Wellcome Trust Case Control Consortium Genome-wide Association Study of Bipolar Disorder

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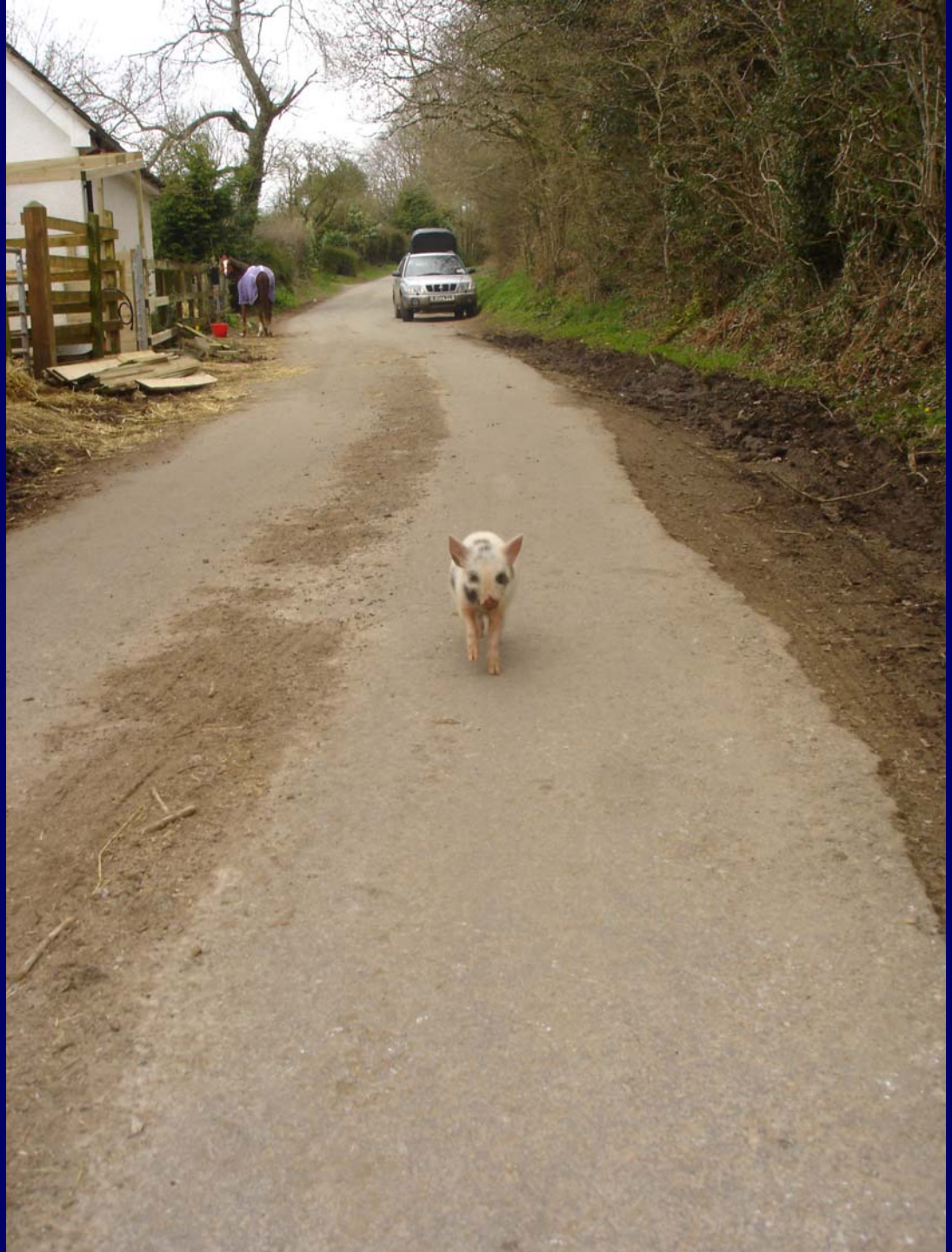

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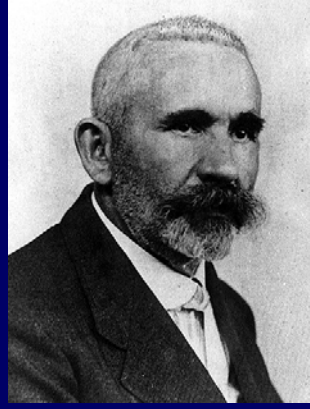
ARTICLES

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. We describe a joint GWA study (using the Affymetrix GeneChip 500K Mapping Array Set) undertaken in the British population, which has examined ~2,000 individuals for each of 7 major diseases and a shared set of ~3,000 controls. Case-control comparisons identified 24 independent association signals at $P < 5 \times 10^{-7}$: 1 in bipolar disorder, 1 in coronary artery disease, 9 in Crohn's disease, 3 in rheumatoid arthritis, 7 in type 1 diabetes and 3 in type 2 diabetes. On the basis of prior findings and replication studies thus-far completed, almost all of these signals reflect genuine susceptibility effects. We observed association at many previously identified loci, and found compelling evidence that some loci confer risk for more than one of the diseases studied. Across all diseases, we identified a large number of further signals (including 58 loci with single-point P values between 10^{-5} and 5×10^{-7}) likely to yield additional susceptibility loci. The importance of appropriately large samples was confirmed by the modest effect sizes

WTCCC. Nature 2007; 447: 661-677 & 56 pages of supplementary online material



Bipolar Disorder: Some Terminology

- Psychosis – delusions & hallucinations
- Depression – low mood
- Mania – energized mood

Disorder	Psychosis	Mania	Depression
Schizophrenia	+	+/-	+/-
Bipolar disorder	+/-	+	+/-
Unipolar depression	+/-	-	+

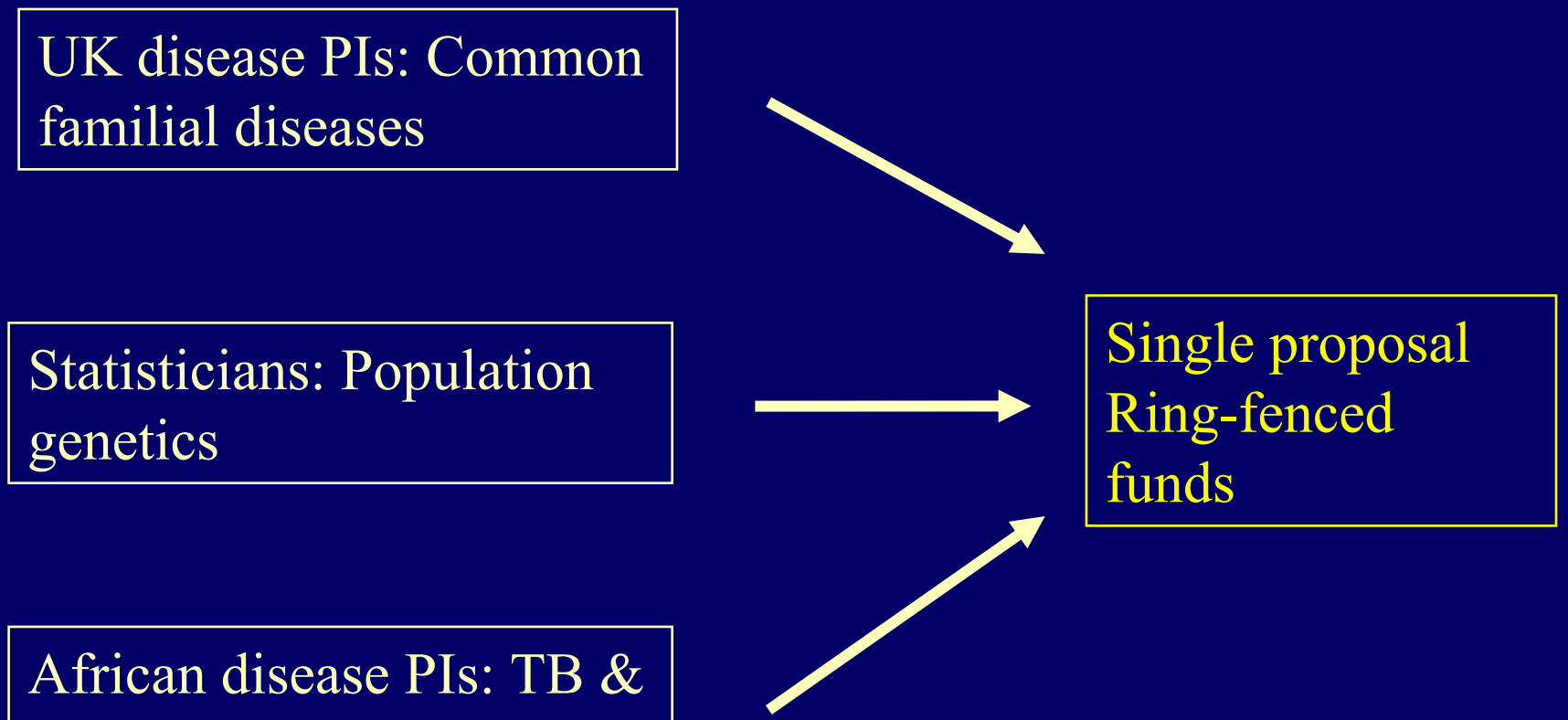
History of WTCCC

UK disease PIs: Common familial diseases

Statisticians: Population genetics

African disease PIs: TB & malaria

History of WTCCC



Bipolar phenotype

- White UK over age 18 years
- Interview & case notes
- RDC
  - BPI/ Manic disorder (76%)
  - SABP (15%)
  - BPII (9%)

Cardiff (33%)

Birmingham (35%)

Newcastle (9%)

London (15%)

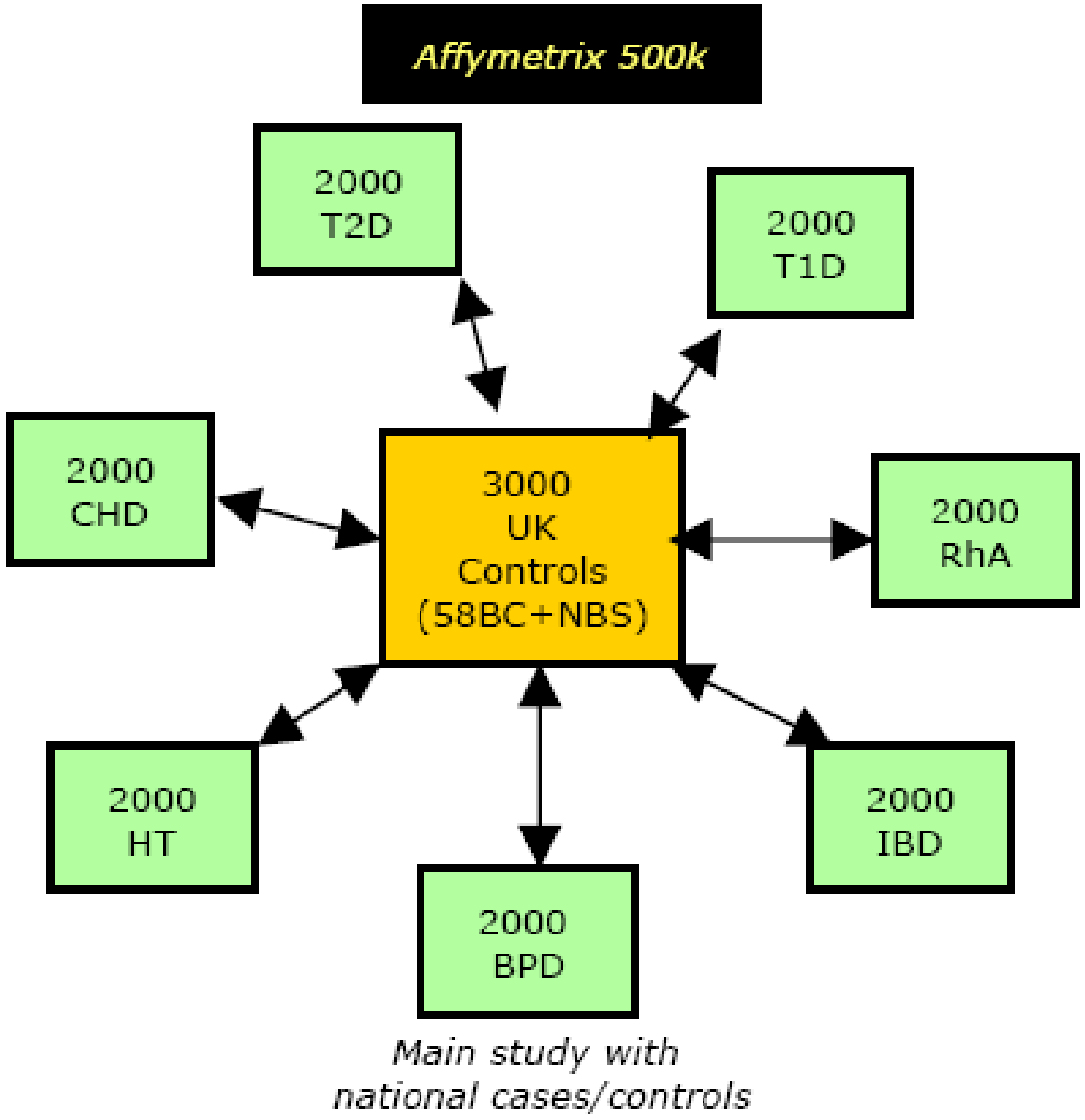
Aberdeen (8%)

WTCCC sample QC procedures

- Picogreen
  - concentration
- DNA run on gel
  - degredation score
- Sequenom panel
  - genotyping success
  - Gender check

→

Select best 2000 samples for each phenotype



WTCCC main Experiment design

GeneChip 500k array typed at Affymetrix South San Francisco Laboratories

Genotype calling

- Chiamo algorithm developed by Marchini & Donnelly for WTCCC
- Bayesian approach using HapMap knowledge about SNP and calling all 17,000 samples simultaneously
- Performs better than Affy algorithms

