Genetic associations in anterior uveitis implicate T-cell co-stimulation and other immune pathways

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Anterior uveitis
• Inflammation of anterior uvea and ciliary body

Aims
• Investigate immune loci in anterior uveitis
• Ankylosing spondylitis patients
• Anterior uveitis patients with unknown AS status
• Associations complicated by AS co-phenotype

Anterior uveitis
• Occurs in 25-40% of ankylosing spondylitis pts
• Annual incidence 17-23 per 100,000 pop
• Prevalence 38-370 per 100,000 population

Impact
— Contributes 10% of annual blindness in the US
— Equates to 30,000 cases per year
— Often affects young working age people

Acharya et al. JAMA Ophthalmology 2013; online Sept 5

Samples
• 194 anterior uveitis (unknown AS status)
• 1,277 AS with uveitis
• Total of 1,471 all uveitis
• 2,112 ankylosing spondylitis (no uveitis) only
• 10,000 Wellcome Trust healthy controls

Disclosures
• No authors have any disclosures related to this work
Genotyping and Analysis

• Genotyped on **Immunochip** microarray
• Imputed with 1000 genomes (**SHAPEIT, IMPUTE2**)
• SNP analysis with **SNPTEST** and principle components (7 eigenvectors)
• GC1K 1.059, no MHC GC1K 1.03, ctl GC1K 1.05
• Classical alleles imputed with **HLA*IMP**
• HLA*IMP analysis – logistic regression with **R**

Ideal strategy

**Ankylosing spondylitis patients**

- **WITH** uveitis
- **WITHOUT** uveitis

AS with uveitis vs AS without uveitis

Adjusted Strategy

- Ankylosing spondylitis patients WITH uveitis
- Ankylosing spondylitis patients WITHOUT uveitis
- Healthy Controls
- Healthy Controls

Experiments

- **AS with uveitis** VS **AS without uveitis**
- **All uveitis** Vs **Healthy controls**
- **AS with uveitis** vs **Healthy controls**
- **AS without uveitis** vs **Healthy controls**
Strong HLA-B27 signal
All Uveitis versus Healthy Controls

Residual Association over HLA-C
HLA-IMP results: HLA-C*1602 $P = 5.7 \times 10^{-4}$

Full HLA*IMP Results

- HLA-B*27 $P < 1 \times 10^{-300}$ OR 60
- HLA-C*1602 $P = 5.7 \times 10^{-4}$ OR 6.1
- HLA-DRB*0402 $P = 3.1 \times 10^{-3}$ OR 5.4
- HLA-B*4701 $P = 4.0 \times 10^{-3}$ OR 3.9
- HLA-B*0702 $P = 5.4 \times 10^{-3}$ OR 0.75
- HLA-DRQ*0505 $P = 5.6 \times 10^{-3}$ OR 1.3
- HLA-DRB*1104 $P = 7.2 \times 10^{-3}$ OR 2.4

MHC signal in HLA-B27 negatives
HLA-B27 negative uveitis vs HLA-B27 negatives controls

Cases = 188 Controls = 8,681

Non-AS Uveitis Loci
Outside the MHC

All Uveitis vs Healthy Controls
Suggestive Associations

$5 \times 10^{-8} > P \text{ value} < 5 \times 10^{-6}$
Chr19: SMARCA4

All Uveitis vs Healthy Controls

Associations

• rs116488202  HLA-B27  $1.0 \times 10^{-300}$
• rs2032890  ERAP1  $3.4 \times 10^{-20}$
• rs11535078  CD80  $2.3 \times 10^{-12}$
• rs6759298  Zp15  $1.3 \times 10^{-10}$
• rs116100554  KIF21B  $1.7 \times 10^{-9}$
• chr12:6451738:D  TNFRSF1A  $6.9 \times 10^{-9}$
• rs79755370  IL23R  $2.7 \times 10^{-8}$
• Rs8103309  SMARCA4  $4.3 \times 10^{-8}$

Differences in association between AS and uveitis

• AS with Uveitis  85%  HLA-B27
• AS without Uveitis  75%  HLA-B27
• Controls  8%  HLA-B27

$uveitis \sim snp + B27 + Z + snp^* Z$

Conclusions

• HLA-C uveitis specific association
• Association in the CD80, IL10-IL19, peptidase
• Functional animal work with the EAU model supports both co-stimulation & IL-10/IL-19
• Further genetic and functional work required to validate the findings

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