

Individual susceptibility to osteolysis in THA

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Modes of THA failure

- Aseptic loosening and periprosthetic osteolysis (OL)
- Dislocation
- Deep sepsis
- Etc.

Number of reoperations per reason and year
primary THRs performed 1979-2007

Reason for reoperation	1979-2002	2003	2004	2005	2006	2007	Total	Share
Aseptic loosening	14,869	1,105	988	996	1,018	952	19,928	58.3%
Dislocation	2,584	255	320	265	256	290	3,970	11.6%
Deep infection	2,185	240	288	281	286	305	3,585	10.5%
Fracture	1,666	168	172	181	164	191	2,542	7.4%
2-stage procedure	993	107	99	98	78	80	1,455	4.3%
Technical error	834	17	17	19	15	36	938	2.7%
Miscellaneous	793	21	36	26	15	27	918	2.7%
Implant fracture	338	35	33	23	23	23	475	1.4%
Pain only	270	11	16	8	15	11	331	1.0%
Secondary infection	0	0	1	1	0	3	5	0.0%
(missing)	36	0	1	6	1	4	48	0.1%
Total	24,568	1,959	1,971	1,904	1,871	1,922	34,195	100%

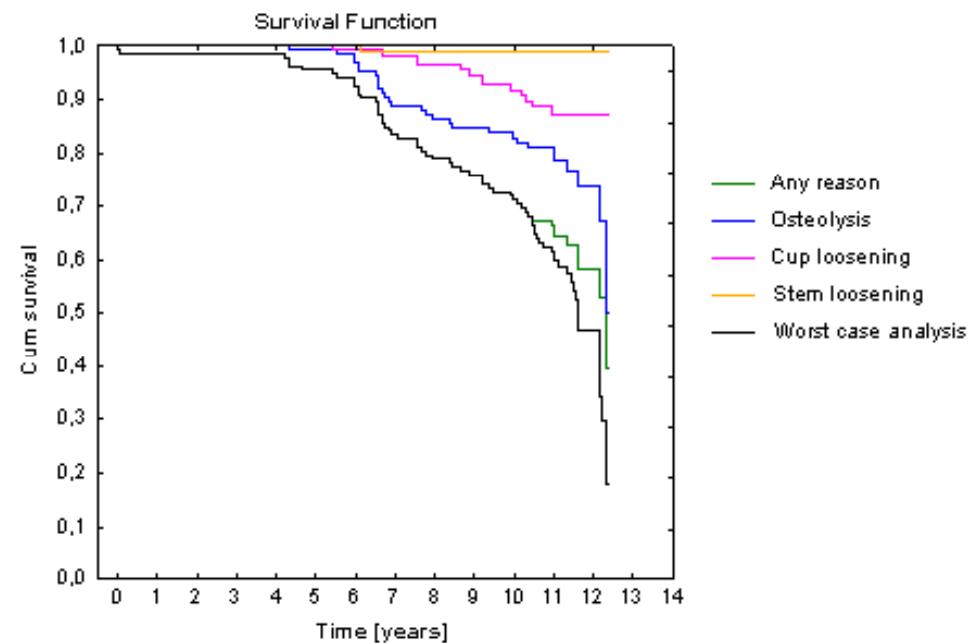
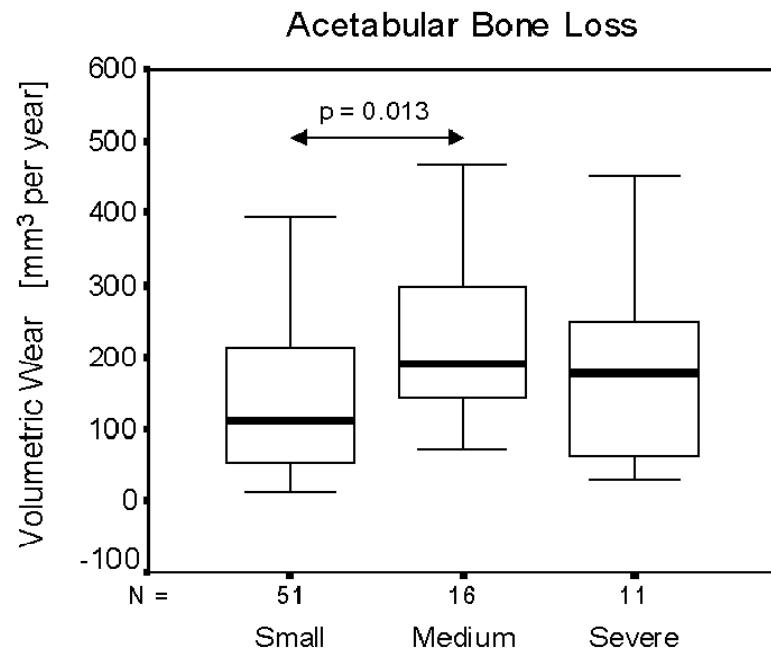
©Stryker 2008 Swedish Hip Arthroscopy Registry

