

Genome-wide linkage scan and high-density association studies implicate chromosome 18q21 with generalized osteoarthritis

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Outline

- Study population & OA phenotype
- Genome wide linkage scan
- High density association study of 18q21

Genetics of Generalised Osteoarthritis (GOGO)

- Participants screened on the basis of clinical hand OA
- Case definition was based upon hand radiography
- A qualifying family consisted of at least 2 siblings affected with radiographic OA (rOA) of the hand
 - Kellgren Lawrence grade ≥ 2 OA involving ≥ 3 joints
 - distributed bilaterally of the DIP, PIP, or CMC joint groups
 - involving at least one DIP on digits 2-5
- Self-reported Caucasian ethnicity

Radiographic Assessment of GOGO Participants

- In addition participants underwent radiography of the hips, and knees with OA defined as KL grade ≥ 2 or a verified history of joint replacement for OA
- Patellofemoral joint (PFJ) OA was defined as osteophyte \geq grade 2
- Lumbar spine x-rays were obtained at the US sites only with OA defined as osteophyte grade ≥ 1 and disc narrowing ≥ 1 at the same vertebral level
- Radiographic procedures standardised between centres and all read by a single radiologist (Dr. Jordan Renner - University of North Carolina at Chapel Hill)

Osteoarthritis Cartilage, 2007,15:120-127

Linkage scan

- deCode 4cM scan
- 1,115 microsatellite markers
- 2,148 subjects, 880 families
- OA Phenotypes - DIP, PIP, CMC, hip, knee, lumbar spine
- Mendelian inheritance inconsistencies were determined (21 families excluded)
- Multipoint nonparametric linkage analysis using MERLIN
- LOD scores calculated using one parameter allele-sharing statistic Z

Linkage scan results

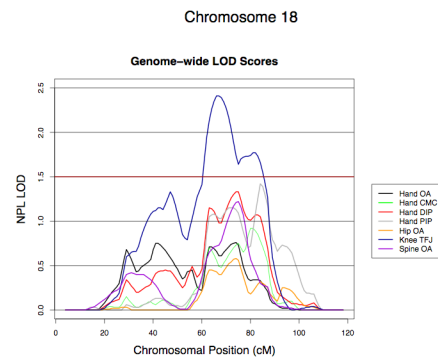
- 1 region of linkage (LOD $>$ 3) - PIP OA
- 11 region of suggestive linkage (1.5 $>$ LOD $<$ 3)

OA phenotype	Regions (n)
CMC	4
Knee	3
PIP	2
Hip	1
Lumbar	1
DIP	0

Linkage scan results

Chr	Location (cM)	1 LOD drop interval (cM)	Phenotype	LOD
1	92.2	69.2-98.2	Hip	1.97
2	158.0	148.0-167.0	CMC	2.16
2	123.0	117.0-129.0	PIP	3.01
7	Telomere	175.7-192.7	Knee	1.90
10	Telomere	0.0-9.2	CMC	2.04
12	Telomere	0.0-14.0	Knee	1.51
17	102.1	9.1-133.1	PIP	1.50
18	66.6	60.1-86.1	Knee	2.41
20	40.0	33.0-46.0	CMC	2.17
	42.5	36.0-77.0	Lumbar	1.60
X	153.2	132.2-163.2	PIP	2.13
	158.7	149.2-161.2	CMC	2.19

Linkage peak chromosome 18



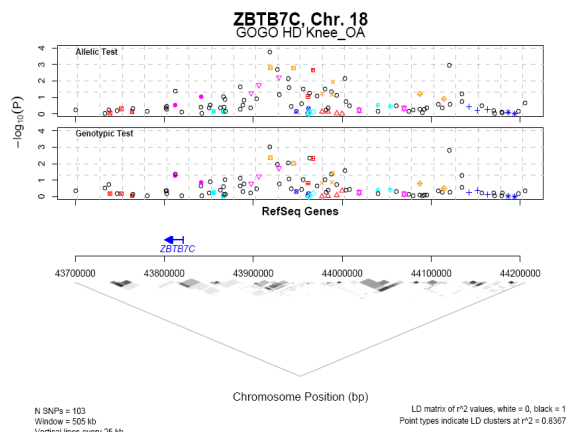
Association study of 18q21

- 511 unaffected controls recruited by Joanne Jordan at UNC (age \geq 57 years, radiological assessment of joints)
- 533 US families (330 single affected sib, 203 >1 affected sib)
- CCREL method used to account for IBD correlations
- 13 Mb region - 1,797 SNPs selected using Carlson algorithm
- Average spacing 7.4 Kb - maximum 50 Kb

Results of association study of 18q21

- 13 SNPs associated with knee OA ($p < 0.01$)
- 10 of these SNPs showed association for at least one other OA phenotype

SNP ID	Position (bp)	Knee OA	
		Allelic Test P-value	Genotypic Test P-value
rs4078130	43,918,613	0.0002	0.001
rs4076363	43,919,228	0.002	0.004
rs9789091	43,939,474	0.008	0.01
rs9947155	43,945,179	0.002	0.009
rs6507823	43,967,036	0.002	0.005
rs1944572	44,120,241	0.001	0.002
rs957142	45,399,715	0.001	0.002
rs7229377	45,402,297	0.003	0.003
rs225956	48,399,088	0.008	0.003
rs10502964	48,886,578	0.006	0.01
rs2234341	52,457,414	0.001	0.0007
rs1437070	52,817,931	0.002	0.004
rs4800958	52,877,051	0.003	0.001



Conclusions

- Linkage of 2q with PIP OA
- Suggestive linkage of 11 other regions with OA phenotypes including 18q21 with knee OA (LOD 2.41)
- Weaker linkage of 18q21 with hand and lumbosacral OA
- Associations of 18q21 SNPs with OA phenotypes
- No obvious candidate genes
- Modest p values
- Replication studies required to determine role of 18q21 in OA

GOGO Consortium Study

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