# Investigation of putative rheumatoid arthritis susceptibility loci identified in the WTCCC study confirms association with a novel locus at 6q23.

Wendy Thomson[1], Anne Barton[1], Xiayi Ke[1], Steve Eyre[1], Anne Hinks[1], John Bowes[1], Rachelle Donn[1], Deborah Symmons[1], Samantha Hider[1], Ian N Bruce[1], Wellcome Trust Case Control Consortium[9], Anthony G. Wilson[2], Ioanna. Marinou[2], Ann Morgan[3], Paul Emery[3], YEAR consortium[10], Angela Carter[4], Sophia Steer[5], Lynne Hocking[6], David M Reid[6], Paul Wordsworth[7], Pille Harrison[7], David Strachan[8], Jane Worthington[1*].

Supplementary Methods

**Methods.**

***Samples:*** DNA from RA patients, over 18 years old and satisfying the American College of Rheumatology criteria for RA[1] was available from 6 centres in the UK and 5 of these centres also provided DNA samples from healthy controls: Manchester 1372 cases, 924 controls (including 357 controls from the 1958 birth cohort, not overlapping with those samples tested in the WTCCC study); Sheffield 979 cases, 995 controls; Leeds 1126 cases, 532 controls; Aberdeen 523 cases, 862 controls; Oxford 736 cases, 536 controls; London 327 cases. Of the cases, 294 were recruited as part of the **arc** National Repository of Family Material[2] and 675 were recruited from the Norfolk Arthritis Register, a primary care-based inception collection[3]. All other cases were recruited from NHS Rheumatology Clinics throughout the UK. Presence of autoantibodies (RF and/ or anti-CCP) and joint erosions was documented for a proportion of the patients (supplementary Table 1).

***Genotyping:*** Genotyping was performed using the Sequenom platform (www.sequenom.com) and assays with a genotyping success rate of >95% were included in the subsequent analysis. All assay results were manually inspected to ensure tight clustering of genotype assignments and good separation of clusters. A single plex of 17 SNPs was created including the 10 SNPs detailed above and proxies in correlation ($r^2 = \geq 0.95$), where available (supplementary Table 5). Assay design failed to multi-plex a proxy SNP for rs3816587 and, unfortunately, that SNP failed genotyping quality control thresholds. One SNP tested in the WTCCC study, rs6684865, failed to genotype but a proxy, rs10910099 ($r^2 = 0.95$) did amplify and results for this are reported instead. For the remaining SNPs, all assays genotyped well so only data for the original SNP has been presented.

***Analysis:*** Genotype and allele frequencies were compared between cases with RA and controls using STATA version 9 (StataCorp, Texas, USA) and PLINK (www.pngu.mgh.harvard.edu/~purcell/plink/). For markers showing evidence of association, further analysis was undertaken stratifying cases according to autoantibody status.


1. F. C. Arnett, *et al.*, "The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis," Arthritis Rheum. **31**(3), 315 (1988).
Ref Type: Journal

2. J. Worthington, *et al.*, "The Arthritis and Rheumatism Council's National Repository of Family Material: pedigrees from the first 100 rheumatoid arthritis families containing affected sibling pairs," Br. J. Rheumatol. **33**(10), 970 (1994).
Ref Type: Journal

3. D. P. Symmons and A. J. Silman, "The Norfolk Arthritis Register (NOAR)," Clin. Exp. Rheumatol. **21**(5 Suppl 31), S94-S99 (2003).
Ref Type: Journal

**Supplementary Table 1.** Clinical characteristics, where available, of the RA subjects tested in the validation study, by centre of recruitment.