Theory of OL – Particle disease

- Wear particles
- Stimulation of mesenchymal cells
- Expression of signal molecules
- Pro-inflammatory/ OL environment

We know it works but

- Association between particle loading and severity of OL/ time to failure is not linear



Therefore

- Another players should be involved to explain differences
 - in symptoms
 - in size of OL
 - in time to failure

Alternative players

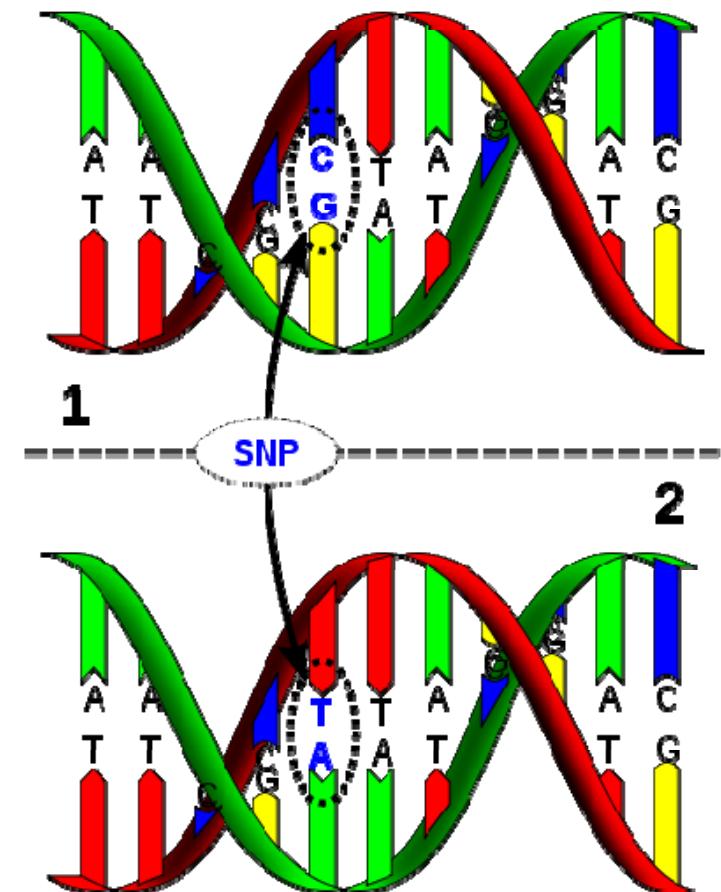
- *Material variables*
- *Design of implant*
- *Surgical variables*
- **INDIVIDUAL HOST RESPONSE**
 - *genetic component (susceptibility)*
e.g. cytokine gene polymorphisms (GP)
 - *hypersensitivity*

Cytokines

- Proteins responsible for communication among:
 - *cells of immune system*
 - *immune system and another organs/ tissues*

Single nucleotide polymorphisms (SNPs)

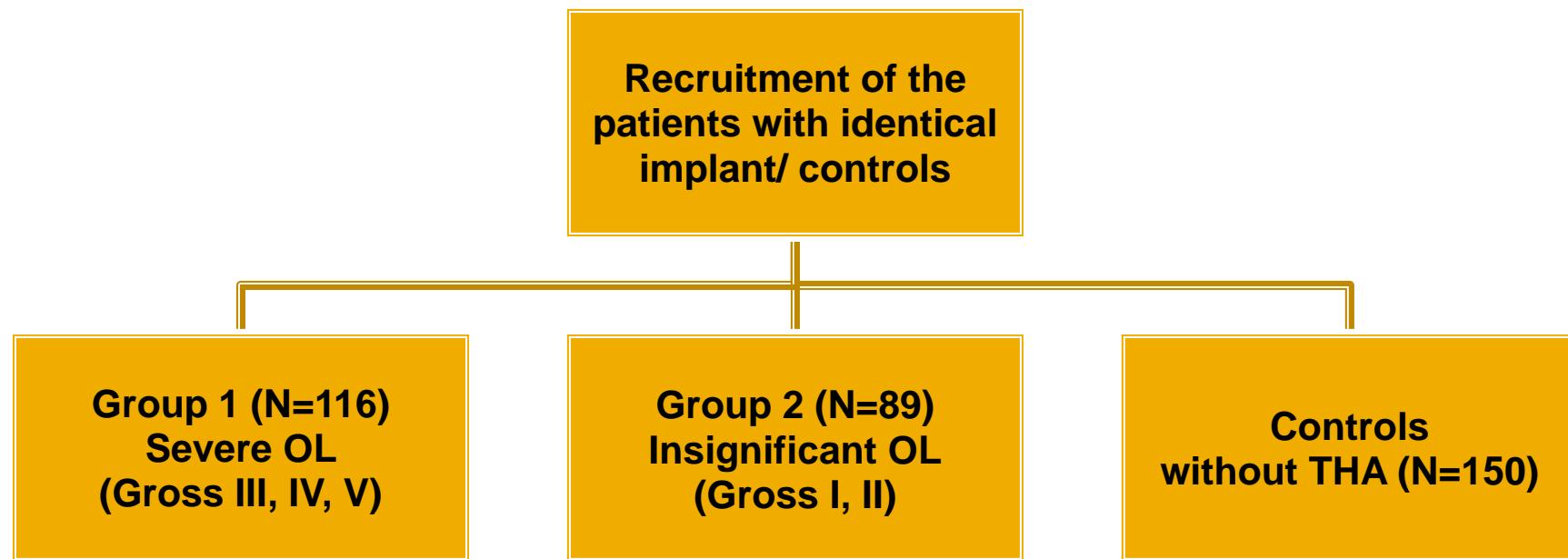
- Change in one nucleotide may lead to significant functional sequelae
- High or low secretor status



