Single nucleotide polymorphisms in genes for cytokines IL-1 alpha, IL-6, and TNF-α are associated with osteolysis in total hip arthroplasty

J. Gallo[1], F. Mrazek[2], Z. Ambruzova[2], Z. Kubistova[2],
J. Onderkova[2], E. Kriegova[2], Martin Petrek[2]

[1] *Department of Orthopedics*
[2] *Laboratory of Immunogenomics, Department of Immunology*
Palacky University and University Hospital Olomouc,
Czech Republic

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Introduction

Periprosthetic osteolysis (OL) is the major long-term complication of total hip arthroplasty (THA).

The **pathogenesis of OL** involves biological mechanisms as well. They are triggered by wear particles („particle disease“) and include local accumulation of macrophages/ monocytes that are the precursors for osteoclast differentiation. Excessive bone resorption comes from a predominance of osteoclasts over osteoblasts. These processes are orchestrated by cytokines (TNF-α, IL-1, M-CSF, RANKL, etc.) and chemokines (MCP-1, IL-8, etc.).

However, **substantial interindividual variability in OL** severity has been observed even in cases of comparable wear rates and identical prostheses.

The explanation for this may lie in **genetic susceptibility to OL** underlined by particular variants of the genes for key signal molecules. This could lead to variable levels and functionality of these molecules affecting the pathways of particle disease.

Hypothesis

There is an association between the variants of cytokine genes and severity of periprosthetic OL.

Study population & design

*Patients after THA (N = 195), identical implant, single-institution case-control study, candidate gene approach, reliable classification of acetabular bone defects**

GROUP 1	**GROUP 2**	**GROUP 3**
Patients with mild OL (Saleh* I or II)	Patients with intermediate OL (Saleh* III)	Patients with severe OL (Saleh* VI or V)
N = 82	N = 86	N = 27

**Saleh et al, J Bone Joint Surg Am, 83: 1040, 2001.*

Methods

Genotyping of cytokine gene polymorphisms

- ✓ 22 selected cytokine gene polymorphisms (Table 1)
- ✓ Polymerase Chain Reaction with Sequence Specific Primers (PCR- SSP)
- ✓ „The Cytokine Typing Tray kit“, University of Heidelberg

Statistics

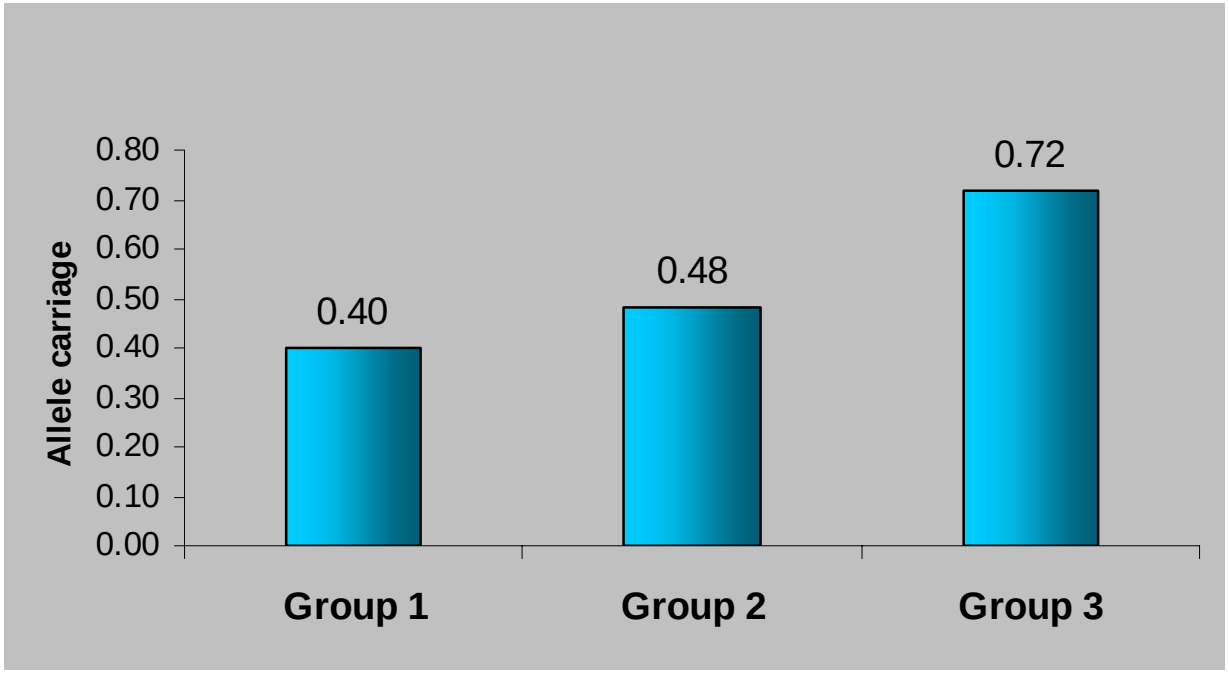
- ✓ **conformity of genotype distribution** to the Hardy-Weinberg equilibrium: Chi-square test
- ✓ differences between allelic, genotype and phenotype („carriage rate“) frequencies: Chi-square test with **Woolf-Haldane correction** for small numbers
- ✓ risk assessment: **odds ratio**, **population attributable risk percentage** (PAR%)
- ✓ $p \leq 0.01$