| **Cohort** | **Total N** | **Manchester N** | **Aberdeen N** | **Leeds N** | **Sheffield N** | **London N** | **Oxford N** | **WTCCC N** |
|---|---|---|---|---|---|---|---|---|
| Controls | 3849 | 924 | 862 | 532 | 995 | 0 | 536 | 1860 |
| Cases | 5063 | 1372 | 523 | 1126 | 979 | 327 | 736 | 2938 |
| Age at onset | 48.8 | 53.2 | 57.9 | 42.3 | 46.9 | 47.7 | 44.2 | |
| **Case Characteristic** | **Total N (%)** | **Manchester N (%)** | **Aberdeen N (%)** | **Leeds N (%)** | **Sheffield N (%)** | **London N (%)** | **Oxford N (%)** | **WTCCC N(%)** |
| Gender | | | | | | | | |
| M | 1229 (33.8) | 391 (28.5) | 125 (24.0) | 355 (31.7) | 263 (27.7) | 70 (22.1) | 209 (28.4) | 470 (25.3) |
| F | 2409 (66.2) | 981 (71.5) | 397 (76.0) | 764 (68.3) | 687 (72.3) | 274 (77.9) | 527 (71.6) | 1390 (74.7) |
| RF | | | | | | | | |
| Negative | 1319 (28.4) | 391 (28.8) | 101 (21.1) | 333 (34.5) | 236 (26.9) | 93 (39.9) | 165 (22.4) | 251 (16.1) |
| Positive | 3329 (71.6) | 355 ((48.2) | 378 (78.9) | 632 (65.5) | 642 (73.1) | 140 (60.1) | 571 (77.6) | 1310 (83.9) |
| Anti-CCP | | | | | | | | |
| Negative | 857 (33.2) | 442 (39.6) | - | 202 (38.0) | 213 (22.9) | - | - | 224 (20.7) |
| Positive | 1724 (66.8) | 675 (60.4) | - | 330 (62.0) | 719 (77.1) | - | - | 884 (79.8) |
| SE (no. copies) | | | | | | | | |
| 0 | 868 (25.4) | 334 (25.8) | - | 113 (26.9) | 197 (21.5) | 53 (22.9) | 171 (31.0) | 286 (20.7) |
| 1 | 1674 (49.0) | 649 (50.0) | - | 220 (52.4) | 427 (46.5) | 114 (49.4) | 264 (47.8) | 680 (49.2) |
| 2 | 876 (25.6) | 314 (24.2) | - | 87 (20.7) | 294 (32.0) | 64 (27.7) | 117 (21.2) | 416 (30.1) |

**Supplementary Table 2** Power of this study to detect the effects of the 9 SNPs associated with RA in the WTCCC study (based on 5063 cases and 3849 controls, assuming disease prevalence at 0.8% and a genotypic model).

| Chr | SNP | Risk allele freq in cases vs controls | GRR[1] | GRR[2] | Power at $p < 0.05$ | Power at $p < 0.006$ |
|---|---|---|---|---|---|---|
| 1 | rs6684865 | 0.71–0.66 | 1.17 | 1.31 | 98% | 99% |
| 1 | rs11162922 | 0.95-0.93 | 1.19 | 1.60 | 100% | 97% |
| 4 | rs3816587 | 0.43-0.41 | 1.00 | 1.19 | 69% | 39% |
| 6 | rs6920220 | 0.26-0.22 | 1.12 | 1.36 | 96% | 84% |
| 7 | rs11761231 | 0.67-0.62 | 1.27 | 1.37 | 99% | 93% |
| 10 | rs2104286 | 0.76-0.71 | 1.26 | 1.40 | 98% | 91% |
| 13 | rs9550642 | 0.11-0.08 | 1.19 | 1.53 | 92% | 74% |
| 21 | rs2837960 | 0.19-0.17 | 1.00 | 1.54 | 60% | 30% |
| 22 | rs743777 | 0.34-0.29 | 1.06 | 1.36 | 96% | 82% |

[1] Genotype relative risk for heterozygotes of risk allele against homozygotes of non-risk allele; [2] Genotype relative risk for homozygotes of risk allele against homozygotes of non-risk allele.

