

# Year in review: genetics and genomics

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# Recent advances in human genetics

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- Genome wide association studies:
  - Genotyping SNP-Chips
  - Large sample sets
  - Replication of identified associations
  - Small effects
  - Significance threshold  $< 5 \times 10^{-8}$
  - Polygenic = larger sample-size to uncover
  - Collaborations!

# Examples from other diseases and traits

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- Height; 253,000 individuals
  - 697 GWS loci
  - Explain 25% variance of height
- Type 2 diabetes; ca. 35,000 cases/ 115,000 controls
  - 70 GWS loci
  - Ca 15% of heritability

# GWS loci for Osteoarthritis

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- 17 genomic loci; 2 Asian specific:
- arcoGEN study: 15,000 cases / 53,000 controls
- TreatOA hipOA meta: 11,000 cases / 67,000 controls
- TreatOA kneeOA meta: 6,700 cases / 44,000 controls
- *GDF5* cand.gene meta: 6,800 knee OA / 10,000 controls

# Publications since OARSI 2014

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- 16 Candidate Gene Studies
- 7 Meta-analyses of publications
- 3 Genome-Wide Association Scans
  
- Genomics: epigenetics and eQTL studies

# Candidate Gene Studies

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Underpowered without replications:

- Most with small sample sizes
  - 9 studies with less than 200 OA patients
  - Largest study 605 OA cases
  - One QTL study of two populations
  - Only one study investigates a GWAS signal (DOTL) (although a different phenotype)
- No replication attempted
- Inconclusive results

# Meta-analyses of public data

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- Four genes analyzed
  - ESR1, VDR, TGF $\beta$ , GDF5
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- Weak evidence of association ESR1, VDR and TGF $\beta$
- Moderate association of GDF5 with knee OA
- None of these genes were associated in published GWA studies

# Genome wide association studies

## Severe osteoarthritis of the hand associates with common variants within the *ALDH1A2* gene and with rare variants at 1p31

Unnur Styrkarsdottir<sup>1</sup>, Gudmar Thorleifsson<sup>1</sup>, Hafdis T Helgadóttir<sup>1</sup>, Nils Bomer<sup>2</sup>, Sarah Metrustry<sup>3</sup>,

Clinical and epidemiological research

Evangelos Evangelou<sup>5,6</sup>, Deborah Hart<sup>3</sup>, Marian Beekman<sup>2,7,8</sup>,  
F Eiriksson<sup>9</sup>, Margret Thorsteinsdóttir<sup>9,10</sup>, Michael L Frigge<sup>1</sup>,  
Jón T Magnússon<sup>1</sup>, Gisli Masson<sup>1</sup>, The TREAT-OA Consortium<sup>11</sup>,  
Mel K Arden<sup>13</sup>, Thorvaldur Ingvarsson<sup>14,15</sup>, Stefan Lohmander<sup>16</sup>,  
Lara<sup>4,12</sup>, Rob G H H Nelissen<sup>19</sup>, Tim Spector<sup>3</sup>, Andre Uitterlinden<sup>4,12</sup>,  
Ingileif Jonsdóttir<sup>1,10</sup>, Ana M Valdes<sup>3,20</sup>, Ingrid Meulenbelt<sup>2,8</sup>,  
Jónsson<sup>1,10</sup>

*Nature Genetics* 46, 498–502 (2014)

VOLUME 46 | NUMBER 5 | MAY 2014 NATURE GENETICS

### EXTENDED REPORT

## Genome-wide association and functional studies identify a role for *IGFBP3* in hip osteoarthritis

Daniel S Evans,<sup>1</sup> Frederic Cailotto,<sup>2</sup> Neeta Parimi,<sup>1</sup> Ana M Valdes,<sup>3</sup>  
Martha C Castañó-Betancourt,<sup>4,5</sup> Youfang Liu,<sup>6</sup> Robert C Kaplan,<sup>7</sup>  
Martin Bidlingmaier,<sup>8</sup> Ramachandran S Vasam, Alexander Toumazou,<sup>9,10</sup>  
Gregory J Tranah,<sup>1,11</sup> Michael C Nevitt,<sup>11</sup> Steven R C  
Elizabeth Barrett-Connor,<sup>13</sup> Jordan B Renner,<sup>14</sup> Joann  
Sally A Doherty,<sup>3</sup> Andre G Uitterlinden,<sup>4,5,15</sup> Joyce B  
Rik J Lories,<sup>2,17</sup> Nancy E Lane<sup>18</sup>