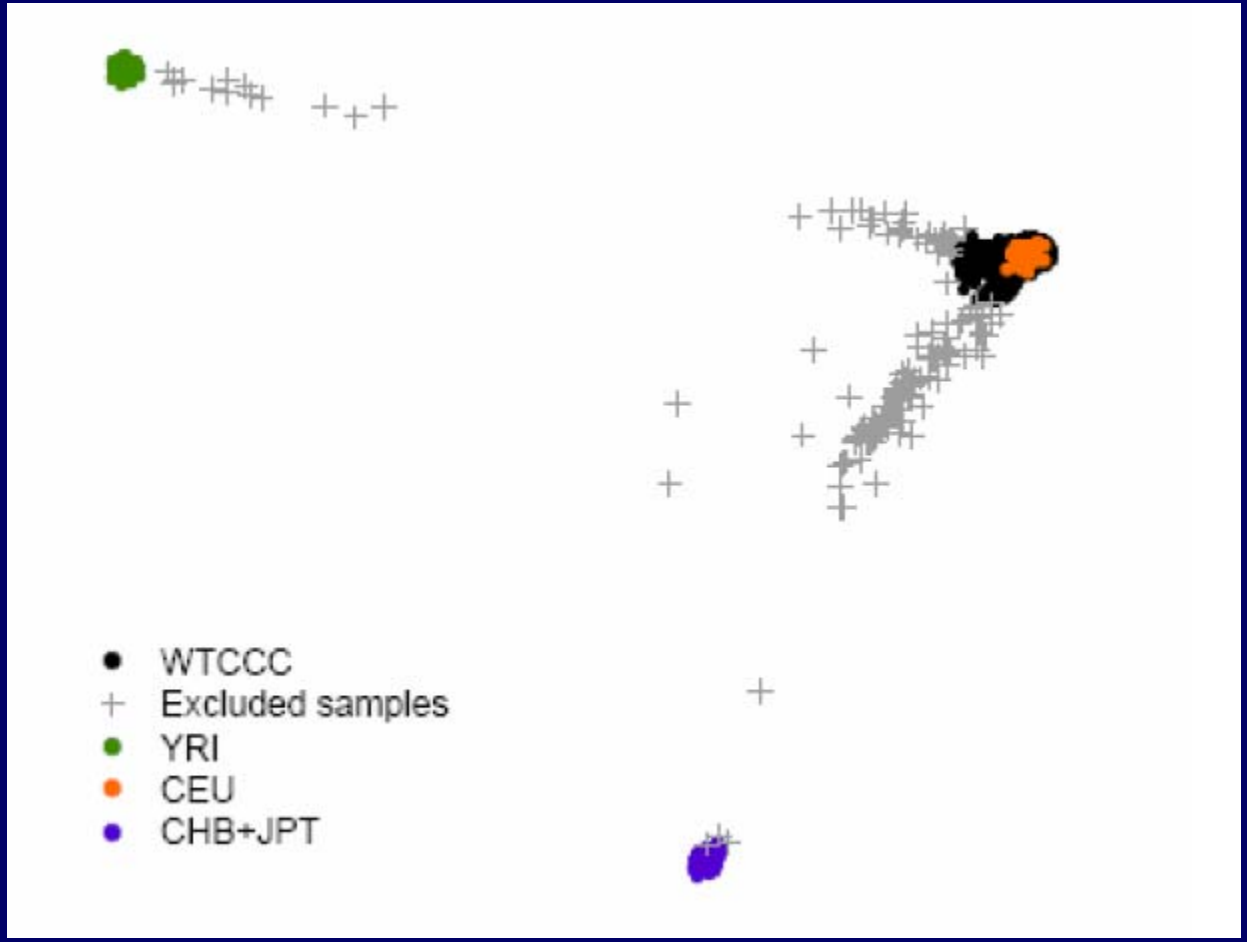
QC of genotype data

- SNPs
  - Poor call rate (<0.95; <0.99)
  - Hardy-Weinberg equilibrium deviation (<6e-7)
  - Substantial differences between controls (<6e-7)

  → 469,557SNPs
- Individual samples
  - Poor call rates (<0.97)
  - Duplicates/ close relatives
  - Substantial non-European ancestry

  → 1868 BD, 2938 controls

Supplementary Figure 5
Multidimensional Scaling (MDS)



Supplementary Table 4: Exclusion summary by collection

Collection	Missingness	Heterozygosity	External discordance	Non-European ancestry	Duplicate	Relative	Total
58C	9	0	4	6	4	1	**24**
UKBS	8	0	5	14	0	15	**42**
BD	30	0	0	9	77	13	**129**
CAD	41	1	0	13	2	5	**62**
CD	43	4	6	54	131	18	**256**
HT	29	0	0	2	6	11	**48**
RA	47	1	0	26	53	9	**136**
T1D	7	2	1	18	6	3	**37**
T2D	36	1	0	11	16	11	**75**
Total	**250**	**9**	**16**	**153**	**295**	**86**	**809**

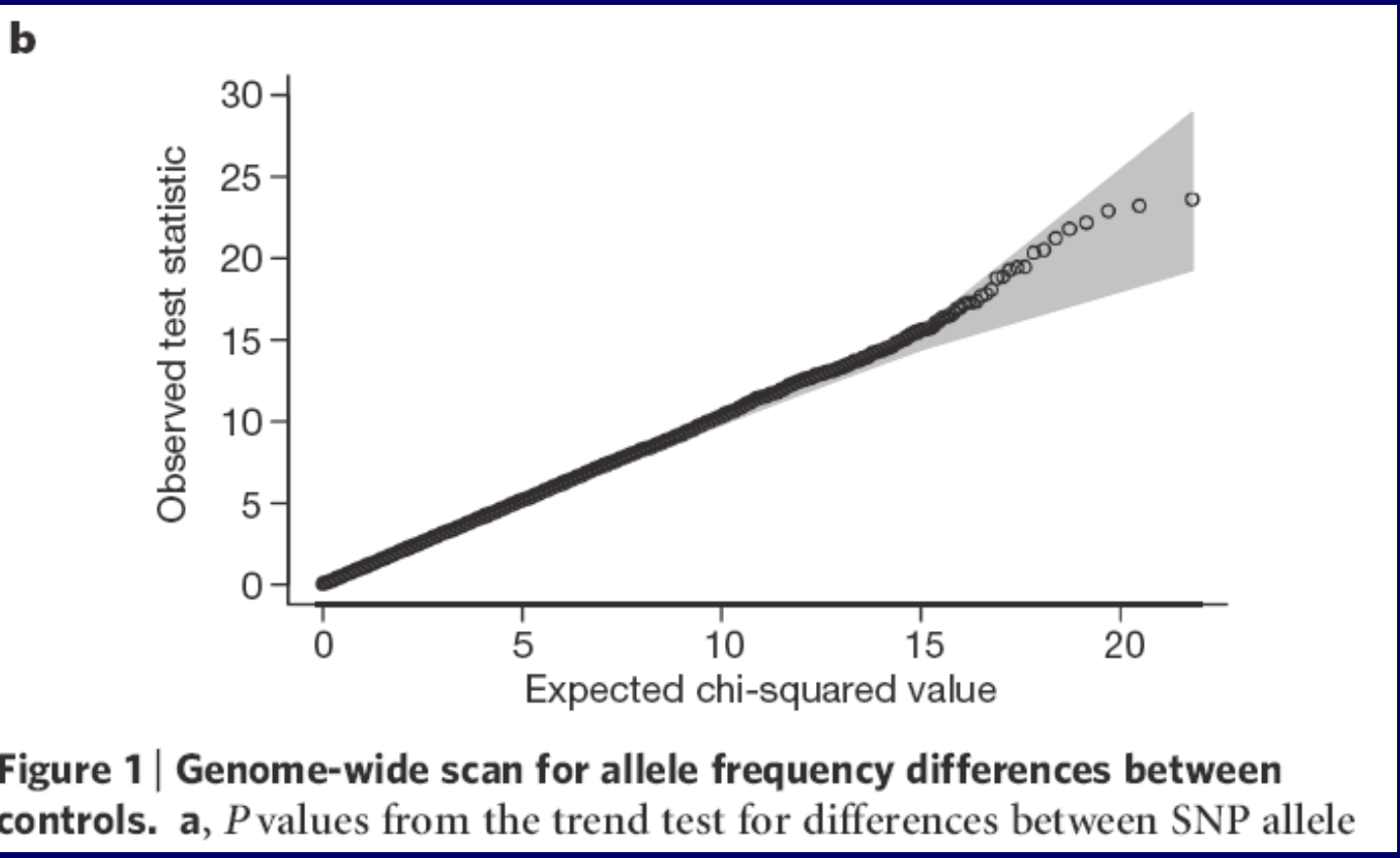
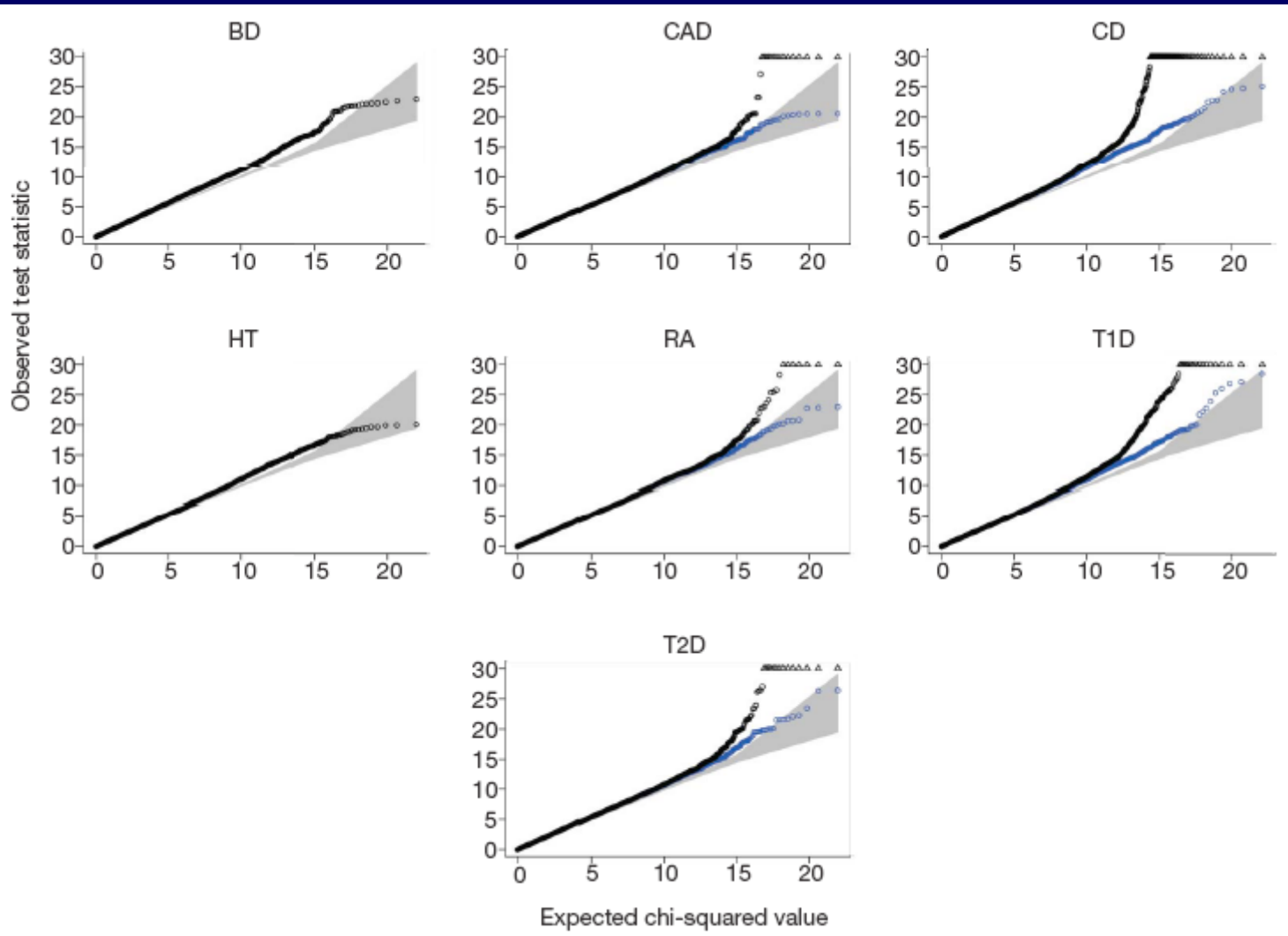


Figure 1 | Genome-wide scan for allele frequency differences between controls. **a**, *P* values from the trend test for differences between SNP allele


BD
CAD
CD
HT
RA
T1D
T2D
Observed test statistic
Expected chi-squared value
0
5
10
15
20
25
30

Basic statistical tests

- Armitage trend test for co-dominant allele effects (1df)
- General genotype test (2df)

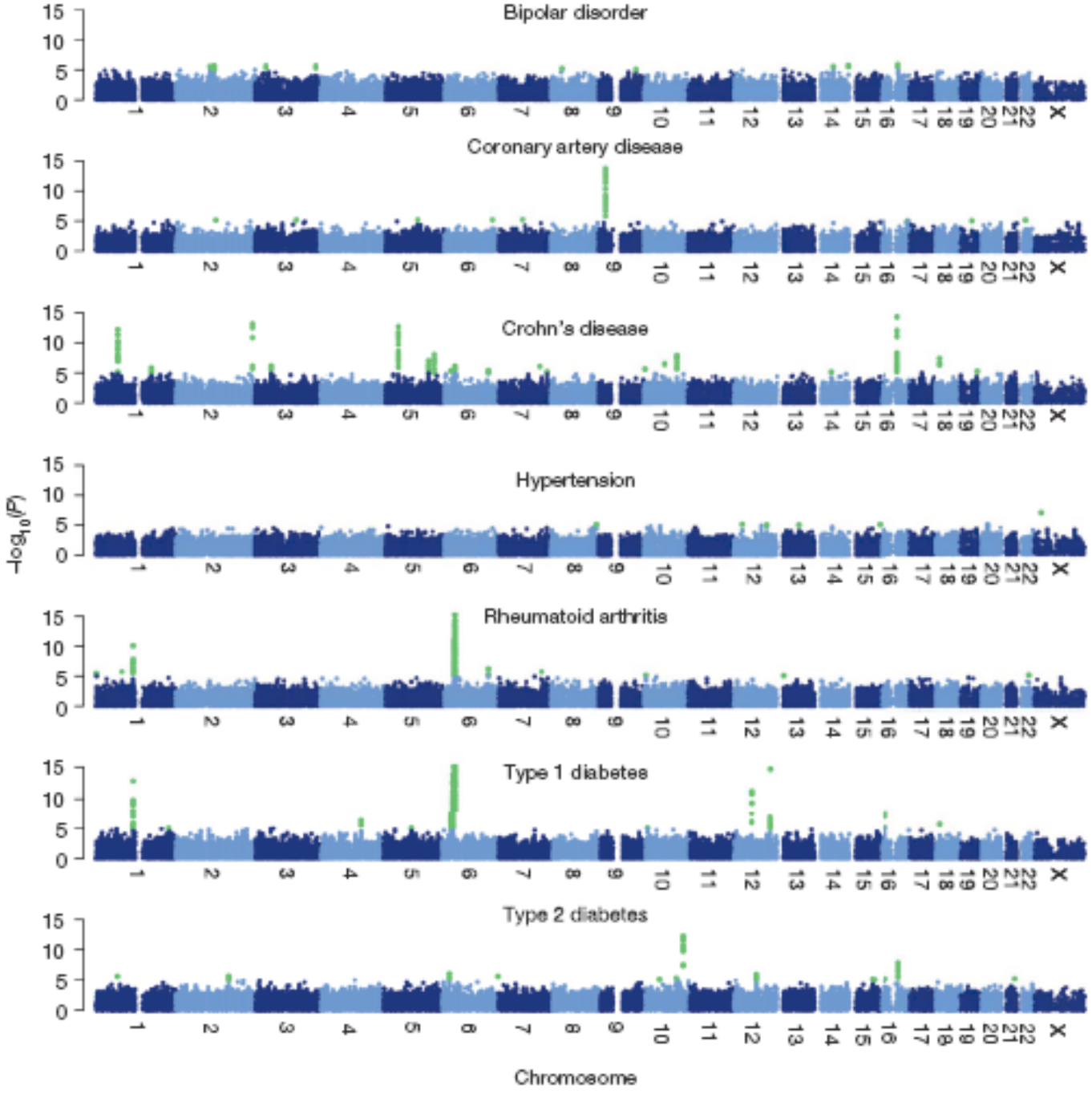
- Imputation of un-typed SNPs

Robustly known associations are detected

Table 2 | Evidence for signal of association at previously robustly replicated loci