**Supplementary Table 3.** Validation of rs6920220 association to RA in different cohorts

| Centre | Case (N) | Control (N) | Genotyping success % (cases – controls) | MAF (cases - control) | Genotype AA – AG – GG (cases) (%) | Genotype AA – AG – GG (controls) (%) | OR (95% CI) | HWE p-value (cases) | HWE p-value (control) | Allelic test (p-value) | Trend test (p-value) | Genotypic test (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Manchester | 1372 | 924 | 95.1 – 95.3 | 0.244 - 0.217 | 5.98 – 36.9 – 57.2 | 3.41 – 36.5 - 60 | 1.17 (1.01-1.35) | NS | 0.029* | 0.037 | 0.034 | 0.02 |
| Aberdeen | 523 | 862 | 97.3 – 97.6 | 0.268 – 0.218 | 6.68 – 40.3 - 53 | 5.47 – 32.7 – 61.8 | 1.31 (1.10 – 1.57) | NS | NS | 0.003 | 0.003 | 0.006 |
| Leeds | 1126 | 532 | 88.7 – 88.0 | 0.243 – 0.206 | 5.11 – 38.4 – 56.5 | 2.78 – 35.7 – 61.5 | 1.24 (1.02 – 1.49) | NS | NS | 0.028 | 0.023 | 0.05 |
| Sheffield | 979 | 995 | 97.2 – 98.1 | 0.253 – 0.202 | 5.88 – 39 – 55.1 | 3.38 – 33.7 – 62.9 | 1.34 (1.15 – 1.56) | NS | NS | $1.5 \times 10^{-4}$ | $1.1 \times 10^{-4}$ | $5.2 \times 10^{-4}$ |
| London | 327 | 0 | 94.8 - NA | 0.253 - NA | 7.42 – 35.8 – 56.8 | NA | NA | NS | NA | NA | NA | NA |
| Oxford | 736 | 536 | 99.5 – 98.7 | 0.229 – 0.201 | 4.78 – 36.2 - 59 | 3.78 – 32.7 – 63.5 | 1.18 (0.97 – 1.43) | NS | NS | NS | NS | NS |
| Validation[1a] | 5063 | 3849 | 95.0 – 96.0 | 0.247 – 0.21 | 5.76 – 37.8 – 56.5 | 3.84 – 34.3 – 61.9 | 1.23 (1.15 – 1.33) | NS | 0.042 | $1.6 \times 10^{-8}$ | $1.1 \times 10^{-8}$ | $5.8 \times 10^{-8}$ |
| Validation[1b] | 5063 | 2925 | 95.0 – 96.2 | 0.247 – 0.208 | 5.76 – 37.8 – 56.5 | 3.98 – 33.5 – 62.5 | 1.25 (1.15 – 1.35) | NS | NS (0.3) | $3.6 \times 10^{-8}$ | $2.8 \times 10^{-8}$ | $2 \times 10^{-7}$ |
| CMH test[1a] | OR = 1.25 (95% CI = 1.15 – 1.34) p-CMH = $1.1 \times 10^{-8}$ | | | | | | | | | | | |
| CMH test[1b] | OR = 1.28 (95% CI = 1.67 – 1.39) p-CMH = $5.9 \times 10^{-8}$ | | | | | | | | | | | |
| Combined[2a] | 6923 | 6787 | 96.2 – 97.7 | 0.251 – 0.216 | 6.06 – 38.1 – 55.8 | 4.09 – 34.9 - 61 | 1.22 (1.15 – 1.29) | NS | 0.008 | $5.9 \times 10^{-12}$ | $3.6 \times 10^{-12}$ | $1.4 \times 10^{-11}$ |
| Combined[2b] | 6923 | 5863 | 96.2 – 98.1 | 0.251 – 0.215 | 6.06 – 38.1 – 55.8 | 4.19 – 34.7 – 61.1 | 1.22 (1.15 – 1.30) | NS | NS (0.051) | $2.8 \times 10^{-11}$ | $1.9 \times 10^{-11}$ | $1.2 \times 10^{-10}$ |
| CMH test[2a] | OR = 1.245 (95% CI = 1.174 – 1.321) p-CMH = $3.1 \times 10^{-8}$ | | | | | | | | | | | |
| CMH test[2b] | OR = 1.262 (95% CI = 1.183 – 1.346) p-CMH = $1.7 \times 10^{-12}$ | | | | | | | | | | | |

[1a]All validation samples were combined. [1b]All validation samples were combined except controls from Manchester. [2a]Both WTCCC and validation samples were combined. [2b]Both WTCCC and validation samples were combined except validation controls from Manchester. No significant heterogeneity was detected by test of homogeneity of odds ratio in 1a, 1b, 2a and 2b. Cochran-Mantel-Haenszel (CMH) test was carried out by stratification of centres (cohorts). *HWD in Manchester validation controls was due to excess heterozygotes (observed frequency of 0.365 versus expected frequency of 0.34).

**Supplementary Table 4** Validation results for the 9 SNPs with evidence for association with RA from the WTCCC study. A total of 5063 cases and 3849 controls were genotyped. Individuals failing 2 or more SNPs were removed (352 cases and 223 controls) and a 95% genotyping success rate was imposed on remaining samples for each SNP.