Table 1. Overview of investigated cytokine single nucleotide polymorphisms (SNPs)

Cytokine	**Gene location**	**Gene polymorphisms (SNP)**
IL-1α	2q14	-889 C/T
IL-1β	2q14	-511 C/T, +3962 C/T
IL-1R	2q12	pstI 1970 C/T
IL-1RA	2q14	Mspa1 11100 T/C
IL-4Ra	16p12	+1902 A/G
IL-12	3q25	-1188 A/C
gIFN	12q14	UTR 5644 A/T
TGFβ	19q13	Codon 10 T/C, Codon 25 G/C
TNFα	6p21	-308 G/A, -238 G/A
IL-2	4q26	-330 T/G, +166 G/T
IL-4	5q31	-1098 T/G, -590 C/T, -33 C/T
IL-6	7p21	-174 G/C, nt 565 G/A
IL-10	1q31	-1082 A/G, -819 C/T, -592 C/A

Results

The carriers of the IL-1A-889*T allele were **more frequent among the patients** with severe OL (Group 3) than in those with mild OL (Group 1).

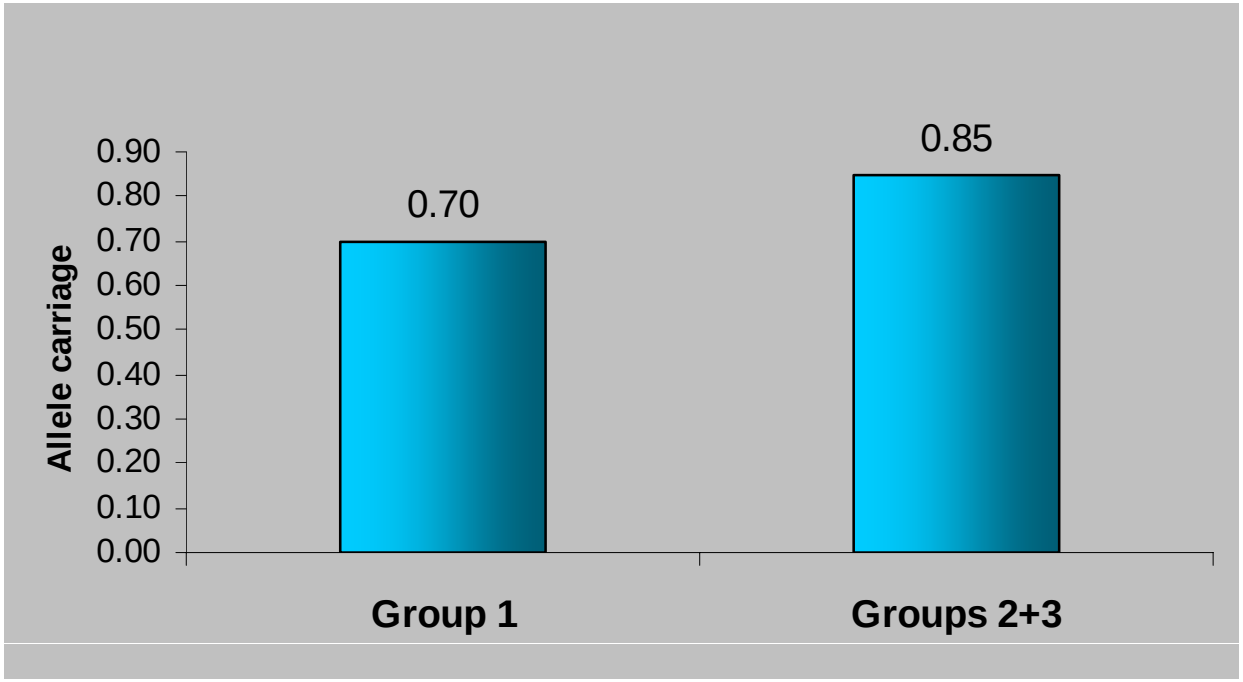


Group 3 *versus* Group 1: **odds ratio=3.6, *p*=0.01**.

** For definition of groups see „Study population & design“ section*

Results

Patients carrying standard IL-6-174*G allele were in **higher risk to develop** intermediate/ severe OL.