Collection	Gene	Chromosome	Reported SNP	WTCCC SNP	HapMap r^2	Trend *P* value	Genotypic *P* value
CAD	*APOE*	19q13	*	rs4420638	-	1.7×10^{-01}	1.7×10^{-01}
CD	*NOD2*	16q12	rs2066844	rs17221417	0.23	9.4×10^{-12}	4.0×10^{-11}
CD	*IL23R*	1p31	rs11209026	rs11805303	0.01	6.5×10^{-13}	5.9×10^{-12}
RA	*HLA-DRB1*	6p21	*	rs615672	-	2.6×10^{-27}	7.5×10^{-27}
RA	*PTPN22*	1p13	rs2476601	rs6679677	0.75	4.9×10^{-26}	5.6×10^{-25}
T1D	*HLA-DRB1*	6p21	*	rs9270986	-	4.0×10^{-116}	2.3×10^{-122}
T1D	*INS*	11p15	rs689	†	-	-	-
T1D	*CTLA4*	2q33	rs3087243	rs3087243	1	2.5×10^{-05}	1.8×10^{-05}
T1D	*PTPN22*	1p13	rs2476601	rs6679677	0.75	1.2×10^{-26}	5.4×10^{-26}
T1D	*IL2RA*	10p15	rs706778	rs2104286	0.25	8.0×10^{-06}	4.3×10^{-05}
T1D	*IFIH1*	2q24	rs1990760	rs3788964	0.26	1.9×10^{-03}	7.6×10^{-03}
T2D	*PPARG*	3p25	rs1801282	rs1801282	1	1.3×10^{-03}	5.4×10^{-03}
T2D	*KCNJ11*	11p15	rs5219	rs5215	0.9	1.3×10^{-03}	5.6×10^{-03}
T2D	*TCF7L2*	10q25	rs7903146	rs4506565	0.92	5.7×10^{-13}	5.1×10^{-12}

Where information on the strength of association at a particular SNP had been previously published and replicated we tabulated the *P* value of both the trend and genotype test at the same SNP (if in our study), or the best tag SNP (defined to be the SNP with highest r^2 with the reported SNP, calculated in the CEU sample of the HapMap project). Positions are in NCBI build-35 coordinates. *Previous reports relate to haplotypes rather than single SNPs. †Not well tagged by SNPs that pass the quality control, see main text.


Bipolar disorder
Coronary artery disease
Crohn's disease
Hypertension
Rheumatoid arthritis
Type 1 diabetes
Type 2 diabetes
−log10(P)
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 X
Chromosome

P values

	$10^{-4} - 10^{-5}$	$10^{-5} - 5 \times 10^{-7}$	$< 5 \times 10^{-7}$
BD	76	14	1
CAD	57	9	1
CD	85	9	9
HT	56	6	0
RA	49	9	2
T1D	55	8	5
T2D	47	10	3
Total	**425**	**65**	**21**

Table 5 | Second tier hits -- For each collection, regions which show association signal. In each case, regions range as far as there are markers with a pvalue of less than 10^{-4} separated by no more than 200KB. In other words, starting at the signal SNP and walking in either direction extend the region until a stretch of 200KB is reached with no SNPs with 10^{-4} or lower.

chromosome	Region/Postion (Mb)	SNP	Gene	Best p value
2	115.63-116.11	rs1375144	DPP10	2.43E-06
2	241.23-241.28	rs2953145	RNPEPL1	6.57E-06
2	11.94-12	rs4027132	-	9.69E-06
2	104.41-104.58	rs7570682	-	3.11E-06
3	184.29-184.4	rs683395	LAMP3	2.30E-06
3	32.26-32.33	rs4276227	CMTM8	4.57E-06
6	42.82-42.86	rs6458307	-	4.35E-06
8	34.22-34.61	rs2609653	-	6.86E-06
9	114.31-114.39	rs10982256	DFNB31	8.80E-06
14	103.43-103.62	rs11622475	TDRD9	2.10E-06
14	57.17-57.24	rs10134944	-	3.21E-06
16	23.3-23.62	rs420259	PALB2	6.29E-08
16	51.36-51.5	rs1344484	-	1.65E-06
20	3.7-3.73	rs3761218	CDC25B	6.71E-06
X	110.32	rs975687	CAPN6	2.09E-06

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2	115.63-116.11			
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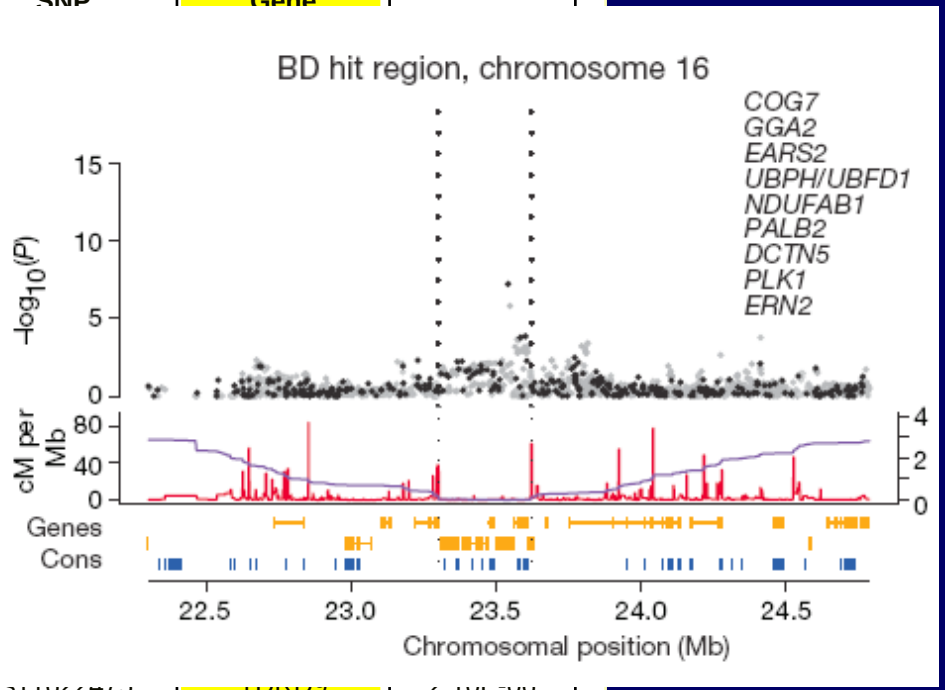

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16	23.3-23.62	rs420259	PALB2	6.29E-08
16	51.36-51.5	rs1344484	-	1.65E-06
20	3.7-3.73	rs3761218	CDC25B	6.71E-06
X	110.32	rs975687	CAPN6	2.09E-06

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Supplementary Information

The Wellcome Trust Case Control Consortium*

June 5, 2007

a) Bipolar Disorder

Chromosome	Region / Position (Mb)	SNP	Type	Trend p-value	Genotypic p-value	log10 BF additive	log10 BF general	Trend p-value	Genotypic p-value
								Sex-differentiat	
Strong or moderate association (autosomes)									
1	60.77	rs2989476	imputed	1.61E-05	7.47E-06	3.09	3.42	6.74E-05	5.71E
2	11.94 - 12.00	rs4027132	chip	1.31E-05	9.69E-06	3.07	3.27	5.15E-05	9.50E
2	104.41 - 104.58	rs7570682	chip	3.11E-06	1.64E-05	3.68	3.23	3.35E-05	3.93E
2	115.63 - 116.11	rs1375144	chip	2.43E-06	1.31E-05	3.80	3.34	1.17E-05	1.25E
2	181.18 - 181.34	rs11888446	imputed	7.01E-07	2.96E-06	4.53	4.16	2.14E-06	1.56E
2	200.99	rs4673905	imputed	9.72E-06	5.44E-05	2.86	2.37	2.98E-05	3.07E
2	241.23 - 241.28	rs2953145	chip	1.11E-05	6.57E-06	3.22	3.50	7.32E-05	1.39E
3	32.26 – 32.33	rs4276227	chip	4.57E-06	2.62E-05	3.52	3.04	3.39E-05	3.38E
3	36.83	rs9834970	imputed	1.21E-06	7.00E-06	4.18	3.72	6.39E-06	6.02E
3	184.29 - 184.40	rs683395	chip	2.30E-06	5.11E-06	3.87	3.73	4.26E-06	2.10E
6	42.82 - 42.86	rs6458307	chip	3.43E-01	4.35E-06	-0.80	2.84	5.14E-01	4.42E
6	123.82	rs6901299	imputed	3.13E-06	1.08E-05	4.08	3.81	1.72E-05	1.08E
7	11.48	rs1405318	imputed	4.54E-06	2.72E-05	3.37	3.06	1.11E-05	5.24E
8	34.22 - 34.61	rs2609653	chip	6.86E-06	2.31E-05	3.44	3.21	2.97E-05	9.51E
9	114.31 - 114.39	rs10982256	chip	8.80E-06	4.41E-05	3.23	2.78	6.76E-06	7.92E
14	57.17 - 57.24	rs10134944	chip	3.21E-06	6.89E-06	3.73	3.59	2.63E-05	9.90E
14	103.43 - 103.62	rs11622475	chip	2.10E-06	8.14E-06	3.87	3.24	9.15E-06	8.01E
16	23.3 – 23.62	rs420259	chip	2.19E-04	**6.29E-08**	1.96	**4.78**	1.16E-03	6.56E
16	51.36 - 51.50	rs1344484	chip	1.65E-06	1.03E-05	3.94	3.41	8.30E-06	3.69E
20	3.70 - 3.73	rs3761218	chip	4.43E-05	6.71E-06	2.58	3.18	1.51E-04	3.44E
Strong or moderate association (X chromsome)									
X	110.32	Rs975687	chip	2.09E-06	9.99E-06				
$1x10^{-5}$ < p-value < $1x10^{-4}$									
1	54.96	rs10888879	chip	1.35E-05	1.00E-00				
1	60.74	rs10889189	chip	5.51E-05	2.09E-04				
1	65.39	rs4916031	chip	3.40E-02	9.80E-05				
1	70.01	rs6691577	chip	9.23E-05	2.37E-04				
1	101.66	rs1776905	chip	5.70E-05	3.03E-04				
1	213.31	rs10779279	chip	3.98E-05	2.15E-04				
1	224.13	rs12070036	chip	9.89E-05	2.85E-04				
2	62.70	rs2049674	chip	7.48E-05	1.00E-00				
2	104.44	rs17029753	chip	8.10E-05	4.17E-04				
2	115.74	rs13386690	chip	5.14E-05	2.43E-04				
2	181.18	rs4407218	chip	8.35E-05	3.73E-04				
2	200.99	rs4673905	chip	2.35E-05	1.30E-04				
3	7.63	rs1485171	chip	1.31E-01	9.73E-05				
3	21.67	rs6762678	chip	7.59E-05	2.31E-04				
3	22.99	rs711715	chip	1.99E-02	5.25E-05				
3	24.25	rs4858694	chip	4.02E-05	2.16E-04				
3	42.38	rs33460	chip	9.56E-06	1.00E-00				
3	61.56	rs13074575	chip	3.45E-05	5.43E-05				
4	46.99	rs7680321	chip	6.23E-06	1.55E-04				
4	54.65	rs1998755	chip	9.28E-05	3.01E-04				
5	23.40	rs6309031	chip	5.17E-06	2.76E-04				
5	116.21	rs1428005	chip	4.02E-05	2.17E-04				
5	136.30	rs17701996	chip	7.15E-06	9.91E-05				
5	162.73	rs999580	chip	9.70E-05	4.78E-04				
6	18.29	rs365237	chip	1.73E-04	8.59E-05				
6	33.96	rs6926599	chip	7.45E-05	1.00E-00				
6	123.86	rs17739564	chip	4.28E-05	2.22E-04				
6	132.77	rs6906574	chip	1.75E-04	8.76E-05				
6	152.62	rs2763025	chip	5.10E-05	1.92E-05				
7	22.76	rs2286492	chip	5.06E-01	2.04E-05				
8	58.48	rs2875734	chip	1.20E-03	3.13E-05				
8	83.20	rs16919670	chip	6.02E-05	1.58E-04				
8	83.83	rs9643449	chip	9.75E-05	1.76E-04				
8	102.35	rs10097578	chip	3.72E-05	1.46E-04				
8	118.68	rs1993980	chip	9.12E-05	2.13E-04				
9	11.21	rs7030123	chip	6.04E-05	3.11E-04				
9	36.89	rs1573257	chip	3.62E-04	7.45E-05				
9	90.66	rs10993698	chip	7.71E-05	3.56E-04				
9	110.28	rs4978927	chip	9.92E-05	5.12E-04				
9	114.33	rs10982246	chip	2.58E-05	1.27E-04				
10	42.76	rs788261	chip	4.93E-05	9.13E-05				
10	60.39	rs10826258	chip	7.26E-05	2.70E-04				
10	79.20	rs1866437	chip	4.72E-02	4.94E-05				
10	94.54	rs7896131	chip	1.56E-04	4.65E-05				
10	129.77	rs2095285	chip	4.64E-05	2.47E-04				
11	81.99	*(no rsID)*	chip	6.50E-05	1.00E-00				
11	129.67	rs858719	chip	1.11E-03	2.87E-05				
12	23.95	rs7136898	chip	1.32E-05	2.97E-05				
12	93.57	rs17306920	chip	8.71E-05	1.00E-00				
13	22.59	rs4770394	chip	1.20E-05	1.00E-00				
13	45.42	rs2806922	chip	7.90E-03	9.45E-05				
13	57.96	rs12584910	chip	5.94E-05	3.14E-04				
14	23.20	rs221703	chip	4.49E-05	1.00E-00				
14	38.38	rs17106400	chip	3.02E-05	2.39E-05				
14	42.67	rs17113911	chip	5.89E-05	1.00E-00				
14	49.23	rs10146912	chip	6.80E-05	3.29E-04				
14	75.15	rs3784005	chip	3.57E-05	1.00E-00				
14	103.42	rs10438244	chip	7.94E-05	1.71E-04				
15	71.95	rs7163602	chip	8.72E-05	3.40E-04				
16	51.43	rs1420239	chip	4.47E-05	2.28E-04				
16	53.86	rs4567705	chip	1.55E-05	6.62E-05				
16	72.66	rs12149894	chip	8.99E-05	2.60E-04				
16	81.17	rs7184080	chip	6.73E-01	3.67E-05				
16	85.85	rs10220973	chip	9.18E-05	1.00E-00				
17	19.75	rs203466	chip	4.02E-05	9.23E-05				
18	8.45	rs7243929	chip	2.86E-05	1.00E-00				
18	8.98	rs1893145	chip	8.13E-05	4.14E-04				
19	12.58	rs12979795	chip	4.12E-05	2.03E-04				
19	48.49	rs7408169	chip	6.09E-05	3.13E-04				
19	48.31	rs2061332	chip	8.72E-05	4.44E-04				
19	63.40	rs7248493	chip	3.07E-05	1.48E-04				
20	3.72	rs4815603	chip	7.50E-05	1.77E-05				
20	43.16	rs6031991	chip	6.18E-05	2.66E-04				
21	31.31	rs2833193	chip	5.74E-05	1.00E-00				
22	31.69	rs11089599	chip	7.16E-05	1.67E-04				
22	35.66	rs16997510	chip	3.70E-05	1.00E-00				

98 regions at $p<10^{-4}$

Supplementary Table 7 | Association results by disease.