| SNP | Genotyping success rate (cases vs controls) (%) | MAF (cases vs controls) | Genotype frequency (cases) (%) | Genotype frequency (controls) (%) | HWE p value (controls) | Allelic OR (95% CI) | Trend p value | Genotypic p value | Comment |
|---|---|---|---|---|---|---|---|---|---|
| rs10910099[a] | 94.8 - 96.1 | 0.32 - 0.33 | 10.6 – 43.2 – 46.2 | 11.1 – 43.1 - 45.9 | NS | 0.98 (0.92 – 1.05) | NS | NS | In LD with rs6684865 |
| rs11162922 | 93.9 - 95.5 | 0.06 – 0.06 | 0.39 - 11.3 - 88.4 | 0.31 - 11.5 - 88.2 | NS | 0.99 (0.87 – 1.13) | NS | NS | |
| rs3816587[b] | 98.0 - 42.5 | | | | | | | | |
| rs6920220 | 95.0 – 96.0 | 0.25 – 0.21 | 5.8 – 37.8 – 56.4 | 3.8 – 34.4 – 61.8 | 0.042 | 1.24 (1.15 – 1.33) | $1.3x10^{-8}$ | $5.9x10^{-8}$ | *OLIG3 – TNFAIP3* |
| rs11761231 | 94.7 - 96.4 | 0.35 – 0.36 | 12.0 - 45.3 - 42.8 | 12.8 - 46.7 - 40.5 | NS | 0.94 (0.88 – 1.00) | 0.042[c] | NS | *PODXL* |
| rs2104286 | 94.4 - 95.9 | 0.25 – 0.27 | 6.7 - 37.3 – 56.0 | 7.0 - 39.2 - 53.8 | NS | 0.94 (0.87 – 1.01) | NS | NS | *IL2RA* |
| rs9550642 | 95.1 - 96.4 | 0.10 – 0.10 | 1.0 - 17.8 - 81.1 | 1.05 - 17.7 - 81.2 | NS | 1.00 (0.91 – 1.11) | NS | NS | *CRYL1* |
| rs2837960 | 94.6 - 95.6 | 0.18 – 0.17 | 3.27 - 28.5 - 68.3 | 2.88 - 28.0 - 69.2 | NS | 1.05 (0.96 – 1.14) | NS | NS | |
| rs743777[d] | 95.1 - 96.2 | 0.33 – 0.32 | 11.4 - 43.4 - 45.2 | 9.47 - 44.4 - 46.1 | NS | 1.07 (1.00 – 1.14) | NS | 0.021 | *IL2RB* |

NA – not analysed due to low numbers in the 2x3 genotype table; NS – not significant at $p < 0.05$; HWE = Test for deviation from Hardy-Weinberg equilibrium.

[a]The marker genotyped and found to be associated with RA in the WTCCC was rs6684865 but the marker genotyped in the current study, rs10910099, shows high correlation ($r^2 = 0.95$) and serves as a proxy for it.

[b]Genotyping success rate was less than the 95% cut-off used in the analysis.

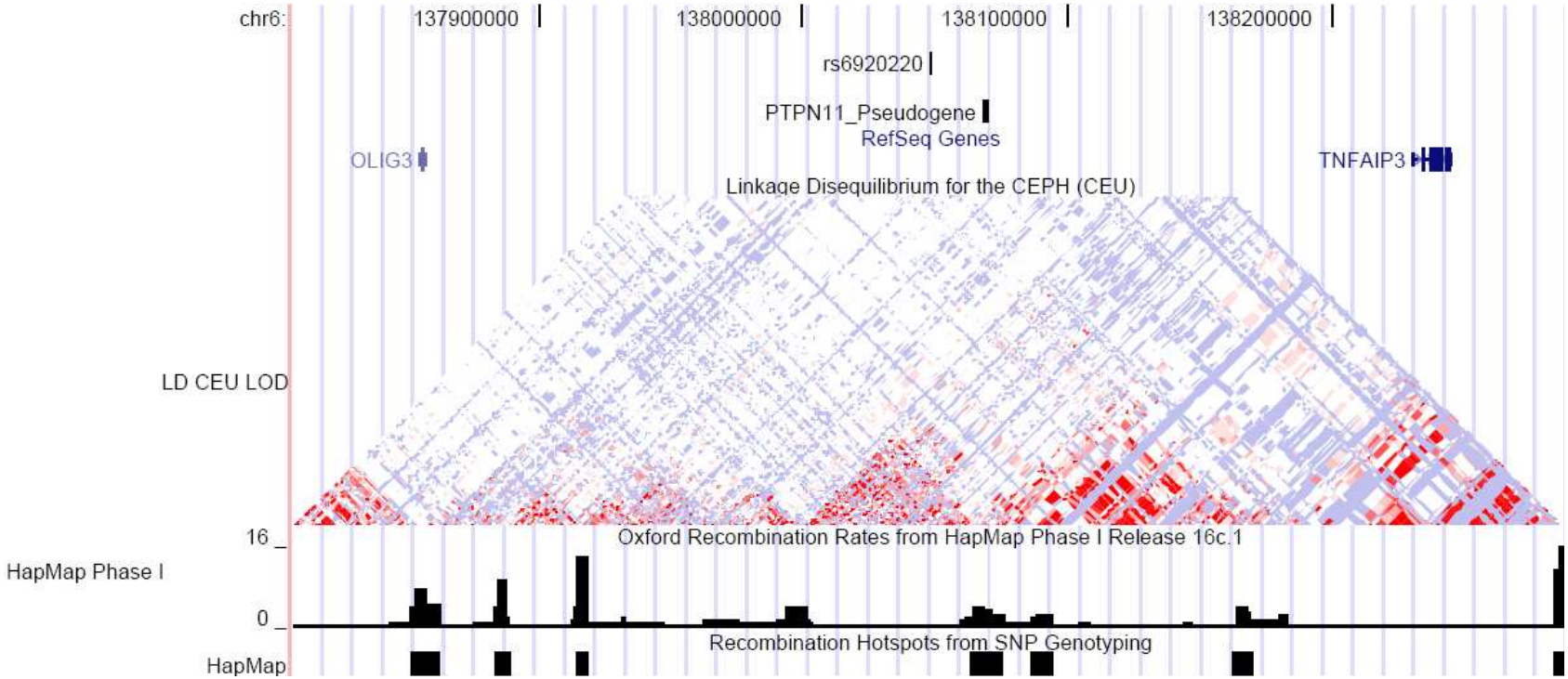
[c]not significant in males but more significant in females (trend $p = 0.025$).