Genetic predisposition of the cytokine response as implications for a variety of major diseases ?

Bennemo, Clin Chem, 2004

Design of our study

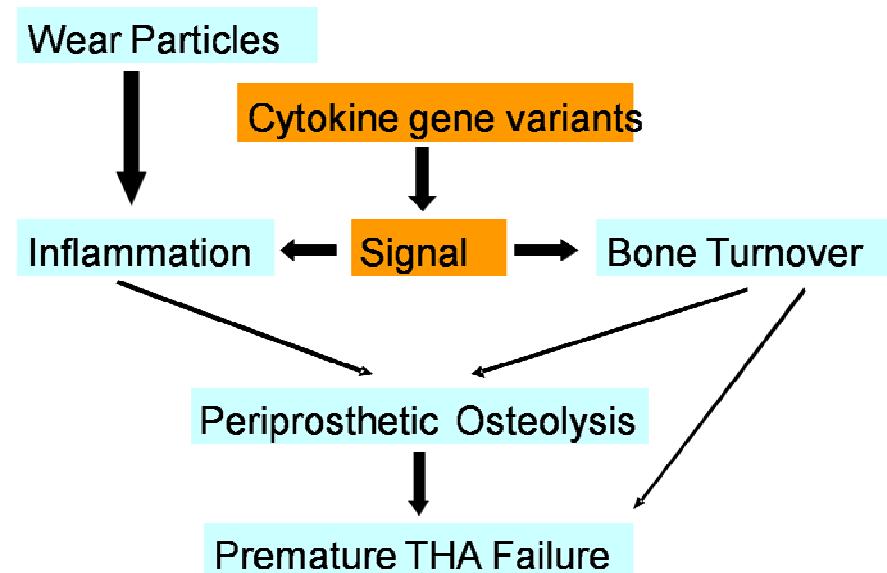


Questions

- Is there any association between the variants of inflammatory cytokine genes

- and size of OL?

- and time to failure?