Interesting higher ranked hits

- *GABRB1* (GABA A receptor β1)
  - rs76803321; $p=6.2 \times 10^{-5}$
- *GRM7* (glutamate receptor, metabatropic 7)
  - rs148517; $p=9.7 \times 10^{-5}$
- *SYN3* (synapsin III)
  - rs11089599; $p=7.2 \times 10^{-5}$

The replication challenge

Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

Eleftheria Zeggini,[1,2]* Michael N. Weedon,[3,4]* Cecilia M. Lindgren,[1,2]* Timothy M. Frayling,[3,4]* Katherine S. Elliott,[2] Hana Lango,[3,4] Nicholas J. Timpson,[2,5] John R. B. Perry,[3,4] Nigel W. Rayner,[1,2] Rachel M. Freathy,[3,4] Jeffrey C. Barrett,[2] Beverley Shields,[4] Andrew P. Morris,[2] Sian Ellard,[4,6] Christopher J. Groves,[1] Lorna W. Harries,[4] Jonathan L. Marchini,[7] Katharine R. Owen,[1] Beatrice Knight,[4] Lon R. Cardon,[2] Mark Walker,[8] Graham A. Hitman,[9] Andrew D. Morris,[10] Alex S. F. Doney,[10] The Wellcome Trust Case Control Consortium (WTCCC),† Mark I. McCarthy,[1,2]‡§ Andrew T. Hattersley[3,4]‡

The molecular mechanisms involved in the development of type 2 diabetes are poorly understood. Starting from genome-wide genotype data for 1924 diabetic cases and 2938 population controls generated by the Wellcome Trust Case Control Consortium, we set out to detect replicated diabetes association signals through analysis of 3757 additional cases and 5346 controls and by integration of our findings with equivalent data from other international consortia. We detected diabetes susceptibility loci in and around the genes *CDKAL1*, *CDKN2A/CDKN2B*, and *IGF2BP2* and confirmed the recently described associations at *HHEX/IDE* and *SLC30A8*. Our findings

Type 2 diabetes follow-up

Region	WTCCC 1924 cases 2938 controls OR (95% CI)	P_{add}	Replication meta-analysis 3757 cases 5346 controls OR (95% CI)	P_{add}	All UK sample meta-analysis 5681 cases 8284 controls OR (95% CI)	P_{add}	DGI 6529 cases 7252 controls OR (95% CI)	P_{add}	FUSION 2376 cases 2432 controls OR (95% CI)	P_{add}	All combined 14,586 cases 17,968 controls OR (95% CI)	P_{add}
FTO	1.27 (1.16–1.37)	2.0×10^{-8}	1.22 (1.12–1.32)	5.4×10^{-7}	1.23 (1.18–1.32)	7.3×10^{-14}	1.03 (0.91–1.17)	0.25	1.11 (1.02–1.20)	0.017	1.17 (1.12–1.22)	1.3×10^{-12}
CDKAL1	1.20 (1.10–1.31)	2.5×10^{-5}	1.14 (1.07–1.22)	8.3×10^{-5}	1.16 (1.10–1.22)	1.3×10^{-8}	1.08 (1.03–1.14)	2.4×10^{-3}	1.12 (1.03–1.22)	9.5×10^{-3}	1.12 (1.08–1.16)	4.1×10^{-11}

Zeggini et al. Science 2007 316: 1336-13341.

Molecular Psychiatry (2007), 1–11

www.nature.com/mp

ORIGINAL ARTICLE

A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder

AE Baum[1], N Akula[1], M Cabanero[1], I Cardona[1], W Corona[1], B Klemens[1,2], TG Schulze[3], S Cichon[4,5], M Rietschel[3], MM Nöthen[4,5], A Georgi[3], J Schumacher[4], M Schwarz[6], R Abou Jamra[4], S Höfels[7], P Propping[4], J Satagopan[8], NIMH Genetics Initiative Bipolar Disorder Consortium[1,9,10,11,12,13,14,15,16,17,18], SD Detera-Wadleigh[1], J Hardy[19] and FJ McMahon[1]

The genetic basis of bipolar disorder has long been thought to be complex, with the potential involvement of multiple genes, but methods to analyze populations with respect to this complexity have only recently become available. We have carried out a genome-wide association study of bipolar disorder by genotyping over 550 000 single-nucleotide polymorphisms (SNPs) in two independent case-control samples of European origin. The initial association screen was performed using pooled DNA, and selected SNPs were confirmed by individual genotyping. While DNA pooling reduces power to detect genetic associations, there is a substantial cost saving and gain in efficiency. A total of 88 SNPs, representing 80 different genes, met the prior criteria for replication in both samples. Effect sizes were modest: no single SNP of large effect was detected. Of 37 SNPs selected for individual genotyping, the strongest association signal was detected at a marker within the first intron of diacylglycerol kinase eta (DGKH; $P = 1.5 \times 10^{-8}$, experiment-wide $P < 0.01$, OR = 1.59). This gene encodes DGKH, a key protein in the lithium-sensitive phosphatidyl inositol pathway. This first genome-wide association study of bipolar disorder shows that several genes, each of modest effect, reproducibly influence disease risk. Bipolar disorder may be a polygenic disease.

Molecular Psychiatry advance online publication, 8 May 2007; doi:10.1038/sj.mp.4002012

Consistency in top genes?

- No compelling support at *DGKH*
- Signals at several genes eg.
  - *RNPEPL1*
    - rs2953174 p=6.42E-06
  - *DFNB31*
    - rs10982256 p=8.80E-06
  - *PTPRG*
    - rs13074575 p=3.49E-05
  - *JAM3*
    - rs11223704 p=1.49E-04

Is there supportive evidence in WTCCC sample for the set of SNPs?

- Imputation dataset
  - Only SNPs on platform used by Baum et al
  - Only SNPs with MAF>0.05
  - Only SNPs with <50% "missing data" in imputation dataset

Observed p values
at set of 76 independent SNPs

cf.

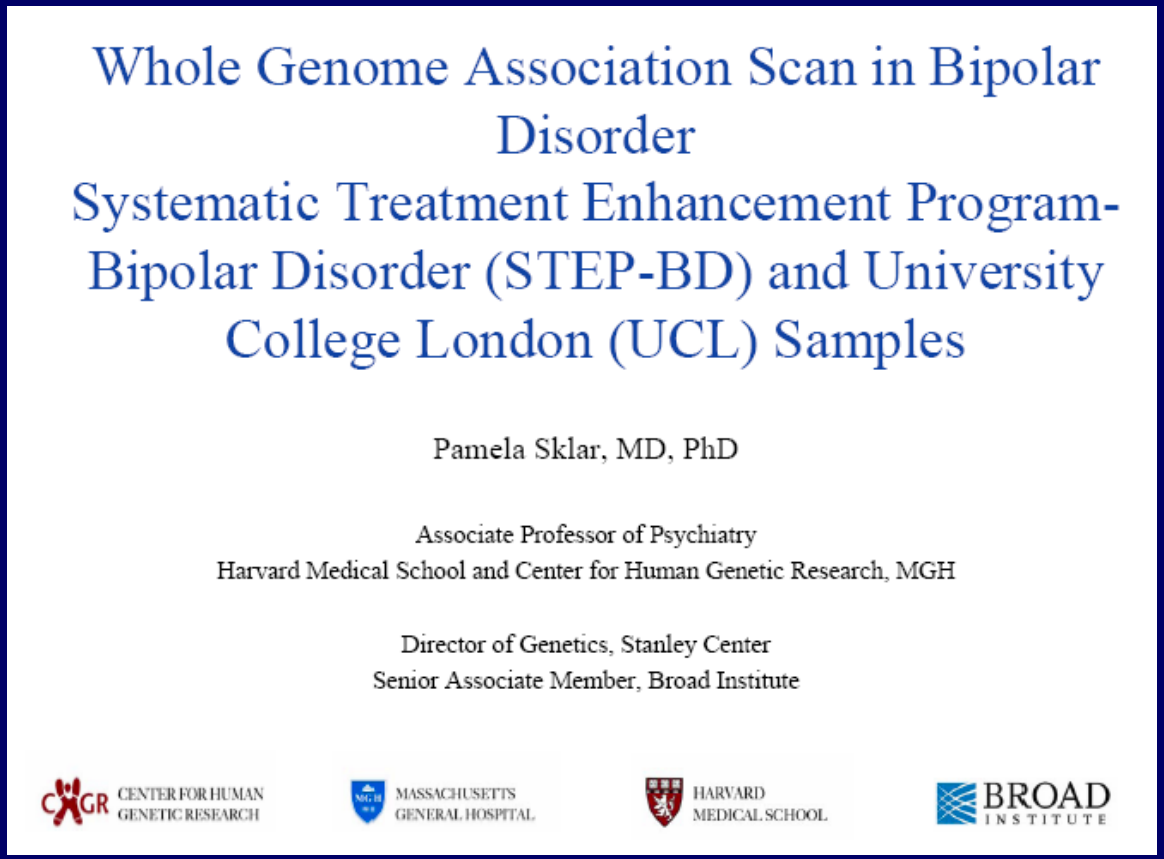
p values in set of 76 SNPs
in random sample 1

p values in set of 76 SNPs
in random sample 2

p values in set of 76 SNPs
in random sample 1,000,000

SNPs significant by pooling in NIMH & Bonn sample

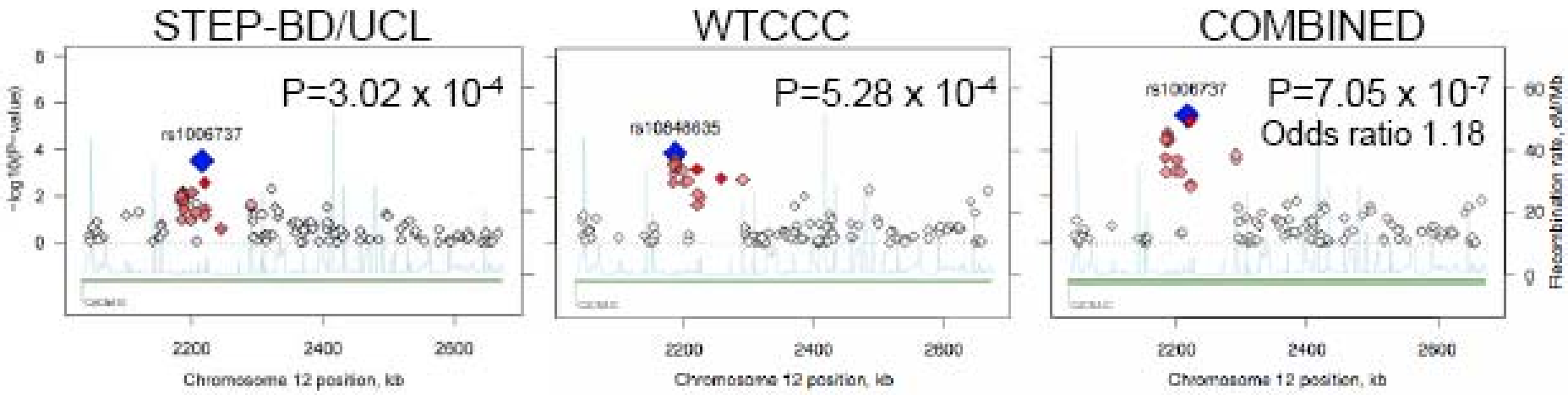
- 5 SNPs significant in same direction
  - *JAM3*: p=0.00013
  - *SLC39A3* p=0.00037
  - *STAB1* p= 0.016
  - *RBMS3* p= 0.029
  - *BRE* p= 0.046
- These 5 p values
  - Significance: p=0.00007 (10^6 simulations)



Pamela Sklar, Shaun Purcell, Hugh Gurling and colleagues

- 1461 BPI cases
- 2008 controls

Meta-analysis with WTCCC



CACNA1C: L-type, voltage-gated calcium channel, alpha1c subunit

CACNA1C
best overall SNP = rs1006737

Sample	Cases (n)	Controls (n)	Case freq	Cont freq	P value	OR
STEP-BD/UCL	1461	2003	0.357	0.315	3.02E-04	1.21
WTCCC	1868	2943	0.359	0.324	5.28E-04	1.17
EXTENSION SAMPLES	960	473	0.346	0.293	4.00E-03	1.28
ALL	**4289**	**5419**	**0.354**	**0.318**	**1.88E-08**	**1.19**

Yan Meng, Manuel Ferreira

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MASSACHUSETTS GENERAL HOSPITAL
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BROAD INSTITUTE

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Stephen Haggarty

Broad
Genetic Analysis Platform
Stacey Gabriel
David Altshuler
Paul deBakker
Biological Sample Platform

Daly lab
Julian Maller
Josh Korn

Sklar and Purcell lab members
Kimberly Chambert
Jes Fagerness
Jinbo Fan
Manuel Ferreira
Brian Galloway
Andrew Kirby
Matthew Ogdie
Yan Meng
Douglas Ruderfer
Jennifer Stone
Kathe Todd-Brown
Lauren Weiss

What about the phenotype?