[d]Most significant under a recessive model in the WTCCC study ($p = 4.8x10^{-7}$) and also in the validation study ($p = 0.005$).

Supplementary Table 5. Oligonucleotide sequences used in the Sequenom genotyping reactions.

| SNP | Gene | 2nd PCR Primer | 1st PCR Primer | Unextended Probe |
|---|---|---|---|---|
| rs10910099 | *MMEL* | ACGTTGGATGATCACTCAGAAAAGGCCCAG | ACGTTGGATGATTGCTGAGTGGCCTCTGAC | GCATTGGGACCCGAGTTGTCGC |
| rs11162922 | Chr1 | ACGTTGGATGGAATTCTAGAGTACTTTCAAG | ACGTTGGATGGGACTATATCTGCTCAATGG | ATAGTACTTTCAAGATTTAAAAGTC |
| rs11761231 | *PODXL* | ACGTTGGATGCTACGTGTGACTACATTTGG | ACGTTGGATGACGTGCAGACCAAATCTGTG | CATTTGGAGATAAGTAGCC |
| rs12722489 | *IL2RA* | ACGTTGGATGTCCTTATGGGACTCTAGTTC | ACGTTGGATGATTTCTAGCTATTGGTGAC | CCTCCAAGACCACTCAGA |
| rs2104286 | *IL2RA* | ACGTTGGATGCCATGCTCAGTAGATCTTAC | ACGTTGGATGCATAAGTTGGTGAGGAGGAG | TCTCAGTAGATCTTACCACATA |
| rs228942 | *IL2RB* | ACGTTGGATGTACTTACGACCCCTACTCAG | ACGTTGGATGGGGAAGACCCTGTGGGTGC | GGGGCCCCCTACTCAGAGGAAGA |
| rs2476601 | *PTPN22* | ACGTTGGATGAGATGATGAAATCCCCCCTC | ACGTTGGATGAACTGTACTCACCAGCTTCC | AACCCTCCACTTCCTGTA |
| rs2837960 | Chr21 | ACGTTGGATGACCCTCAGTGCACTTCCACA | ACGTTGGATGTGTGAAGTGGGATCTGATGC | GGTTCAACGATTGCCGCC |
| rs3218253 | *IL2RB* | ACGTTGGATGAACTGCACCTGACCAGGTTC | ACGTTGGATGAAGAAACGGGTCAACCTCTC | CTCTATGCCCTTCTCG |
| rs3218273 | *IL2RB* | ACGTTGGATGTCCGAGGATCAGGTTGCAG | ACGTTGGATGGAAAGGCGGTGGAACCAAAC | TAGGTTGCAGGCCCAG |
| rs3816587 | *ANAPC4* | ACGTTGGATGGTTTAGGAATAGGATCAGAC | ACGTTGGATGTGCCCTTGATGTGGGAAGTG | GAATAGGATCAGACTCAGTTA |
| rs6920220 | *OLIG3* | ACGTTGGATGGATCACTGTCTGCATATGCC | ACGTTGGATGTGCTTCCATCTGTTAGCAGG | ATTGTTCTACAGAACCATATC |
| rs743776 | *IL2RB* | ACGTTGGATGCTTCCCAGTGCATTCACAG | ACGTTGGATGGAGATGAAGATGGGGCAGTC | TCAGTCTTGACCCACA |
| rs743777 | *IL2RB* | ACGTTGGATGCTCTTCCCTTGCCATTTTAC | ACGTTGGATGCCACATTCTGGTAGGATGAC | ACAGGCCAGGAAACC |
| rs743779 | *IL2RB* | ACGTTGGATGTCCTGTTCCCTCTGAACTGC | ACGTTGGATGAATGATGGCAGGGTGCAAGT | GGGTTCCATACCAGTCCCAC |
| rs791590 | *IL2RA* | ACGTTGGATGCCAGATTTCCTGGGCGATG | ACGTTGGATGCCTGGAACCTACTCTTTCTC | GGGTGCCATTCATTGAG |
| rs9550642 | *CRYL1* | ACGTTGGATGCAGGGAACCTTGAGTACTGG | ACGTTGGATGTCTTTCCTCTCTGTCTACCC | TGGATGTGTATAGGGTGAC |