*Ann Rheum Dis* 2014;0,1-7

Moon et al. *BMC Musculoskeletal Disorders* (2015) 16:76  
DOI 10.1186/s12891-015-0531-4

### RESEARCH ARTICLE

Open Access

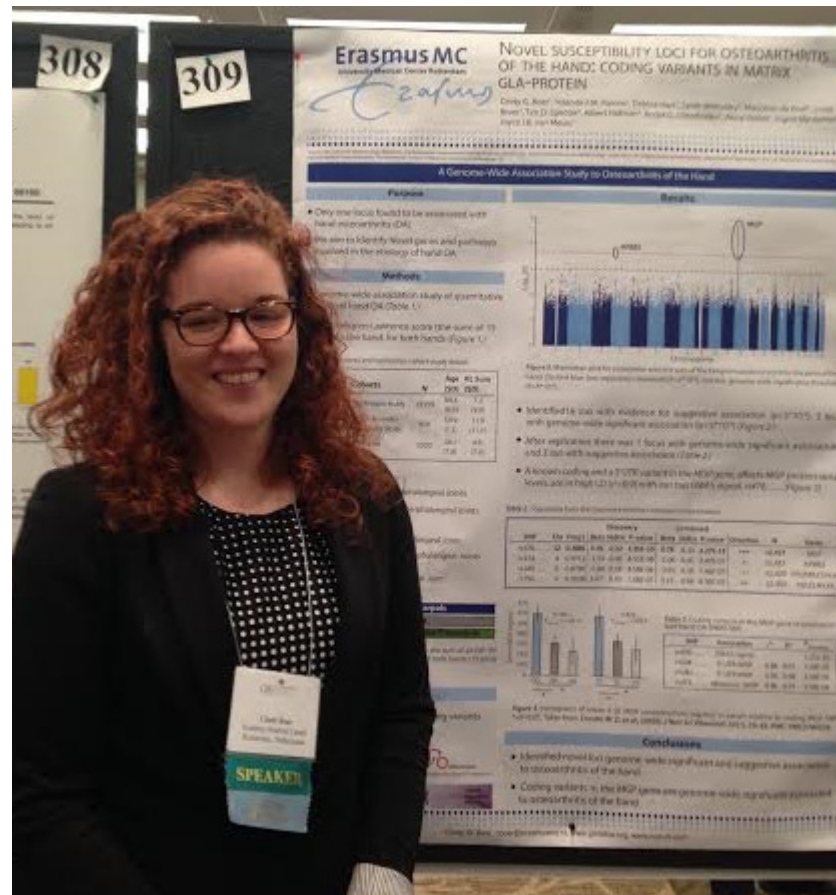
## A genome-wide association study of copy-number variation identifies putative loci associated with osteoarthritis in Koreans

Sanghoon Moon<sup>1†</sup>, Bhumsuk Keam<sup>1,2†</sup>, Mi Yeong Hwang<sup>1</sup>, Young Lee<sup>1</sup>, Suyeon Park<sup>1,4</sup>, Ji Hee Oh<sup>1</sup>,  
Yeon-Jung Kim<sup>1</sup>, Heun-Sik Lee<sup>1</sup>, Nam Hee Kim<sup>1</sup>, Young Jin Kim<sup>1</sup>, Dong-Hyun Kim<sup>3</sup>, Bok-Ghee Han<sup>1</sup>,  
Bong-Jo Kim<sup>1</sup> and Juyoung Lee<sup>1\*</sup>