Psychiatric diagnoses: the weak component of modern research

JULES ANGST
Zurich University Psychiatric Hospital, Lenggstrasse 31, Mail Box 1931, 8032 Zurich, Switzerland

Kraepelin's dichotomy is built on Kahlbaum's large monograph (1) on the pelin's cases, which documented a continuum at the symptom level between the two groups (5).

Multiple studies subsequently confirmed the existence of a group of conditions between schizophrenia and affec-

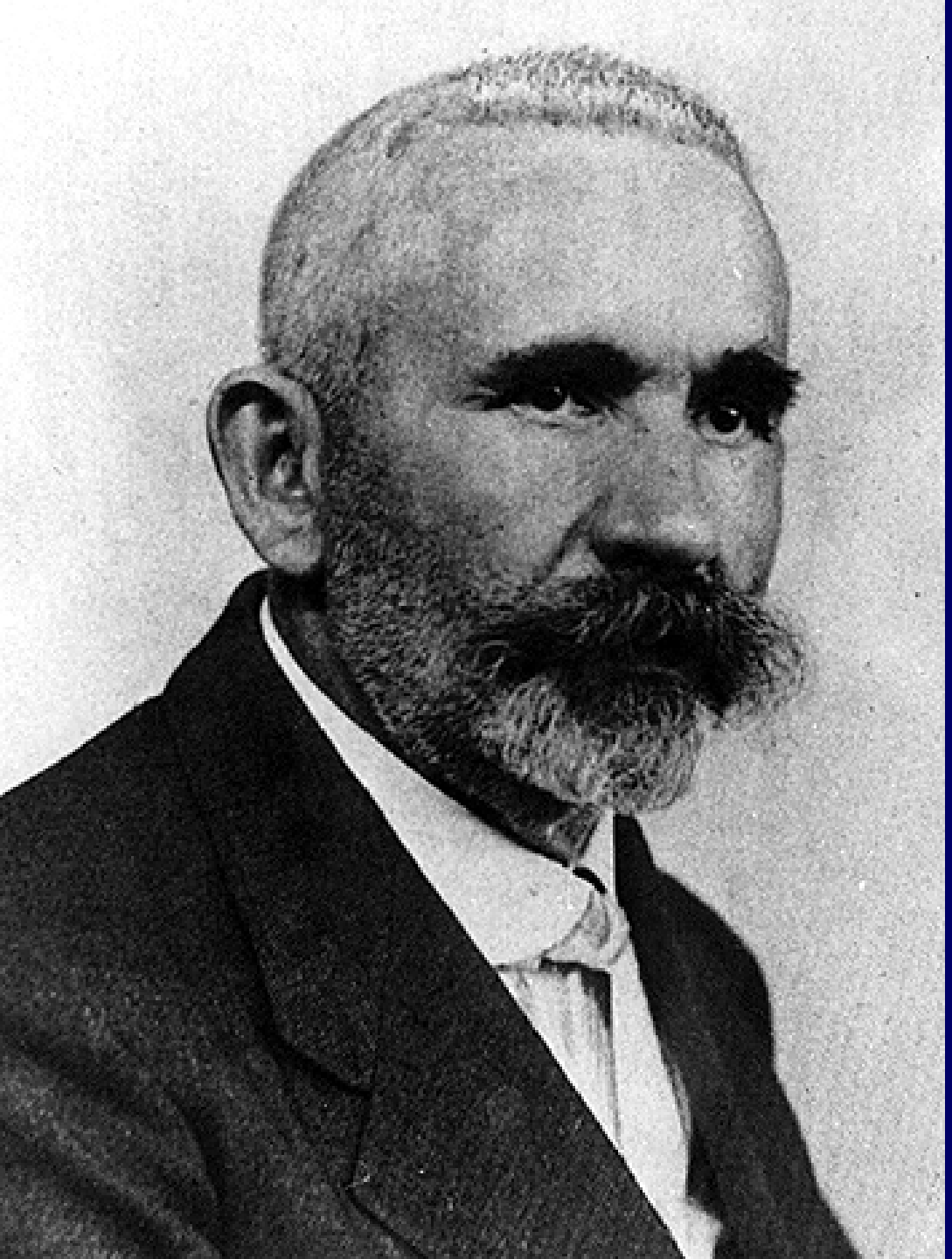
Angst. World Psychiatry 6: 30-21.

Phenotypic and genetic complexity of psychosis

Table 1 Factors affecting issues of genetic and phenotypic complexity in psychiatric genetic studies

Issue	Factors affecting	
	Clinical phenotype	Genotype
Population studied	Environment	Genetic differences
	Sociocultural factors	Population stratification/'structure'
	Service provision	
Subject ascertainment	Severity	Genetic loading
	Symptom pattern	Selection for simple inheritance patterns
	Course of illness	
	Impairment	
	Treatment response	
Underlying model	Unknown phenotype (disease) model requires analytical strategies that do not rely on knowing model precisely	Unknown genetic model requires analytical strategies that do not rely on knowing model precisely
Measurement	Consistency of assessment methods	Consistency of genotyping methods
	Variable use of standard terminology	Genotyping error
	Phenotype measurement error	

Craddock, O'Donovan, Owen. *Br J Psychiatry*.2007; 190: 200-203

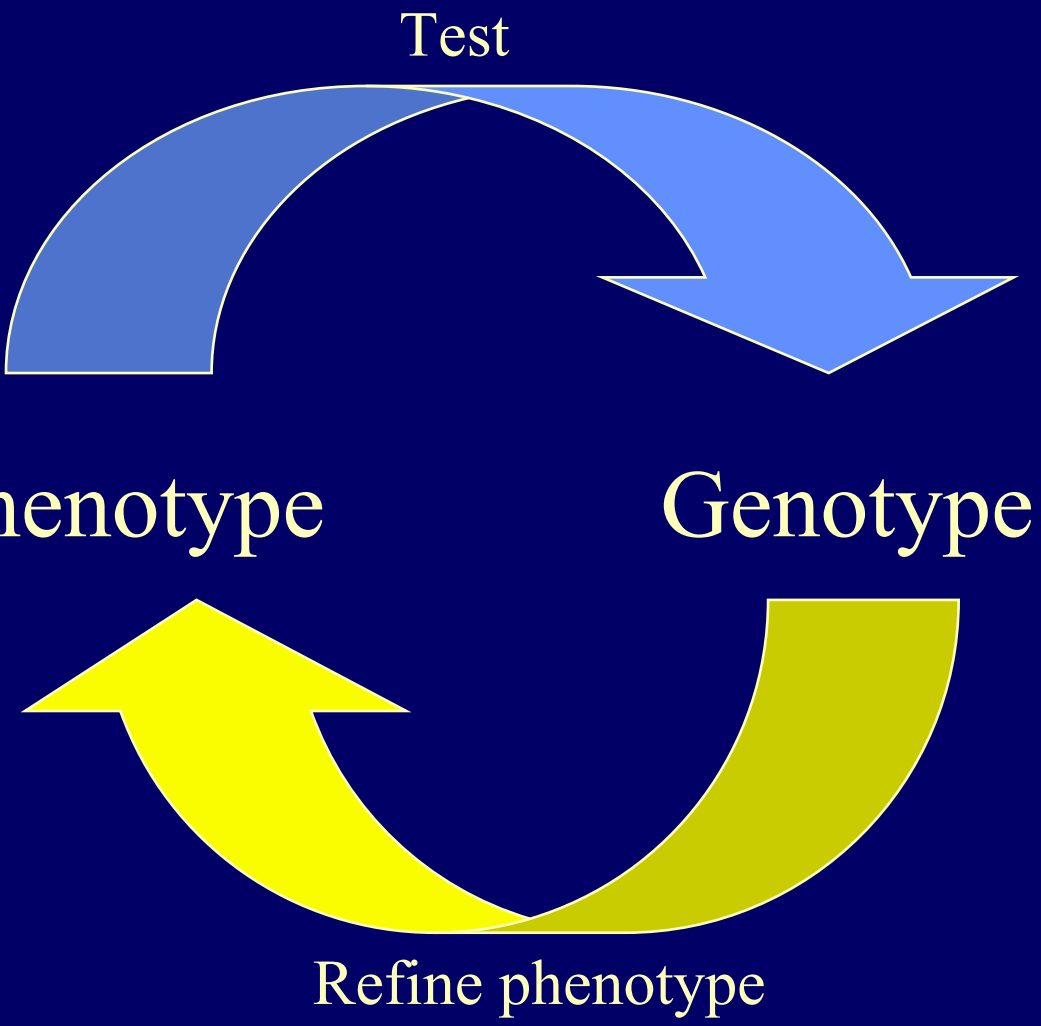


Emil Kraepelin

Reliability

Validity

An iterative approach to the phenotype



Craddock et al. *Mol Psychiatry*. 2006; **11**:446-58

Vol 447 | 7 June 2007 | doi:10.1038/nature05911 nature

ARTICLES

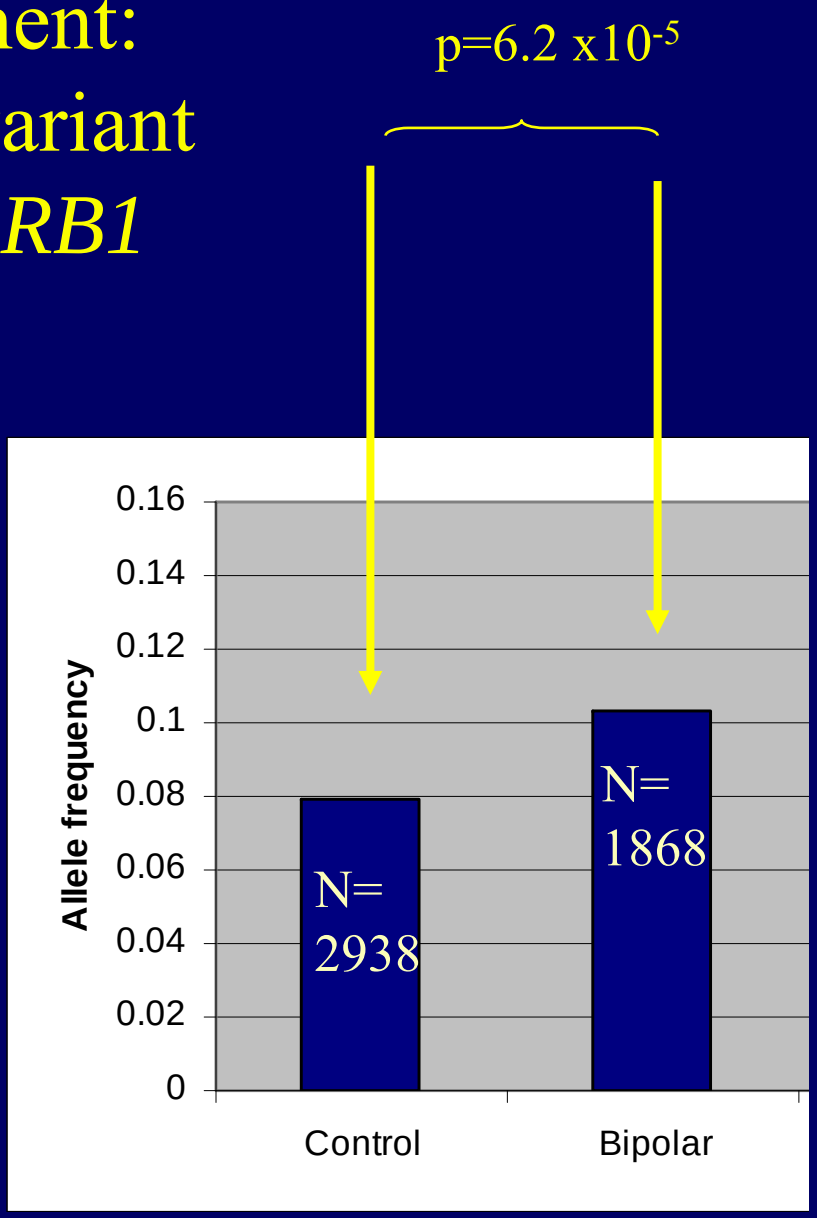
Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