**Supplementary Figure 1.** Plot showing linkage disequilibrium, recombination sites, base pair position, presence of genes and associated marker in the 6q23 region.



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Stephen G. Ball[26], Anthony J. Balmforth[26], Jennifer H. Barrett[26], D. Timothy Bishop[26], Mark M. Iles[26], Azhar Maqbool[26], Nadira Yuldasheva[26], Alistair S. Hall, (Leeds)[26], Peter S. Braund[10], Paul R. Burton[1], Richard J. Dixon[10], Massimo Mangino[10], Suzanne Stevens[10], Martin D. Tobin[1], John R. Thompson[1] & Nilesh J. Samani, (Leicester)[10]

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## Rheumatoid Arthritis

Anne Barton[40], The Biologics in RA Genetics and Genomics (BRAGGS)[55], Ian N. Bruce[40], Hannah Donovan[40], Steve Eyre[40], Paul D. Gilbert[40], Samantha L. Hider[40], Anne M. Hinks[40], Sally L. John[40], Catherine Potter[40], Alan J. Silman[40], Deborah P. M. Symmons[40], Wendy Thomson[40] & Jane Worthington[40]

## Type 1 Diabetes

David G. Clayton[2], David B. Dunger[2,41], Sarah Nutland[2], Helen E. Stevens[2], Neil M. Walker[2], Barry Widmer[2,41] & John A. Todd[2]

## Type 2 Diabetes

Timothy M. Frayling[42,43], Rachel M. Freathy[42,43], Hana Lango[42,43], John R. B. Perry[42,43], Beverley M. Shields[43], Michael N. Weedon[42,43], Andrew T. Hattersley, (Exeter)[42,43], Graham A. Hitman, (London)[44], Mark Walker, (Newcastle)[45], Kate S. Elliott[3,7], Christopher J. Groves[7], Cecilia M. Lindgren[3,7], Nigel W. Rayner[3,7], Nicholas J. Timpson[3,46], Eleftheria Zeggini[3,7] & Mark I. McCarthy, (Oxford)[3,7]

## Tuberculosis

Melanie Newport[47], Giorgio Sirugo, (Gambia)[47], Emily Lyons[3], Fredrik Vannberg[3] & Adrian V. S. Hill, (Oxford)[3]

## Ankylosing Spondylitis

Linda A. Bradbury[48], Claire Farrar[49], Jennifer J. Pointon[48], Paul Wordsworth[49] & Matthew A. Brown[48,49]

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Jayne A. Franklyn[50], Joanne M. Heward[50], Matthew J. Simmonds[50] & Stephen C. L. Gough[50]

## Breast Cancer

Sheila Seal[51], Breast Cancer Susceptibility Collaboration (UK)[55], Michael R. Stratton[51,52] & Nazneen Rahman[51]

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Maria Ban[53], An Goris[53], Stephen J. Sawcer[53] & Alastair Compston[53]

## Gambian Controls

David Conway[47], Muminatou Jallow[47], Melanie Newport[47], Giorgio Sirugo, (Gambia)[47], Kirk A. Rockett[3] & Dominic P. Kwiatkowski, (Oxford)[3,5]

## DNA, Genotyping, Data QC and Informatics

Suzannah J. Bumpstead[5], Amy Chaney[5], Kate Downes[2,5], Mohammed J. R. Ghori[5], Rhian Gwilliam[5], Sarah E. Hunt[5], Michael Inouye[5], Andrew Keniry[5], Emma King[5], Ralph McGinnis[5], Simon Potter[5], Rathi Ravindrarajah[5], Pamela Whittaker[5], Claire Widden[5], David Withers[5], Panos Deloukas, (Wellcome Trust Sanger Institute Hinxton)[6], Hin-Tak Leung[2], Sarah Nutland[2], Helen E. Stevens[2], Neil M. Walker[2] & John A. Todd, (Cambridge)[2]