*BMC Musculoskeletal Disorders* 2015, 16:7



# Poster#309: Hand OA QTL - MGP

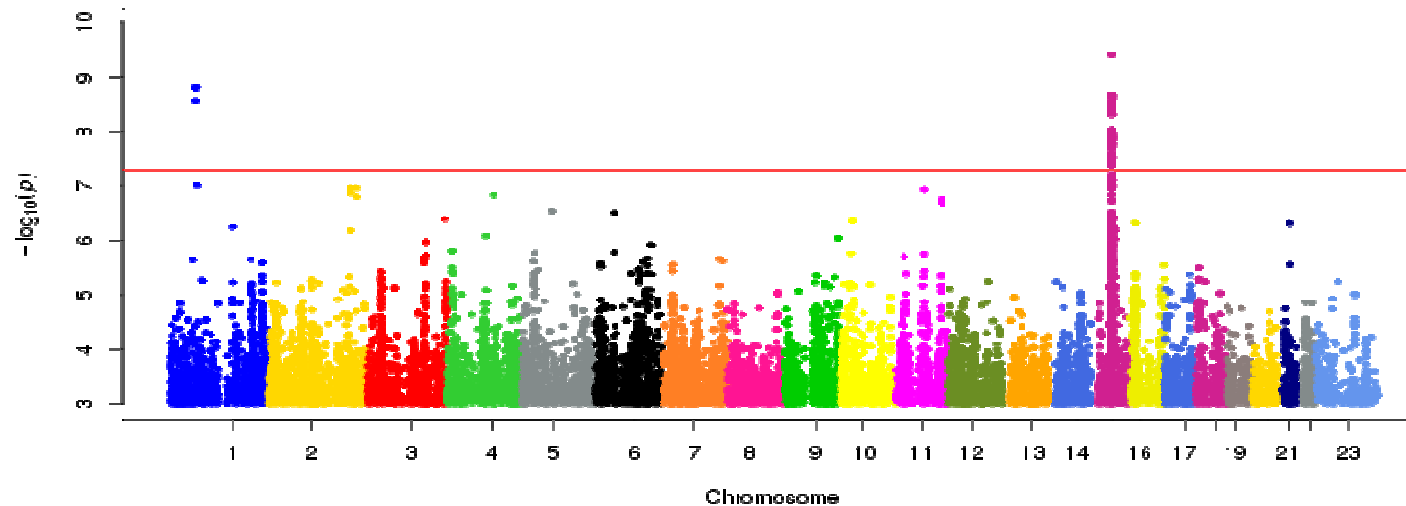


# Severe osteoarthritis of the hand associates with common variants within the *ALDH1A2* gene and with rare variants at 1p31

*Nature Genetics* 46, 498–502 (2014)

623 severe hand OA cases / 69,153 controls

Test 30 million sequence variants from WGS (rare and common)



Rare familial variants  
(0.02%, OR 50)

Common variants  
(41-54%, OR 1.5)

OARSI, 2015

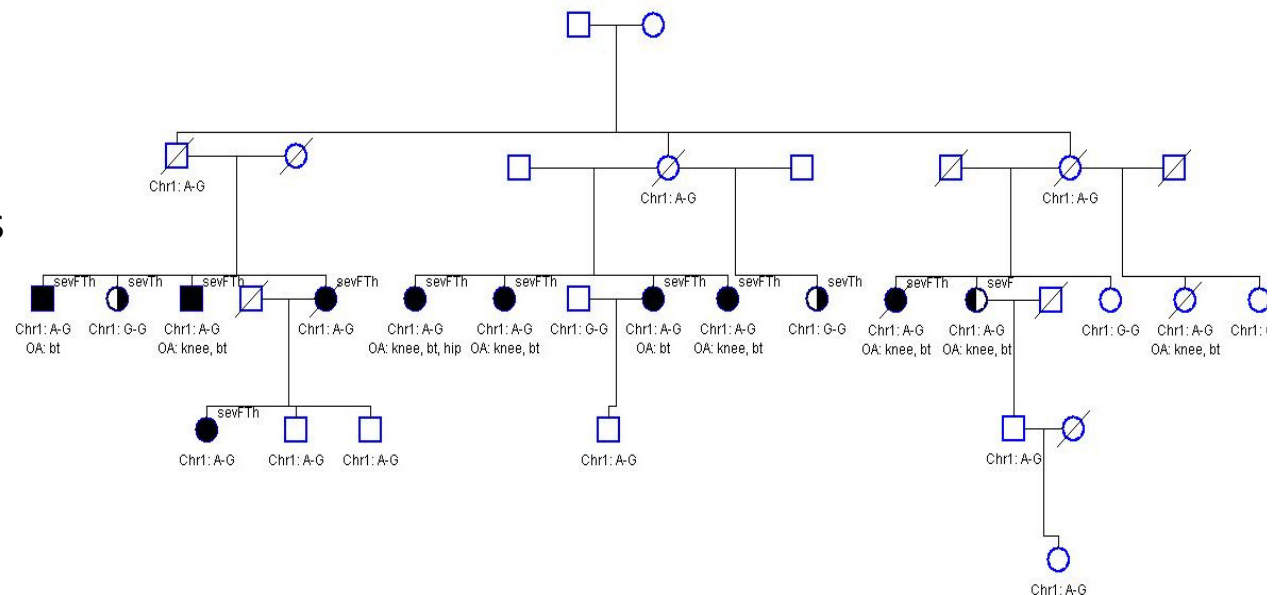
## Severe osteoarthritis of the hand associates with common variants within the *ALDH1A2* gene and with rare variants at 1p31