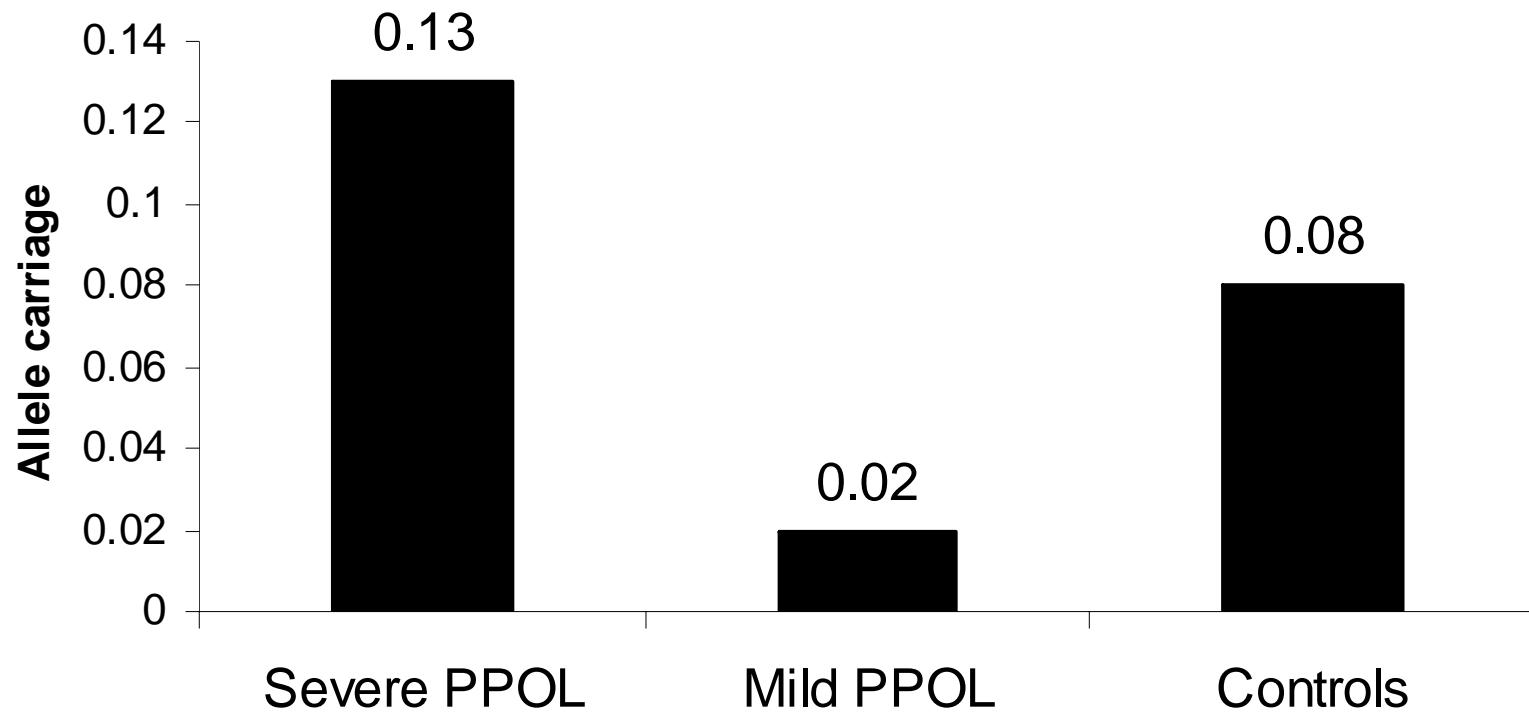


Methods

- Sample of peripheral blood
- Extraction of DNA
- Genotyping – Heidelberg kit (22 SNPs)
- Statistical analysis
 - *Chi² test for main outcomes*
 - *multivariable analysis*
 - *survival analysis*

