenotypes in TwinsUK, with heritability estimates ranging from 39.2 ± 4.1% to 46.3 ± 3.8% for RHOA phenotypes, and between 59.0 ± 3.1% for BMD_UU and 61.0 ± 2.4% for BMD_UR. RHOP phenotypes in Chuvash pedigrees exhibited statistically significant heritability for all tested phenotypes, including both bone mass and size: 34.5 ± 5.7% (BMD_C) – 59.8 ± 7.0% (B_AREA), confirming again that these phenotypes are under the genetic control.

The analysis of IL-6 polymorphisms showed that they made modest but statistically significant contribution in both samples. In TwinsUK, rs10156056 was consistently associated with K/L grading, OSP and JSN. We also found significant associations between several polymorphisms, rs2056576, rs1554606, rs4722166 and BMD_UR. However, while rs4722166 is located in the same haploblock, as rs10156056 (22.702, 971–22,720,613) and is in extremely high LD with it (D = 0.97), two other SNPs (rs2056576, rs1554606) mapped to a different haploblock (22,721,293–22,754,799) (Fig. 1). BMD_UU showed only marginally significant association with these SNPs, but was associated significantly (p = 0.014) with rs10242595, which is in relatively high LD (D = 0.84) with rs1554606.

In the Chuvash sample, we found a significant association between rs1800797 and several RHOA phenotypes, namely, BMD_T, BMD_C and MCI. In addition, BMD_T and BMD_C were significantly associated with rs1829927, which had D = 0.81 with rs1800797. Thus despite some heterogeneity in the specific association signals, the corresponding SNPs tend to be located closely in the IL-6 genomic region. Remarkable also was a good correspondence in results between the samples. Although different SNPs were genotyped, they were mapped to the same haploblock(s), and were in high LD with one another. The similar trend was observed with RHOA. For instance, rs10156056, the most significantly associated with RHOA phenotypes in twins, was in

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**Fig. 4.** Summary of the variance component analysis of hand/wrist radiographic hand osteoporosis (RHOP) in two study samples. The heritability and the environmental effect estimates are given for the most parsimonious models (MPM) after adjustment for age, age^2 and BMI in both sample and also for sex, in Chuvash sample. Phenotypes definitions: K/L – Kellgren/Lawrence scores, OSP – osteophytes, JSN – joint space narrowing. Variance components: AD – additive genetic, CE – common family environment; COV – covariates effect (age and BMI), RS – residual variance component. BMD_T and BMD_C – bone mineral density in total and compact compartment, B_AREA – bone surface area, MCI – metacarpal cortical index, BMD_UU and BMD_UR-bone mineral density at ultradistal radius and ulna.
$D' = 0.81$ with rs1546762, associated with JSN in Chuvash pedi-
gies. Because of this LD and similar effect estimate/direction: $\beta_{\text{Chuvash}} = -0.1603 \pm 0.0504$ and $\beta_{\text{Twins}} = -0.1003 \pm 0.0269$, we con-
sidered these two SNPs as representing the same haploblock. As two samples are independent, we estimated the combined proba-
(bility (metaanalysis) of no association using corresponding Fisher’s test [44]. The observed $\chi^2 = 30.85$ with $p = 0.000003$ strongly con-
ffirmed our working hypothesis. The $\beta_{1800797}$ significantly associ-
ated with BMD_UR in Chuvash, was in $D' = 0.83$ with rs2056576 associated with BMD_UR in twins; rs1829927 associated with BMD_T and BMD_C in Chuvash was in $D' = 0.97$ with rs1554606, associated with BMD_UR in TwinsUK. Thus the data
suggest association of the SNPs from the same haploblock with the phenotypes belonging to the same category of the phenotypes in
both samples.

However, the LD between the markers associated with two
categories of phenotypes, RHOA vs. RHOP has more complicated
pattern (Fig. 1). For example, aforementioned rs10156056 associated
with RHOA was in $D' = 0.92$ with rs4722166 associated with BMD_UR, but in low LD ($D' < 0.30$) with rs1800797 associated with BMD_C and MCI, in Chuvash, and rs10242595 associated with BMD_UU, in TwinsUK, respectively.

The significant associations between the polymorphisms in IL-6 and
RHOA and RHOP-related phenotypes were expected. Despite the
controversy in published data in this respect [13–21], the involve-
mnt of key inflammatory factors in development and man-
ifestation of OA and osteoporosis is well established [41] and the pre-
sent data confirm this. The present data also confirm that RHOA
and hand RHOP-phenotypes correlate with BMI, representing the
widely accepted measure of obesity. However, the hands are not
weight bearing joints and bones, so it seems likely that the
observed correlation was caused by the adipose production of
inflammatory cytokines, including IL-6 [25]. Of note associations
between IL-6 polymorphisms and RHOA observed in this study
were independent of BMI, and also of RHOP phenotypes after
adjustment for age, so are not suggestive of pleiotropic effects.

In conclusion, our study supports the conjecture that inflamma-
tion mediated by variation in the IL-6 genomic region is associated
with hand osteoarthritis and osteoporosis-related phenotypes.
Both displayed association with several markers located in the
same haploblock in both populations. Comparing the SNP associ-
ated with RHOA and RHOP-phenotypes within the same popula-
tions revealed that there are common-(mapped to the same
haploblock) and phenotype-specific SNPs (mapped to different
haploblocks). In addition, we confirm a significant genetic effect
(heritability) on each studied phenotype in both samples. How-
ever, this study also demonstrates that the discrepancies in the
prevalence and heritability estimates of K/L and OSP could be
due to cultural, socio-economic and ethnic differences between
the middle class British women in comparison to rural post-Soviet
peasants, living in one of the less developed regions of Russia. As a
result, clear age x environment x heredity interaction appears as
an important factor of RHOA prevalence.

**Authors’ contributions**

GL, AV and OB, designed the study. OB and GL performed statistical
analysis of the data. OB, GL, and FW prepared the first draft of the
manuscript. IM created statistical package MAN and scripts for
radiographic data analysis. GL designed and supervised the entire
Chuvash Pedigree project including assessment of corresponding
RKOAA- and RHOP-related phenotypes. TS and designed and super-
vised the entire Twins UK project, including follow-up. TS, FW and
DH organized and supervised present study data collection, includ-
ing assessment of the corresponding RKOAA- and RHOP-related
phenotypes in Twins UK study. All authors contributed to the final
manuscript preparation.

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**Conflict of interest**

The authors certify that there is no conflict of interest related to
work presented.

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**Appendix A. Supplementary material**

Supplementary data associated with this article can be found,
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