Rare signal at 1p31:

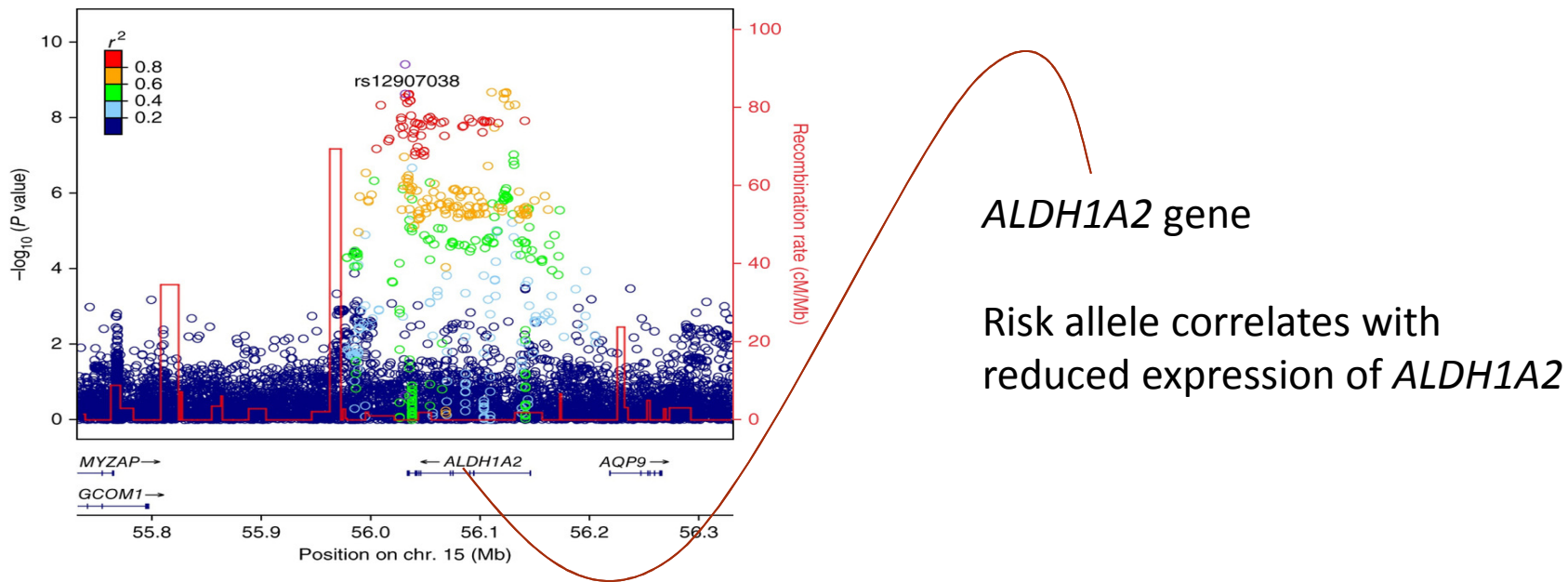
Allele freq = 0.02%

OR = 50,  $P = 9.8 \times 10^{-10}$

Present in other populations  
– needs very large sample sets to replicate association



## Severe osteoarthritis of the hand associates with common variants within the *ALDH1A2* gene and with rare variants at 1p31



**Table 1. Markers at 15q22, rs4238326-C (freq. 41%) and rs3204689-C (freq. 52%), associate with severe hand osteoarthritis**