Results

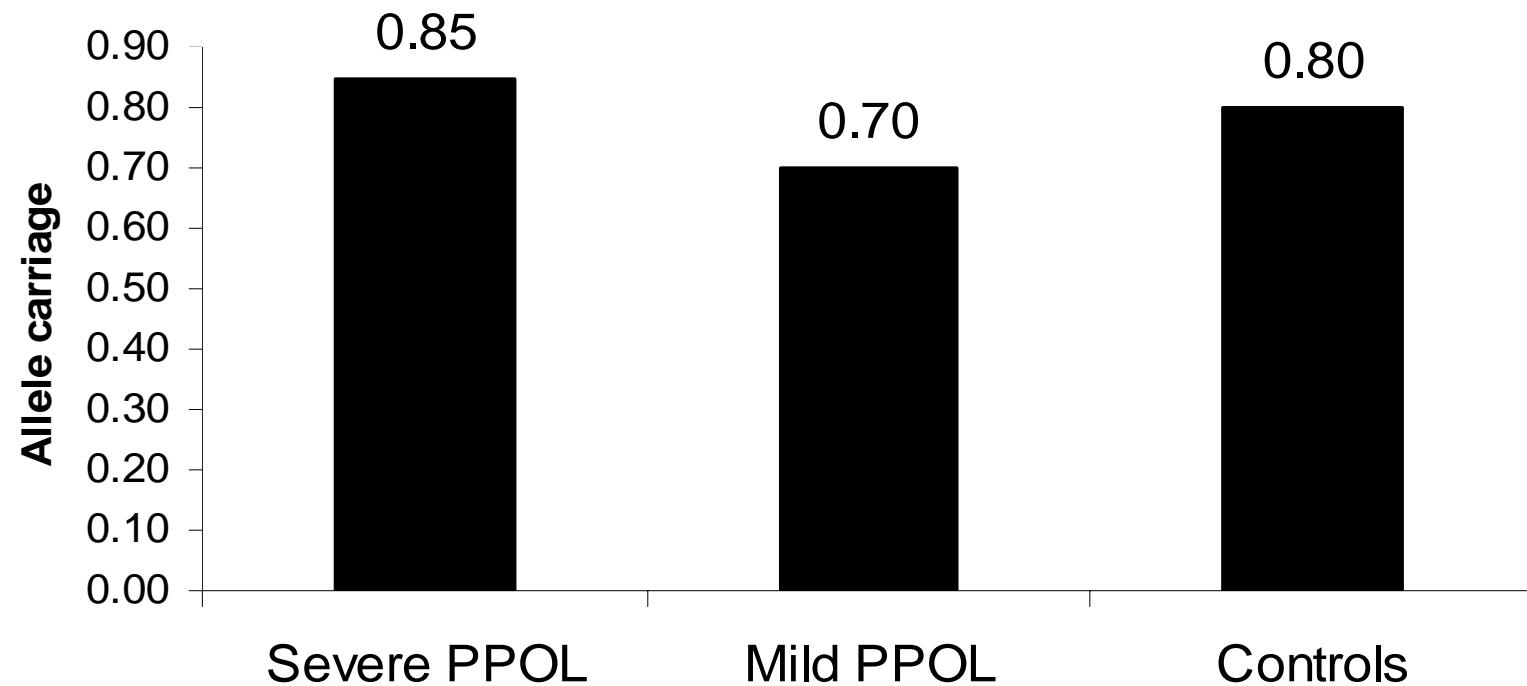
A) TNF-238*A allele carriage



TNF-238*A: $p=0.005$, OR = 6.59 (95% CI: 1.47-29.64), PAR% = 5.2

Results