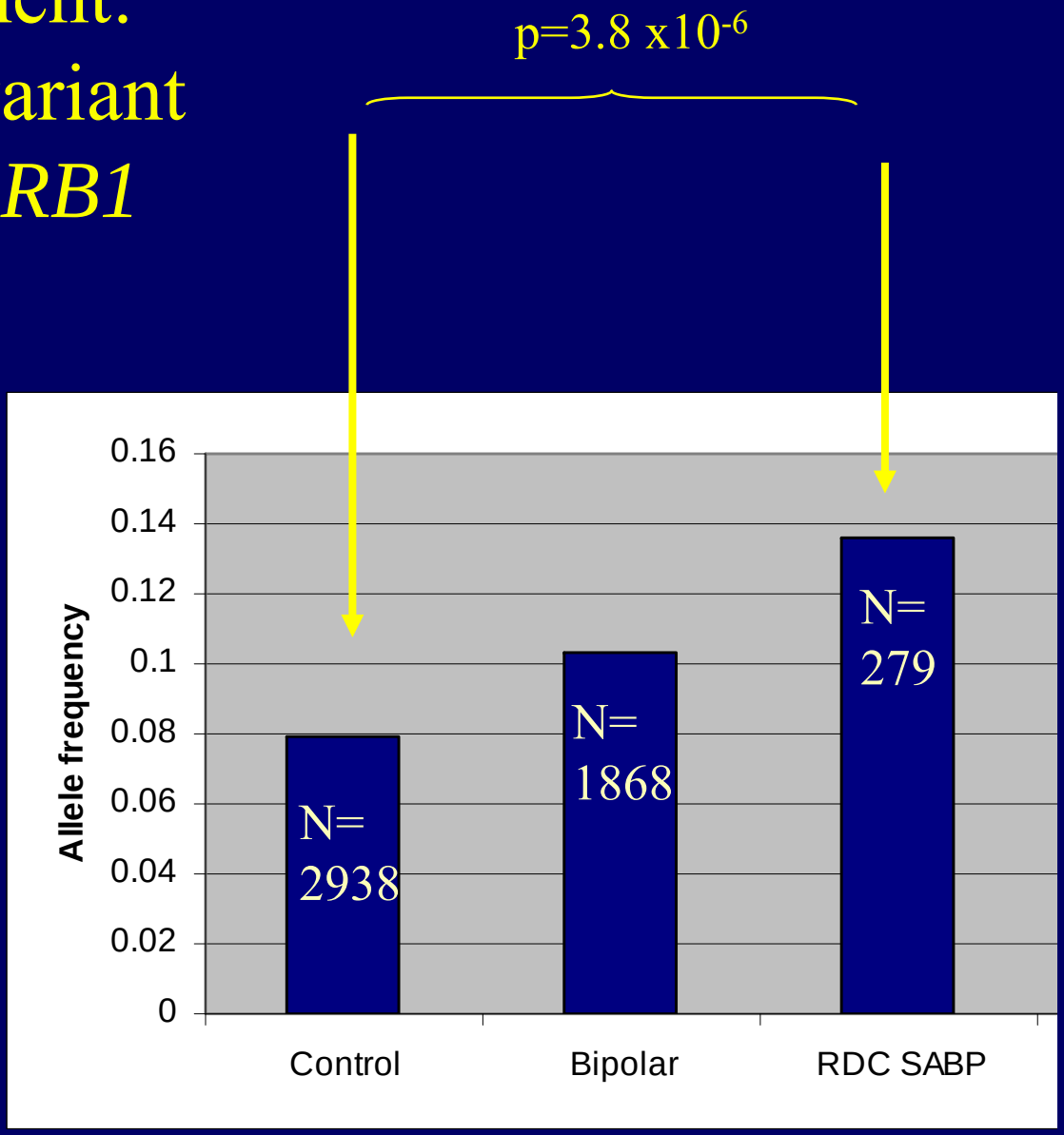
There is increasing evidence that genome-wide association (GWA) studies represent a powerful approach to the identification of genes involved in common human diseases. We describe a joint GWA study (using the Affymetrix GeneChip 500K Mapping Array Set) undertaken in the British population, which has examined ~2,000 individuals for each of 7 major diseases and a shared set of ~3,000 controls. Case-control comparisons identified 24 independent association signals at $P < 5 \times 10^{-7}$: 1 in bipolar disorder, 1 in coronary artery disease, 9 in Crohn's disease, 3 in rheumatoid arthritis, 7 in type 1 diabetes and 3 in type 2 diabetes. On the basis of prior findings and replication studies thus-far completed, almost all of these signals reflect genuine susceptibility effects. We observed association at many previously identified loci, and found compelling evidence that some loci confer risk for more than one of the diseases studied. Across all diseases, we identified a large number of further signals (including 58 loci with single-point P values between 10^{-5} and 5×10^{-7}) likely to yield additional susceptibility loci. The importance of appropriately large samples was confirmed by the modest effect sizes

WTCCC. Nature 2007; 447: 661-677 & 56 pages of supplementary online material

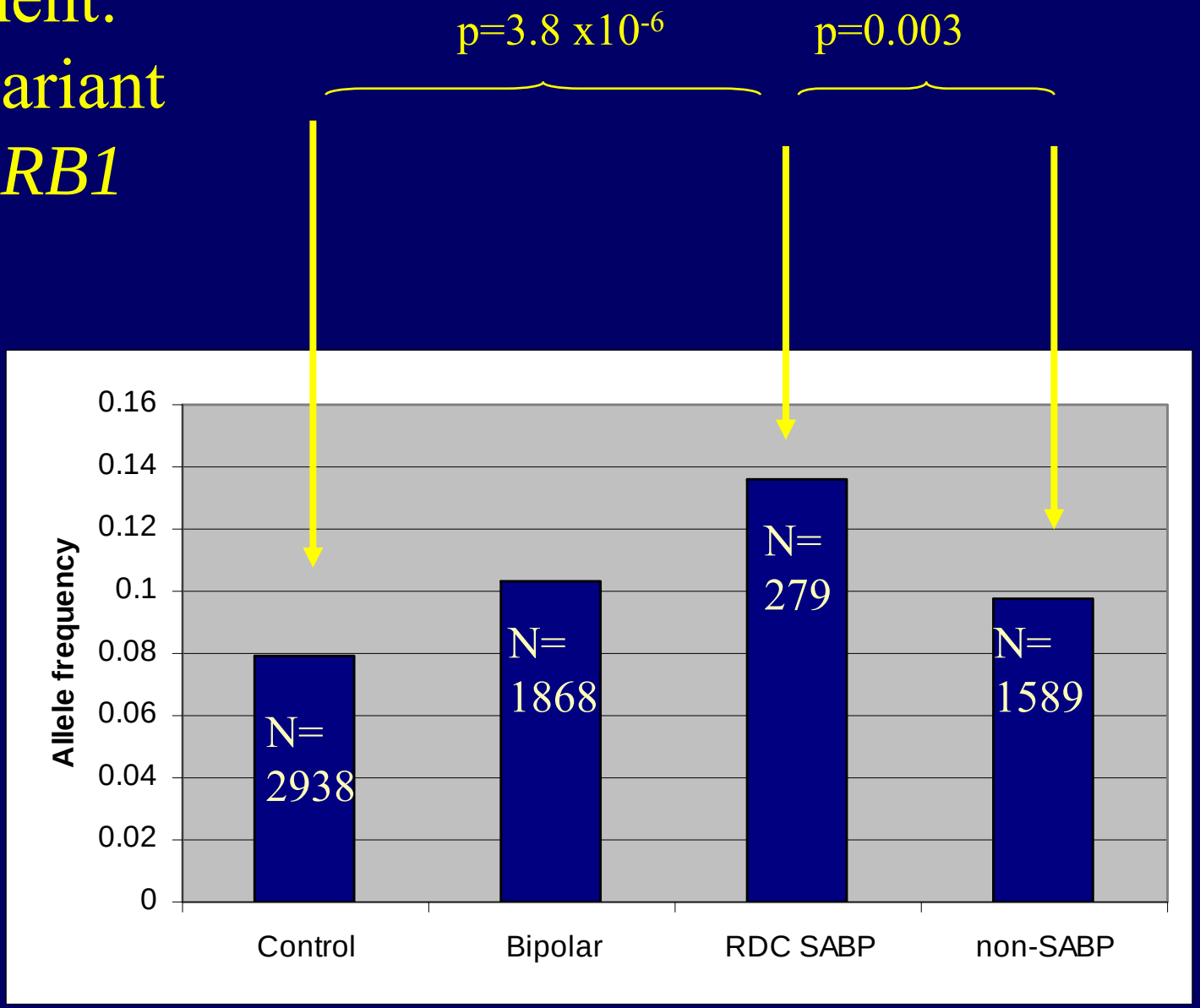
Phenotype refinement: index variant in *GABRB1*