## Statistics

Doug Easton[12], David G. Clayton, (Cambridge)[2], Paul R. Burton[1], Martin D. Tobin, (Leicester)[1], Jeffrey C. Barrett[3], David Evans[3], Andrew P. Morris[3], Lon R. Cardon, (Oxford)[3], Niall J. Cardin[11], Dan Davison[11], Teresa Ferreira[11], Joanne Pereira-Gale[11], Ingileif B. Hallgrimsdóttir[11], Bryan N. Howie[11], Jonathan L. Marchini[11], Chris C. A. Spencer[11], Zhan Su[11], Yik Ying Teo[3,11], Damjan Vukcevic[11] & Peter Donnelly, (Oxford)[11]

## Primary Investigators

David Bentley[5,54], Matthew A. Brown[48,49], Lon R. Cardon[3], Mark Caulfield[38], David G. Clayton[2], Alistair Compston[53], Nick Craddock[23], Panos Deloukas[5], Peter Donnelly[11], Martin Farrall[39], Stephen C. L. Gough[50], Alistair S. Hall[26], Andrew T. Hattersley[42,43], Adrian V. S. Hill[3], Dominic P. Kwiatkowski[3,5], Christopher G. Mathew[29], Mark I. McCarthy[3,7], Willem H. Ouwehand[8,9], Miles Parkes[27], Marcus Pembrey[18,20], Nazneen Rahman[51], Nilesh J. Samani[10], Michael R. Stratton[51,52], John A. Todd[2] & Jane Worthington[40]

1. Genetic Epidemiology Group, Department of Health Sciences, University of Leicester, Adrian Building, University Road, Leicester LE1 7RH, UK.
2. Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge

Institute for Medical Research, University of Cambridge, Wellcome Trust/MRC Building, Cambridge CB2 0XY, UK.
3. Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK.
4. Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK.
5. The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK.
6. The Wellcome Trust, Gibbs Building, 215 Euston Road, London NW1 2BE, UK.
7. Oxford Centre for Diabetes, Endocrinology and Medicine, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK.
8. Department of Haematology, University of Cambridge, Long Road, Cambridge CB2 2PT, UK.
9. National Health Service Blood and Transplant, Cambridge Centre, Long Road, Cambridge CB2 2PT, UK.
10. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK.
11. Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG, UK.
12. Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK.
13. National Health Service Blood and Transplant, Sheffield Centre, Longley Lane, Sheffield S5 7JN, UK.
14. National Health Service Blood and Transplant, Brentwood Centre, Crescent Drive, Brentwood CM15 8DP, UK.
15. The Welsh Blood Service, Ely Valley Road, Talbot Green, Pontyclun CF72 9WB, UK.
16. The Scottish National Blood Transfusion Service, Ellen's Glen Road, Edinburgh EH17 7QT, UK.
17. National Health Service Blood and Transplant, Southampton Centre, Coxford Road, Southampton SO16 5AF, UK.
18. Avon Longitudinal Study of Parents and Children, University of Bristol, 24 Tyndall Avenue, Bristol BS8 1TQ, UK.
19. Division of Community Health Services, St George's University of London, Cranmer Terrace, London SW17 0RE, UK.
20. Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, UK.
21. University of Aberdeen, Institute of Medical Sciences, Foresterhill, Aberdeen AB25 2ZD, UK.
22. Department of Psychiatry, Division of Neuroscience, Birmingham University, Birmingham B15 2QZ, UK.
23. Department of Psychological Medicine, Henry Wellcome Building, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK.
24. SGDP, The Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.
25. School of Neurology, Neurobiology and Psychiatry, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK.
26. LIGHT and LIMM Research Institutes, Faculty of Medicine and Health, University of Leeds, Leeds LS1 3EX, UK.