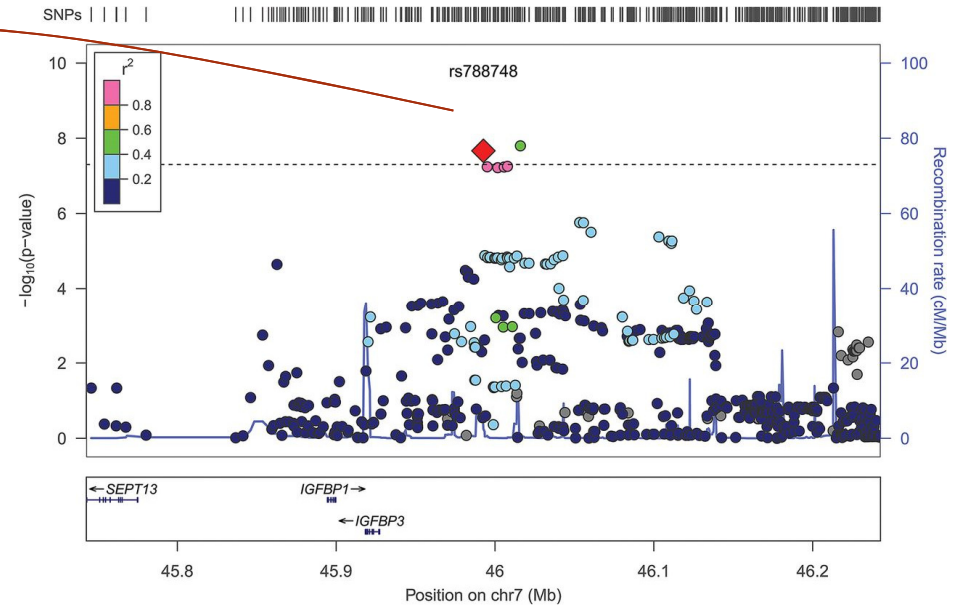
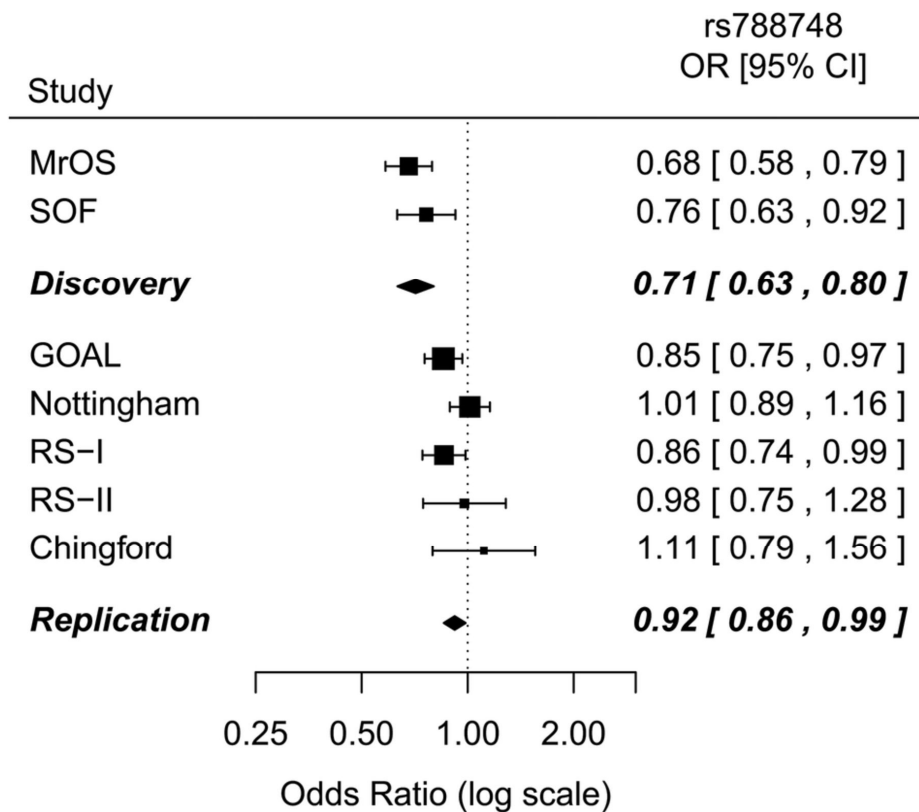
Hand OA phenotype	marker	OR (95% CI)	Overall	
			P value	N cases /controls
Severe thumbs and severe fingers	rs4238326	1.44 (1.29-1.60)	$8.6 \times 10^{-11}$	837 / 77325
	rs3204689	1.46 (1.31-1.63)	$1.1 \times 10^{-11}$	