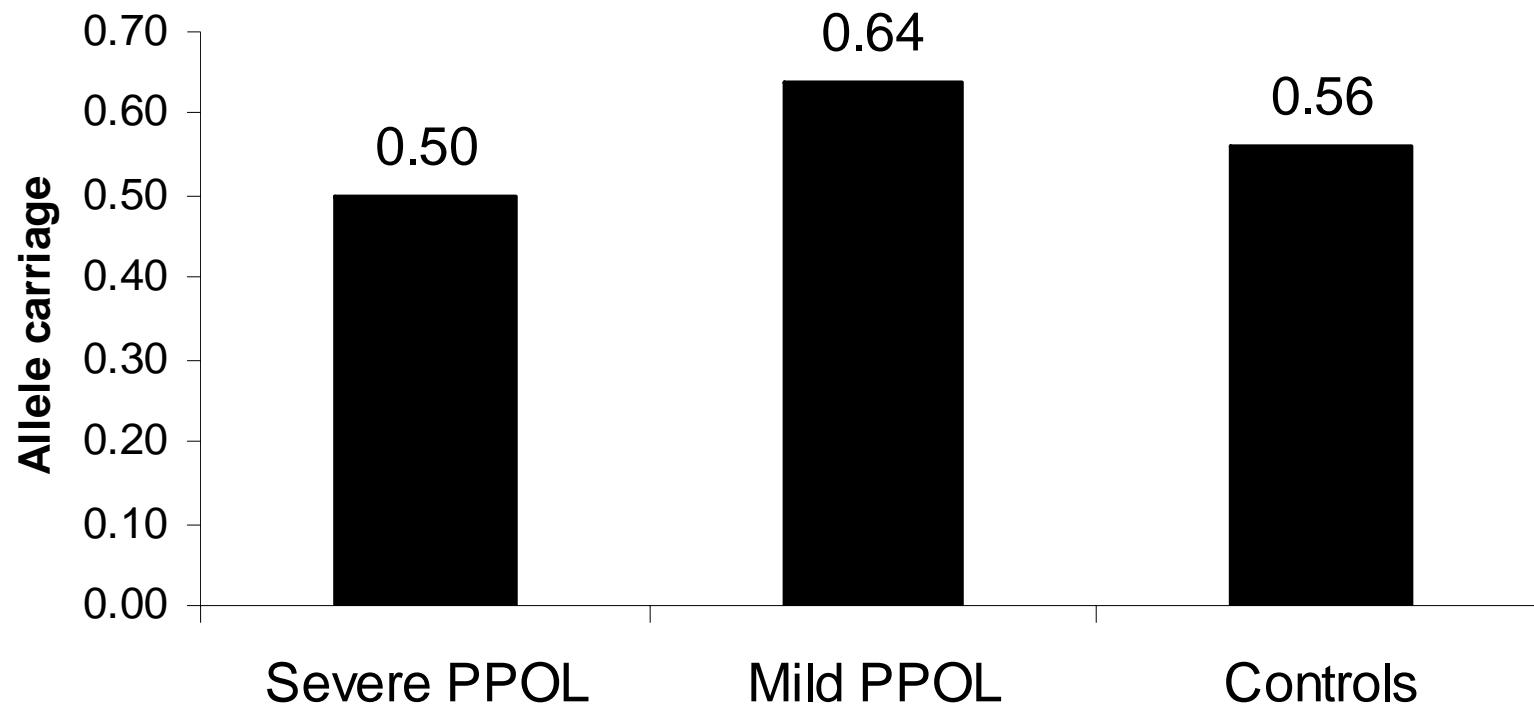
B) IL-6-174*G allele carriage



IL-6-174*G: $p=0.007$, OR = 2.51, (95% CI: 1.27-4.98), PAR% = 31.5