27. IBD Research Group, Addenbrooke's Hospital, University of Cambridge, Cambridge CB2 2QQ, UK.
28. Gastrointestinal Unit, School of Molecular and Clinical Medicine, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK.
29. Department of Medical & Molecular Genetics, King's College London School of Medicine, 8th Floor Guy's Tower, Guy's Hospital, London SE1 9RT, UK.
30. Institute for Digestive Diseases, University College London Hospitals Trust, London, NW1 2BU, UK.
31. Department of Gastroenterology, Guy's and St Thomas' NHS Foundation Trust, London SE1 7EH, UK.
32. Department of Gastroenterology & Hepatology, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP, UK.
33. Gastroenterology Unit, Radcliffe Infirmary, University of Oxford, Oxford OX2 6HE, UK.
34. Medicine and Therapeutics, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Grampian AB9 2ZB, UK.
35. Clinical Pharmacology Unit and the Diabetes and Inflammation Laboratory, University of Cambridge, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ, UK.
36. Centre National de Genotypage, 2, Rue Gaston Cremieux, Evry, Paris 91057, France.
37. BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, UK.
38. Clinical Pharmacology and Barts and The London Genome Centre, William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine, Charterhouse Square, London EC1M 6BQ, UK.
39. Cardiovascular Medicine, University of Oxford, Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK.
40. arc Epidemiology Research Unit, University of Manchester, Stopford Building, Oxford Rd, Manchester M13 9PT, UK.
41. Department of Paediatrics, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.
42. Genetics of Complex Traits, Institute of Biomedical and Clinical Science, Peninsula Medical School, Magdalen Road, Exeter EX1 2LU, UK.
43. Diabetes Genetics, Institute of Biomedical and Clinical Science, Peninsula Medical School, Barrack Road, Exeter EX2 5DU, UK.
44. Centre for Diabetes and Metabolic Medicine, Barts and The London, Royal London Hospital, Whitechapel, London E1 1BB, UK.
45. Diabetes Research Group, School of Clinical Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK.
46. The MRC Centre for Causal Analyses in Translational Epidemiology, Bristol University, Canynge Hall, Whiteladies Rd, Bristol BS2 8PR, UK.
47. MRC Laboratories, Fajara, The Gambia.
48. Diamantina Institute for Cancer, Immunology and Metabolic Medicine, Princess Alexandra Hospital, University of Queensland, Woolloongabba, Qld 4102, Australia.
49. Botnar Research Centre, University of Oxford, Headington, Oxford OX3 7BN, UK.

50. Department of Medicine, Division of Medical Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
51. Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Road, Sutton SM2 5NG, UK.
52. Cancer Genome Project, The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK.
53. Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK.
54. †Present address: Illumina Cambridge, Chesterford Research Park, Little Chesterford, Nr Saffron Walden, Essex CB10 1XL, UK.

Membership of YEAR Consortium

YEAR Consortium:
**Management Team:** Professor Paul Emery[1], Professor Philip Conaghan[1], Dr Mark Quinn[2], Dr Ann Morgan[1], Anne-Maree Keenan[1], Dr Elizabeth Hensor[1], Julie Kitcheman[1]
**Consultants:** Dr Andrew Gough[3], Dr Michael Green[2,3], Dr Richard Reece[4], Dr Lesley Hordon[5], Dr Philip Helliwell[1,6], Dr Richard Melsom[6], Dr Sheelagh Doherty[7], Dr Ade Adebajo[8], Dr Andrew Harvey[9], Dr Steve Jarrett[9], Dr Gareth Huson[1], Dr Amanda Isdale[2], Dr Mike Martin[1], Dr Zinaid Karim[9], Dr Dennis McGonagle[1,10], Dr Colin Pease[1], Dr Sally Cox[1]
**SpRs:** Dr Victoria Bejarano[1], Dr Jackie Nam[1]
**Nurses:** Claire Brown[1], Christine Thomas[1], David Pickles[1], Alison Hammond[1], Beverley Neville[3], Alan Fairclough[4], Caroline Nunns[4], Anne Gill[2], Julie Green[2], Belinda Rhys-Evans[1], Barbara Padwell[1], Julie Madden[10], Lynda Taylor[10], Sally Smith[1], Heather King[1], Jill Firth[6], Jayne Heard[7], Linda Sigsworth[6]
**Lab Staff:** Diane Corscadden[1], Karen Henshaw[1], Lubna-Haroon Rashid[1], Stephen G Martin[1], James I Robinson[1]

[1]Section of Musculoskeletal Disease, LIMM, Leeds, UK
[2]York District Hospital, York, UK
[3]Harrogate District Hospital, Harrogate, UK
[4]Huddersfield Royal Infirmary, Huddersfield, UK
[5]Dewsbury District and General Hospital, Dewsbury, UK
[6]St Luke's Hospital, Bradford, UK
[7]Hull Royal Infirmary, Hull, UK
[8]Barnsley District General Hospital, Barnsley, UK
[9]Pinderfields General Hospital, Wakefield, UK
[10]Calderdale Royal Hospital, Halifax, UK