EXTENDED REPORT

Genome-wide association and functional studies identify a role for *IGFBP3* in hip osteoarthritis

*Ann Rheum Dis* 2014;0,1-7

Discovery: 654 hip OA / 4,697 controls  
 Repl: 3,243 hip OA / 6,891 controls



Overall  $P = 1 \times 10^{-6}$   
 (not GWS)

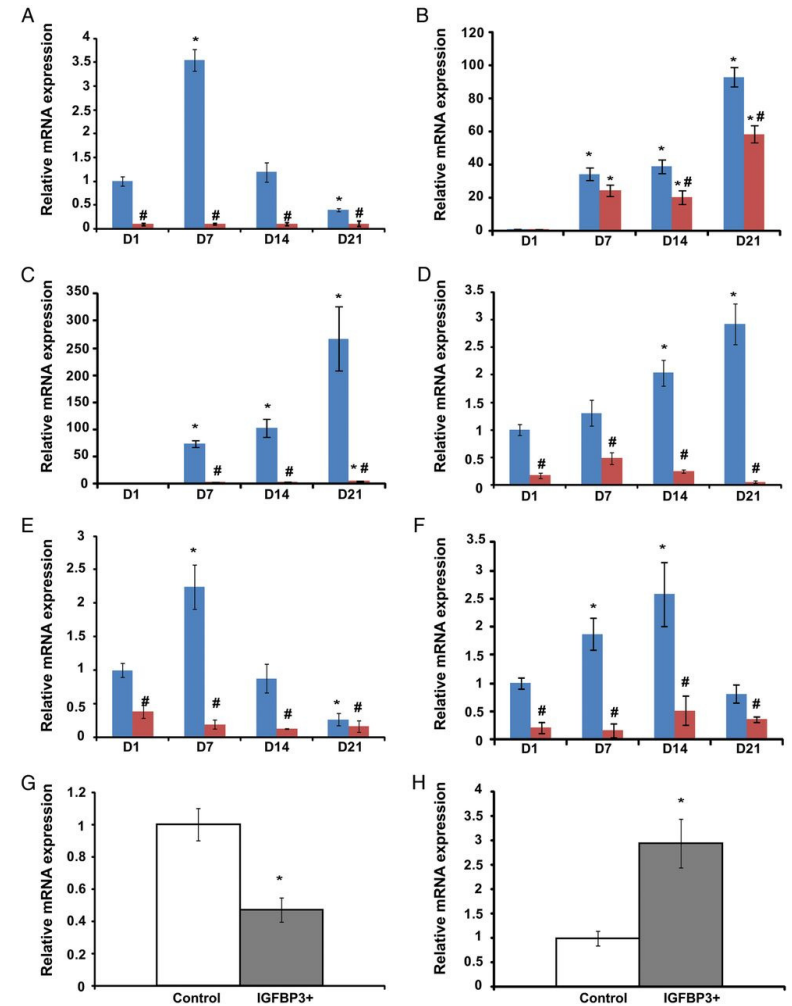
## EXTENDED REPORT

Genome-wide association and functional studies identify a role for *IGFBP3* in hip osteoarthritis

Associates with lower levels of circulating IGFBP1

Knockdown and overexpression of IGFBP3 had measureable effects in chondrogenic models

➤ Additional replication needed



**Figure 3** Impact of IGFBP3 knockdown and overexpression on markers of cartilage homeostasis.

RESEARCH ARTICLE

Open Access

# A genome-wide association study of copy-number variation identifies putative loci associated with osteoarthritis in Koreans