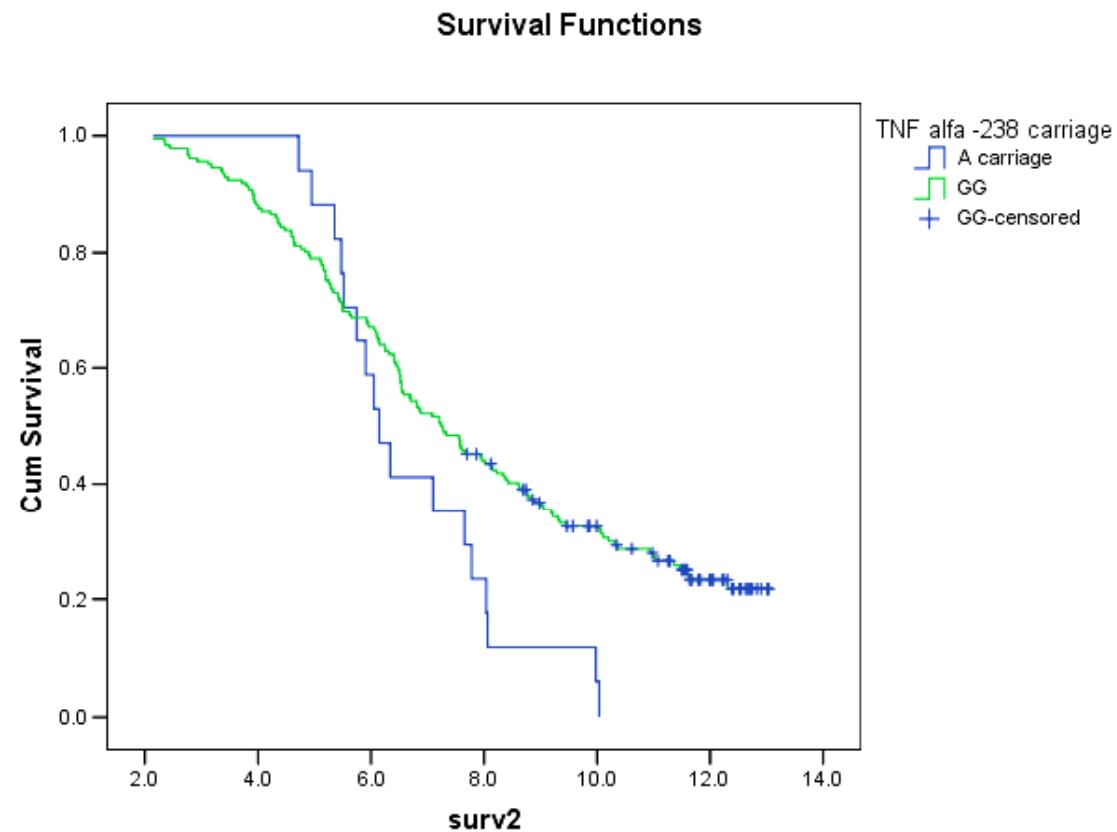
Results

C) IL-2-330*G allele carriage



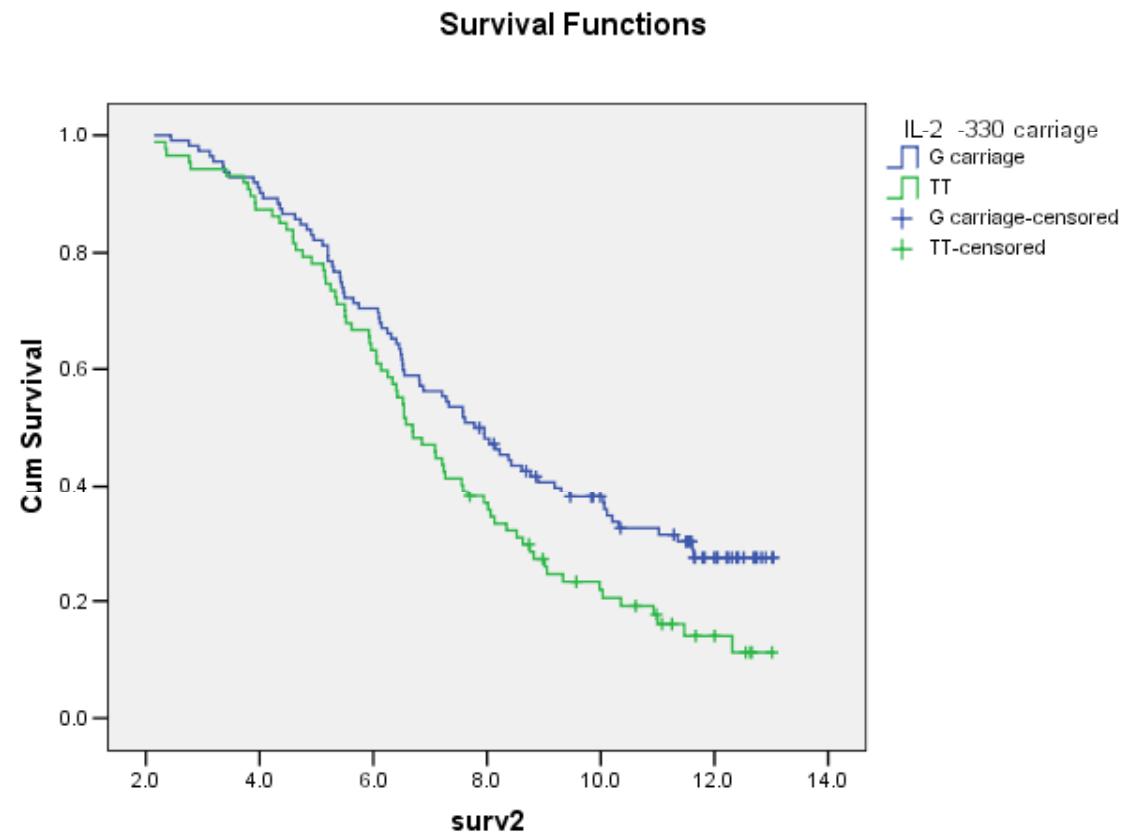
IL-2-330*G: $p=0.043$, OR = 0.55, (95% CI: 0.31-0.98)