Phenotype refinement: index variant in *GABRB1*

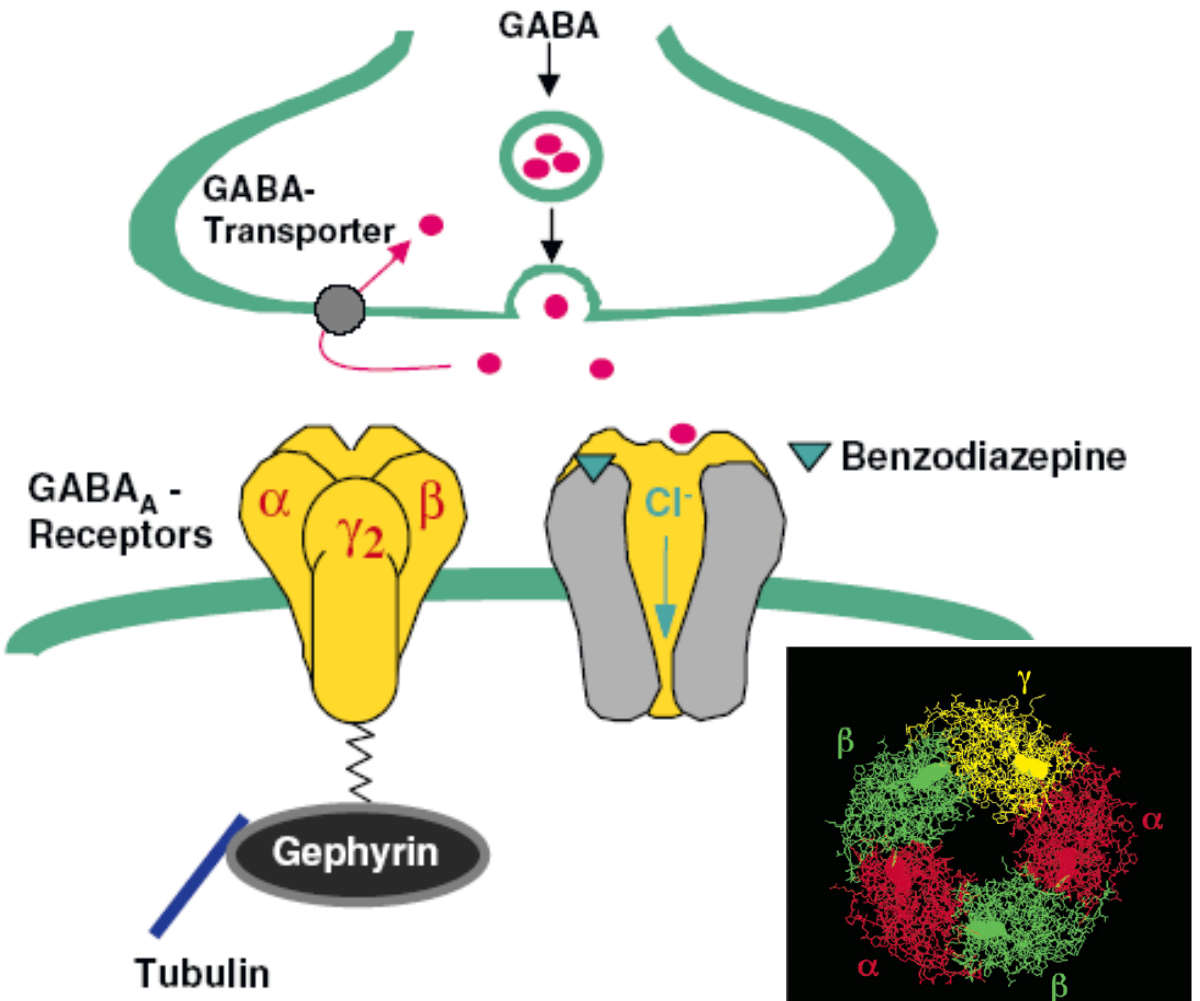


Phenotype refinement: index variant in *GABRB1*



Hypothesis test of specific biological system using refined phenotype

- Test variants in $GABA_A$ receptor genes in RDC SABP subset of cases

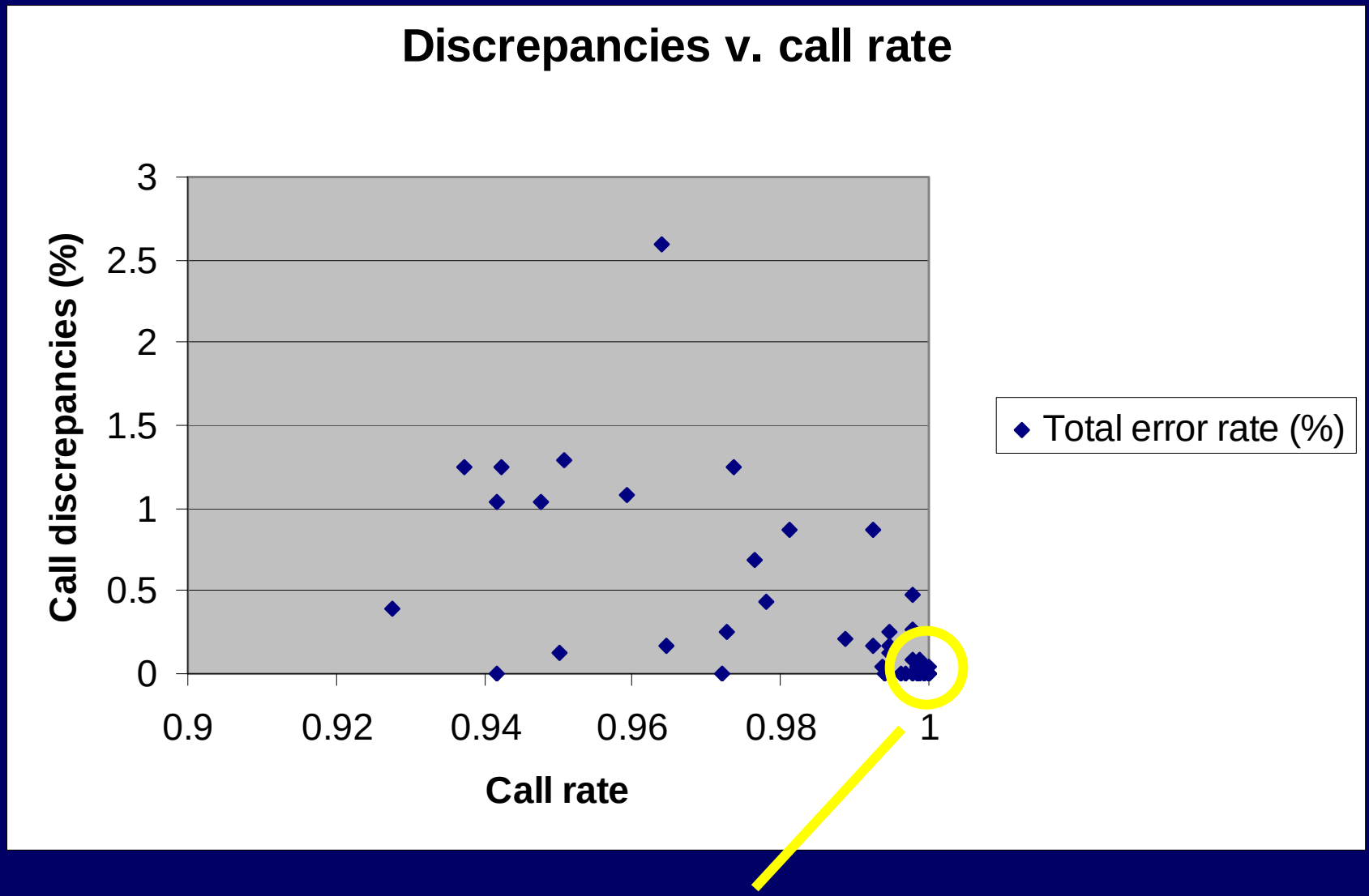


Subunit repertoire	
α	1-6
β	1-3
γ	1-3
δ	1
ε	1
θ	1
ρ	1-3

Mohler. Cell Tissue Res (2006) 326:505–516

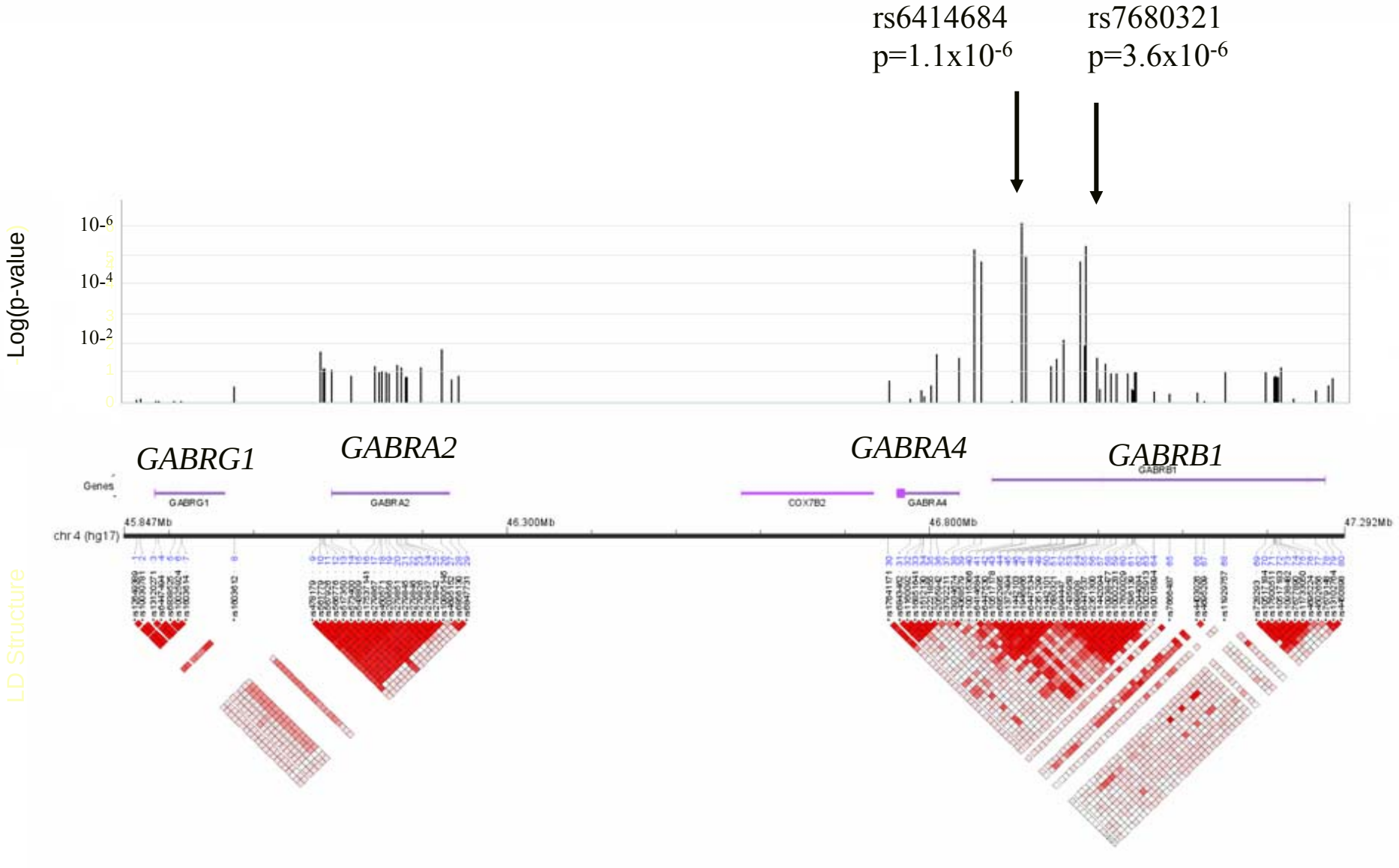
Set of SNPs at $GABA_A$ receptor genes

- 63 SNPs across the 4p12-13 cluster
  - GABRB1, GABRA4, GABRA2, GABRG1
- 64 SNPs across the 5q31-q25 cluster
  - GABRB22, GABRA6, GABRA1, GABRG2
- 70 SNPs across the 15q11-q13 cluster
  - GABRB3, GABRA5, GABRG3
- 22 SNPs across the Xq28 cluster
  - GABRQ, GABR3, GABRE
- 21 SNPs across the pair of genes at 6q15
  - GABRR1, GABRR2
- 16 SNPs across the gene at 5q35.1
  - GABRP
- 12 SNPs across the at 3q11.2
  - GABRR3.

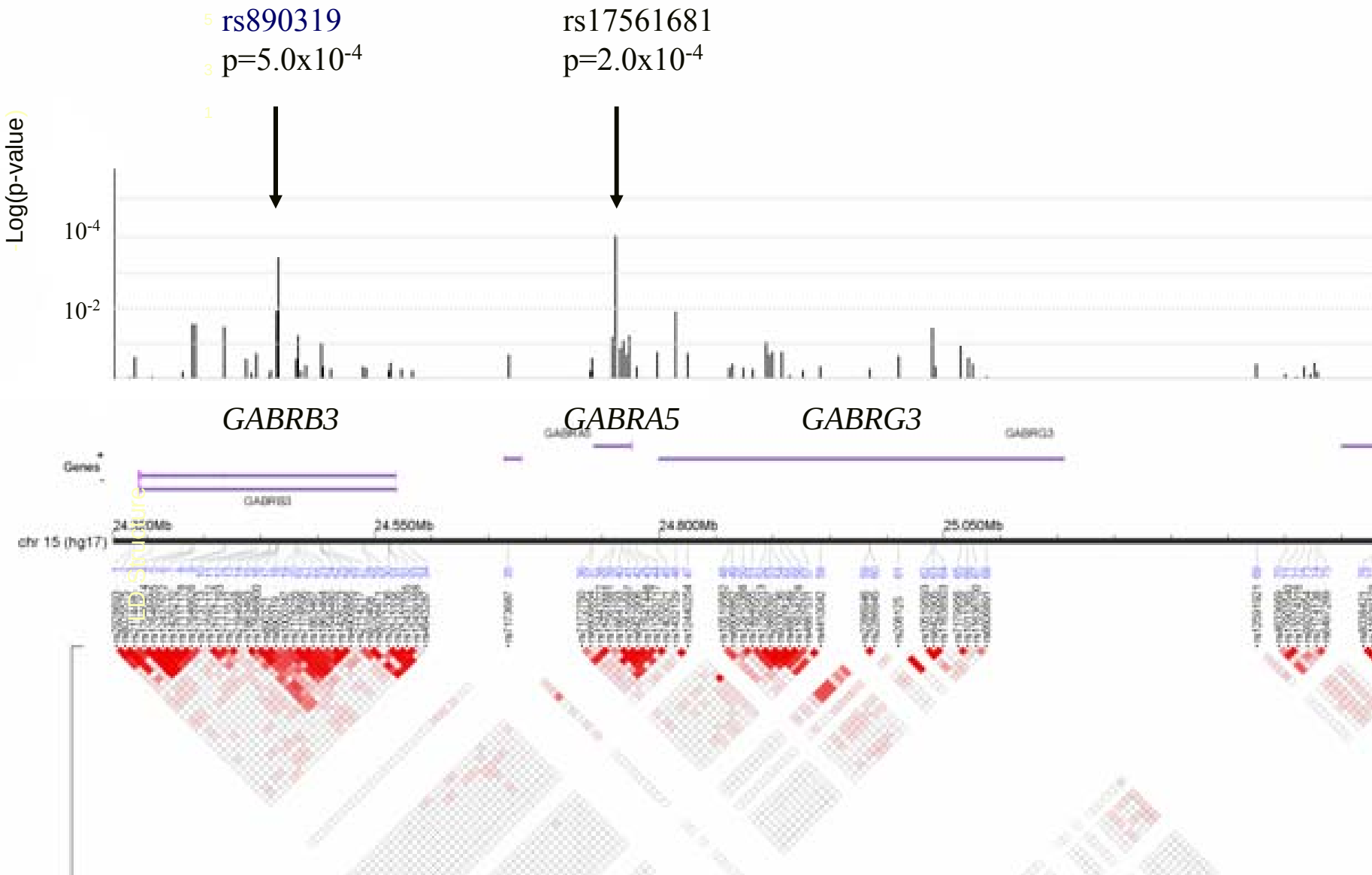


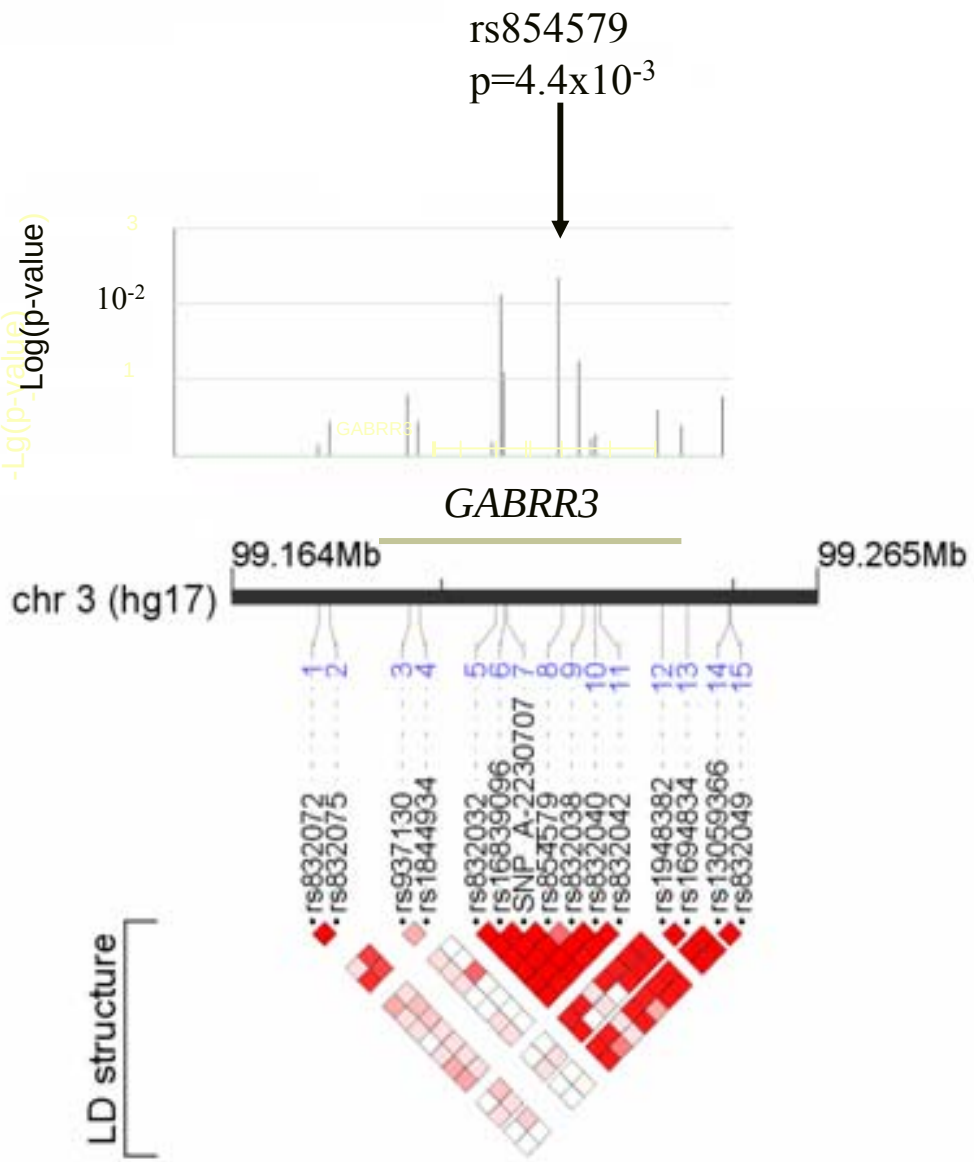
Call rate >99.5%, MAF>0.05: genotyping agreement 99.95%

4p12-13 cluster



15q11-q13 cluster




rs854579
p=4.4x10-3
Log(p-value)
10-2
GABRR3
chr 3 (hg17)
99.164Mb
99.265Mb
rs832072
rs832075
rs937130
rs1844934
rs832032
rs16839096
SNP_A-2230707
rs854579
rs832038
rs832040
rs832042
rs1948382
rs1694834
rs13059366
rs832049
LD structure

Association at $GABA_A$ β receptor genes in SABP cases compared with controls and with non-SABP bipolar cases

Gene	Most significant SNP	Controls frequency of risk allele	SABP v. controls OR (95% CI)	SABP v. controls allelic p value	SABP v. Non-SABP BD allelic p value
GABRB1	rs6414684	0.4910	1.56 (1.27-1.91)	1.1×10^{-6}	0.001
GABRB2	-	-	-	NS	NS
GABRB3	rs890319	0.3231	1.38 (1.11-1.71)	5.0×10^{-4}	0.0059

Independent evidence at β receptor genes : p=0.00024

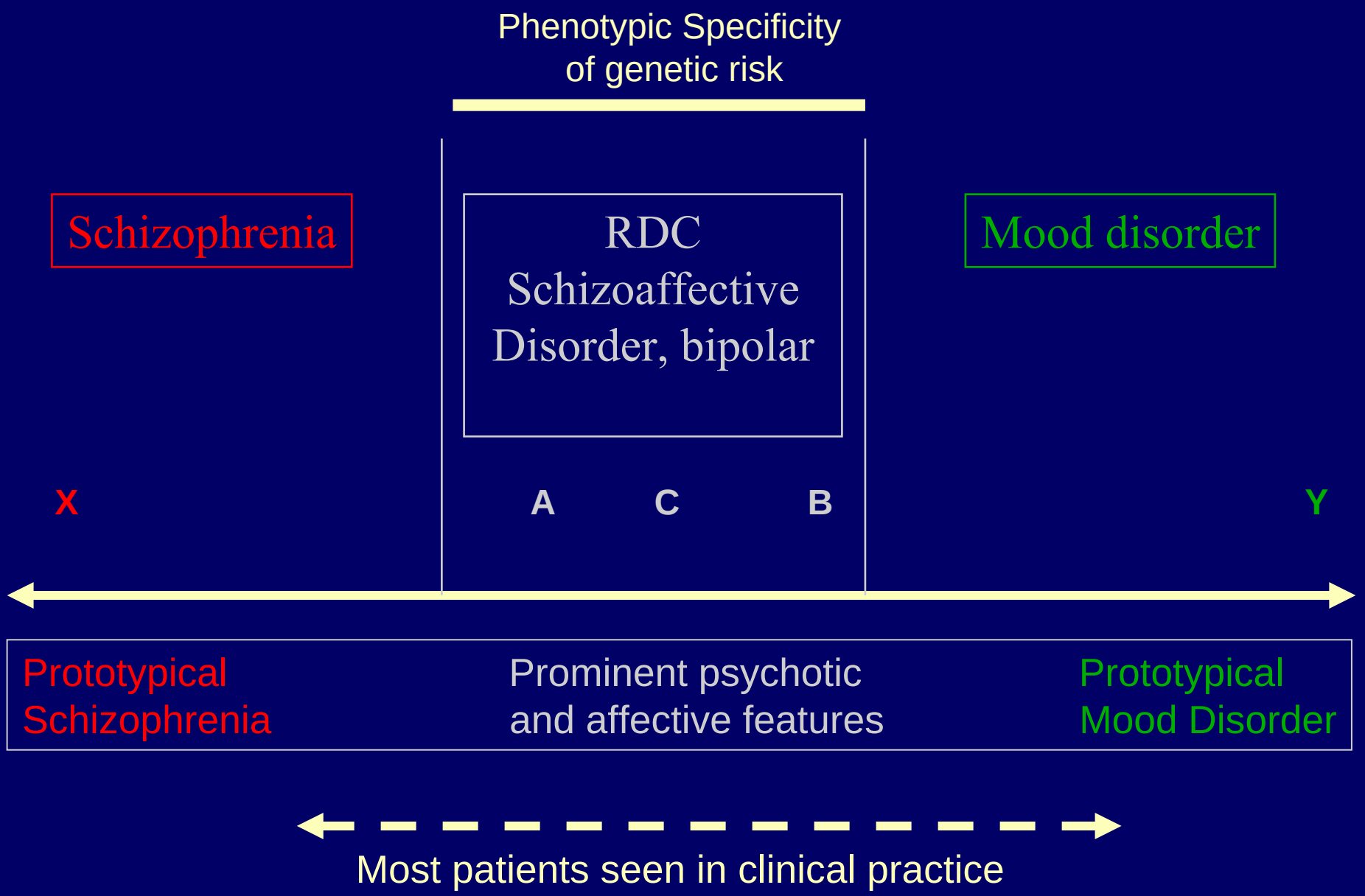
Hypothesis test of specific biological system using refined phenotype