Sanghoon Moon<sup>1†</sup>, Bhumsuk Keam<sup>1,2†</sup>, Mi Yeong Hwang<sup>1</sup>, Young Lee<sup>1</sup>, Suyeon Park<sup>1,4</sup>, Ji Hee Oh<sup>1</sup>, Yeon-Jung Kim<sup>1</sup>, Heun-Sik Lee<sup>1</sup>, Nam Hee Kim<sup>1</sup>, Young Jin Kim<sup>1</sup>, Dong-Hyun Kim<sup>3</sup>, Bok-Ghee Han<sup>1</sup>, Bong-Jo Kim<sup>1</sup> and Juyoung Lee<sup>1\*</sup>

Test 1123 CNVs

204 hand OA, 167 knee OA, 467 controls

No association GWS ( $< 4.5 \times 10^{-5}$ )

No replication

# Epigenetics and eQTL studies

Gee et al. *BMC Medical Genetics* 2014, **15**:53  
<http://www.biomedcentral.com/1471-2350/15/53>



## RESEARCH ARTICLE

Open Access

### Allelic expression analysis of the osteoarthritis susceptibility locus that maps to chromosome 3p21 reveals *cis*-acting eQTLs at *GNL3* and *SPCS1*

Fiona Gee\*, Cl...

OPEN ACCESS Freely available online



### Genes Involved in the Osteoarthritis Process Identified through Genome Wide Expression Analysis in Articular Cartilage; the PAK Study



#### Abstract

**Background:** high linkage disequilibrium and therefore associated tissues and w...  
**Methods:** We... each allele of joint tissues o... exact test was...  
**Results:** *GNL3*... AEI = 1.04, *p* =... of the OA-ass...  
**Conclusions:** signal at chro...  
**Keywords:** O...

Yolande F. M. Ramos<sup>1,2</sup>,  
 Breggen<sup>1</sup>, Nico Lakenberg<sup>1</sup>,  
 Rob G. H. H. Nelissen<sup>4</sup>,

<sup>1</sup> Department of Molecular Epidemiology, Leiden-Rotterdam, The Netherlands, <sup>2</sup> University Medical Center, Leiden, Th...

#### Abstract

**Objective:** Identify gene... changing during the dise...  
**Methods:** Genome wide... same joint using microar... RT-qPCR and immunohis... enrichment for specific p...  
**Results:** Among the 1717... we found significant en... inflammatory genes such... comparing preserved cart... high up-regulation of *NG2*... changes of 2-fold or hi... expression. Most of these...

#### Basic and translational research

#### CONCISE REPORT

### Knee and hip articular cartilage have distinct epigenomic landscapes: implications for future cartilage regeneration approaches

W den Hollander,<sup>1</sup> Y F M Ramos,<sup>1</sup> S D Bos,<sup>1,2</sup> N Bomer,<sup>1,3</sup> R van der Breggen,<sup>1</sup> N Lakenberg,<sup>1</sup> W J de Dijcker,<sup>1</sup> Bouke J Duijnisveld,<sup>4</sup> P E Slagboom,<sup>1,2,3</sup> Rob G H H Nelissen,<sup>4</sup> I Meulenbelt<sup>1,2</sup>

Handling editor: Tore K Kvien

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2014-205980>).

<sup>1</sup>Department of Molecular Epidemiology, LUMC, Leiden, The Netherlands  
<sup>2</sup>Genomics Initiative, sponsored

#### ABSTRACT

**Objective:** landscape o... affected knee...  
**Methods:** BeadChip ar... measured in... pairs (14 kn... a total joint...

### Genome-Wide DNA Methylation Study Identifies Significant Epigenomic Changes in Osteoarthritic Cartilage

Matlock A. Jeffries,<sup>1</sup> Madison Donica,<sup>2</sup> Lyle W. Baker,<sup>3</sup> Michael E. Stevenson,<sup>4</sup> Anand C. Annan,<sup>4</sup> Mary Beth Humphrey,<sup>5</sup> Judith A. James,<sup>1</sup> and Amr H. Sawalha<sup>6</sup>

**Background:** Osteoarthritis (OA) is a joint characteri... and often accor... of other tissue... logical studies... major genetic c... susceptibility al... cently, several... have identified... The UK arc... significant loci... 3p21.1, was ass...



# Future of OA genetics research?

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- Small portion of heritability explained
  - Polygenic
  - Heterogeneity of phenotype
- Larger sample size
- More detailed phenotyping
- Collaborations

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# Thank you

Unnur Styrkársdóttir, OARSI, May 3<sup>rd</sup>, 2015