Results



TNF-238*A: carriers (mean survival: 6.7 years) *versus* non-carriers (8.0 yrs): $p=0.022$

Results

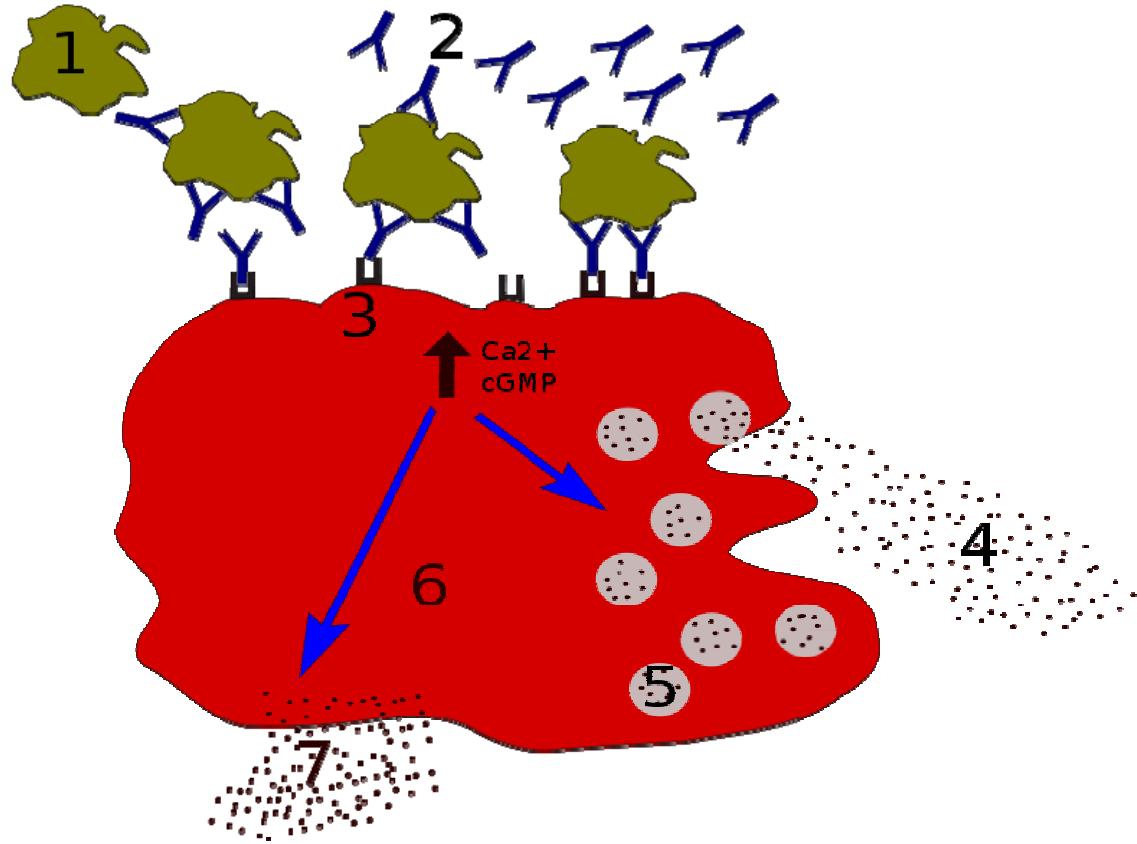


IL-2-330*G: carriers (7.8 yrs) *versus* non-carriers (6.7 yrs): $p=0.018$

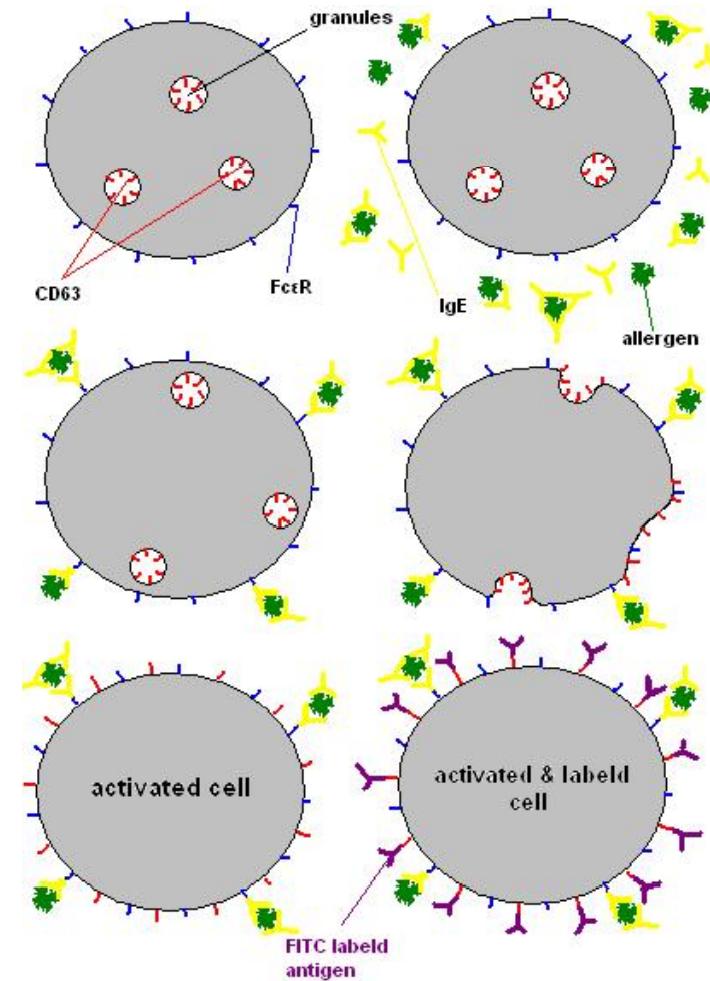
List of suggested SNPs

Author	Time to failure (yrs.)	Risk for aseptic loosening/ osteolysis
Wilkinson, 2003	10±4	<i>TNF-238*A</i>
Malik, 2006	5.1	<i>RANK+575*T</i>
Malik, 2007	5.1	<i>MBL-550*C, MBL-55*G, MMP1-1*C</i>
Kolundzic, 2006	15	<i>TGF-β1-29*C, IL-6-597*A, IL-6-572*C</i>
Gordon, 2007	10±5	<i>FRZB 200Trp, FRZB 200Arg: 324Arg</i>
Gordon, 2008	11	<i>IL1RA +2018C, IL6 haplotype -174G/-572G/-597A</i>
Bachmann, 2008	<10	<i>GNAS1 T393C</i>
Godoy-Santos, 2009	?	<i>MMP-1</i>
Our study, 2009	2-13 (9/6)	<i>TNF-238*A, IL6-174*G, IL2-330*G</i>

Hypersensitivity



1-allergen, 2-IgE, 3-Fc ϵ RI receptor, 4+7-histam., proteases, chemok., 6-mast cells



Source: Wikipedia

Allergy to wear/corrosion products

- Metallic/ UHMWPE/ PMMA substances
- Delayed type hypersensitivity– *induced/ pre-existing*
- Premature failure, groin pain, pseudotumors, osteolysis

Evidence for such concept in THA failure

Category	
History	Skin-, eye-, nose-related symptoms
Laboratory	IgE, basophils+CD123, HLA-DR
Testing for sensitivity	Dermal, intradermal, functional in vitro assays
Histology	Lymphocyte dominated inflammation
Epidemiological	Observational*, case-control studies
	Metaanalysis

*Thomas et al, *Allergy* 2009; Zustin et al, *Virchows Arch* 2009; Huber et al, *Acta Biomaterialia* 2009; Pandit et al, *Virchows Arch* 2008

How to deal with hypersensitivity?

- Poorly defined tools
- No evidence for routine preoperative testing for metal hypersensitivity
- Patients at risk: history => funct. assays
- Implants at risk: MOM, MOP (?)

Conclusion

- Individual host response in THA is the fact
- Risk variants of cytokine/ metalloproteinase genes
- Induced delayed hypersensitivity
- Both approaches need to be investigated