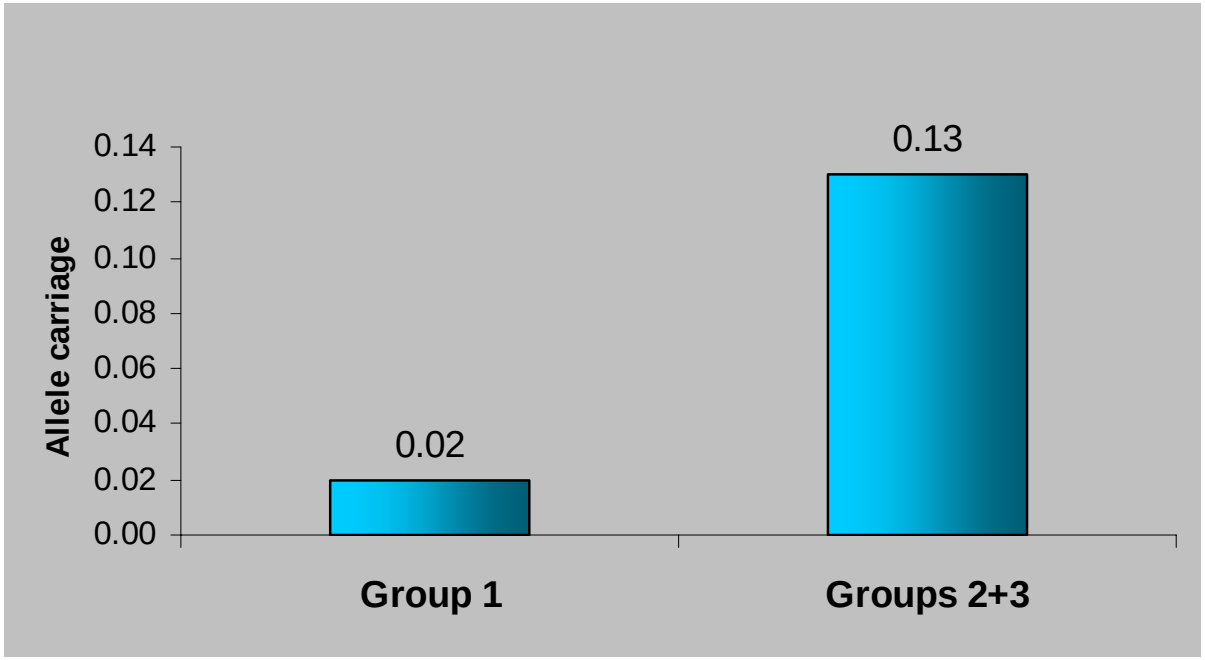


Groups 2+3 *versus* Group 1: **odds ratio=2.4, *p*=0.01, PAR%*=30%**.

** PAR% - population attributable risk percentage – percentage of the incidence of a disease in the population that is due to certain exposure.*

Results

Carriage of mutant TNF-238*A allele implied **a trend** for susceptibility to intermediate/ severe OL.



Groups 2+3 *versus* Group 1: **odds ratio=4.8, *p*=0.02, PAR%=5%**.

** For definitions of groups and PAR% see above.*

Discussion

Earlier studies have pointed to the potential role of cytokine gene SNPs in THA failure (Tab. 2) in the hope that this would give substance to particle disease theory by offering new explanations for interindividual differences found in clinical practice.

This is the **first report** on the role of SNP in genes for TNF-α, IL-1 and IL-6 as a potential risk factor for severe OL.

Our findings are **in accordance** with the current paradigm because multifunctional cytokines TNF-α, IL-1 and IL-6 are also involved in the regulation of bone metabolism, development of OL and aseptic loosening of THA.

Risk for OL/ aseptic loosening	SNPs in genes for regulatory/ effector molecules
Wilkinson, *J Bone Min Res 2003*	TNF-238*A
Malik, *Int Orthop 2006, J Arthroplasty 2007, Ann Rheum Dis 2007*	RANK+575*T, MBL-550*C, MBL-55*G, MMP1-1*C
Kolundzic, *J Orthop Sci 2006*	TGF-β1-29*C, IL-6-597*A, IL-6-572*C
Gordon, *J Orthop Res, 2007*	FRZB 200Trp, FRZB 200Arg: 324Arg haplotype

Table 2. Overview of genetic association studies investigating relationships between particular gene SNPs and failure of THA.

Conclusions

This study further **supports** the concept of genetic susceptibility to periprosthetic OL.

The alleles **TNF-238*A, IL-1A-889*T** and **IL-6-174*G** may **predispose** patients after THA to the development of **severe OL** at the site of acetabulum.

Our data are preliminary and **need confirmation** in a well-organized replication genotype-fenotype association study.