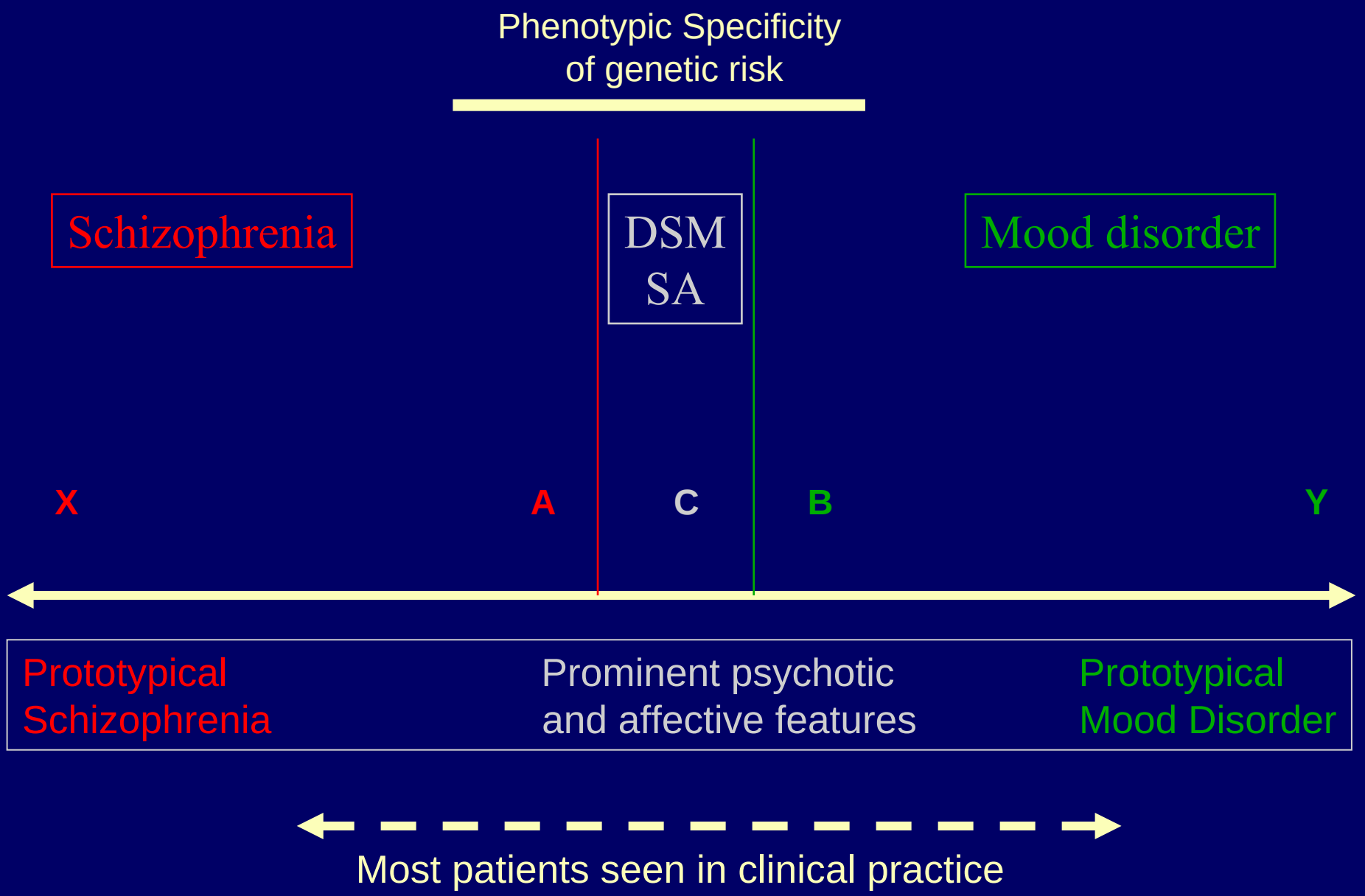
- Independent of index signal there is strong support for system involvement
  - $p=4.8x10^{-5}$
- Several genes implicated
  - *GABRB1*, *GABRB3*, *GABRA4*, *GABRA5* *GABRR1*

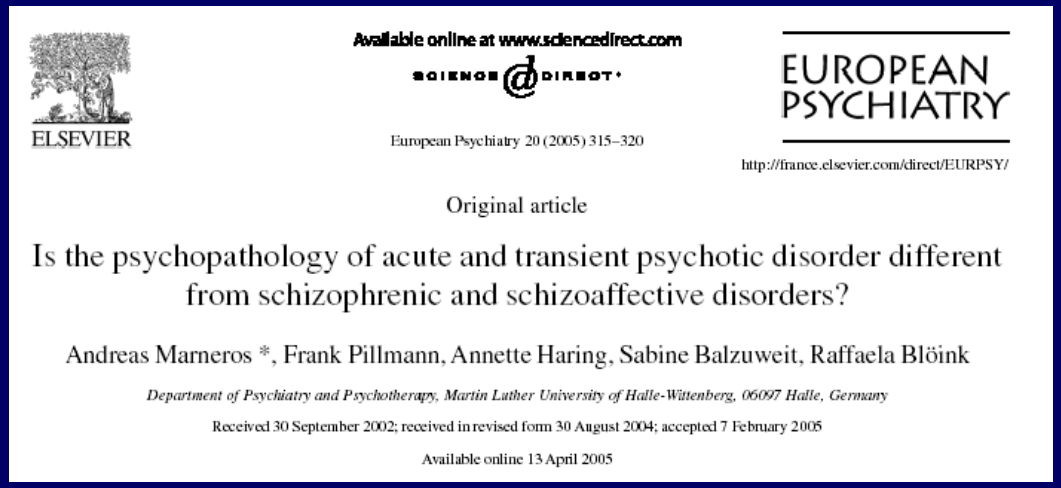
What are implications?

- More biologically homogeneous sub-set of bipolar cases
- Can provide a theoretical base to guide treatment choice
- Can help to explain commonly observed "co-morbidities" with bipolar disorder
  - Anxiety/ panic
  - Alcohol abuse

What does this mean for diagnosis?


Phenotypic Specificity
of genetic risk
Schizophrenia
RDC
Schizoaffective
Disorder, bipolar
Mood disorder
X
A
C
B
Y
Prototypical
Schizophrenia
Prominent psychotic
and affective features
Prototypical
Mood Disorder
Most patients seen in clinical practice


Phenotypic Specificity
of genetic risk
Schizophrenia
DSM
SA
Mood disorder
X
A
C
B
Y
Prototypical
Schizophrenia
Prominent psychotic
and affective features
Prototypical
Mood Disorder
Most patients seen in clinical practice



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European Psychiatry 20 (2005) 315–320

EUROPEAN PSYCHIATRY

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Original article

Is the psychopathology of acute and transient psychotic disorder different from schizophrenic and schizoaffective disorders?

Andreas Marneros *, Frank Pillmann, Annette Haring, Sabine Balzuweit, Raffaela Blöink

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Received 30 September 2002; received in revised form 30 August 2004; accepted 7 February 2005

Available online 13 April 2005

Marneros et al.
European Psychiatry
2005; 20: 315–320

Acute and transient psychotic disorders (ICD10)

- Cycloid psychoses (Germany)
- Psychogenic psychoses (Scandinavia)
- Bouffée délirante (France)
- Good prognosis schizophrenia (USA)

BRITISH JOURNAL OF PSYCHIATRY (2005), 186, 364–366

EDITORIAL

The beginning of the end for the Kraepelinian dichotomy

NICK CRADDOCK and MICHAEL J. OWEN

For the past hundred years most clinical work and research in psychiatry has proceeded under the assumption that schizophrenia and bipolar affective disorder (or the corresponding earlier terms, such as dementia praecox and manic–depressive illness) are distinct entities with separate underlying disease processes and treatments. This so-called 'Kraepelinian dichotomy' has pervaded Western psychiatry since Emil Kraepelin (1919) 'crystallised dementia

increased risk of schizophrenia but not bipolar disorder in the relatives of probands with schizophrenia, and vice versa in corresponding studies of bipolar disorder. It is also true that groups of individuals classified as having typical schizophrenia can be discriminated from sets of individuals classified as having typical bipolar disorder on the basis of clinical features and outcome.

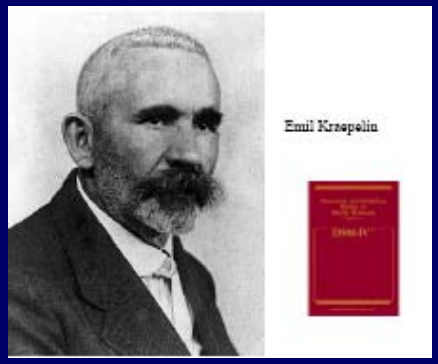
As well as having apparent empirical

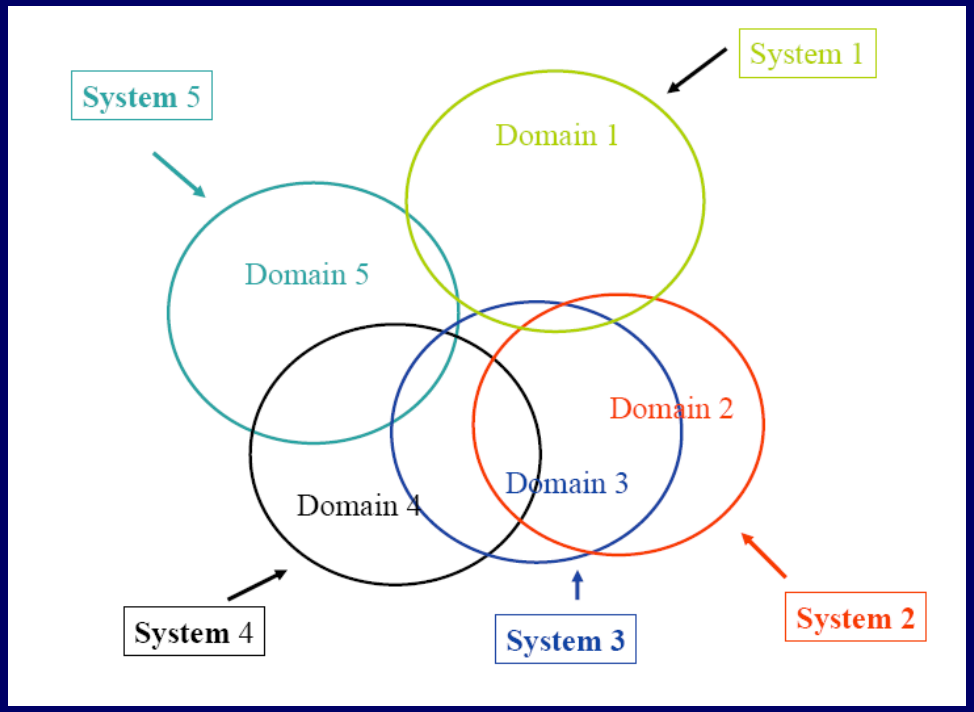
and bipolar illness and between schizoaffective disorders and both bipolar disorder and schizophrenia (reviewed by Craddock *et al*, 2005).

(b) A recent twin study – the only one that has used an analysis unconstrained by the diagnostic hierarchy inherent in current classification systems – demonstrated an overlap in the genetic susceptibility to mania and schizophrenia (Cardno *et al*, 2002) and provided evidence that there are genes that confer susceptibility across the Kraepelinian divide, to schizoaffective disorder and to some cases of schizophrenia and bipolar disorder. This study also confirmed the traditional notion that there are genes specific to the two prototypical disorders.

(c) Systematic, whole-genome linkage studies of schizophrenia and bipolar disorder have implicated some chromosomal regions in common; this is

Br J Psychiatry 2005; 186: 364-366





19th Century

21st Century

World Psychiatry

OFFICIAL JOURNAL OF THE WORLD PSYCHIATRIC ASSOCIATION (WPA)

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ISSN 1723-8617

FORUM – DO THE DISADVANTAGES OF THE KRAEPELINIAN DICHOTOMY NOW OUTWEIGH THE ADVANTAGES?

Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages 20
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Rethinking psychosis 31
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Physis does not take leaps, neither does Psyche 32
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When the paradigms languish 33
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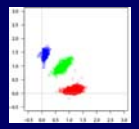
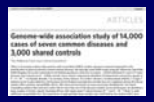
Classifying psychosis: when is the time ripe for changes? 35
O. Gureje

World Psychiatry June 2007

Take Home Messages

- The beginning …
  - Some of genes/ systems being implicated relate to known hypotheses
  - Close attention to QC essential
  - Multiple large samples needed – collaboration
  - Think beyond traditional diagnostic categories





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The Wellcome Trust Case Control Consortium

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Statistical analyses of main WTCCC dataset

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Management committee

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Some comments about controls

- Non-screened controls
- Common controls within an experiment
- Common controls across experiments

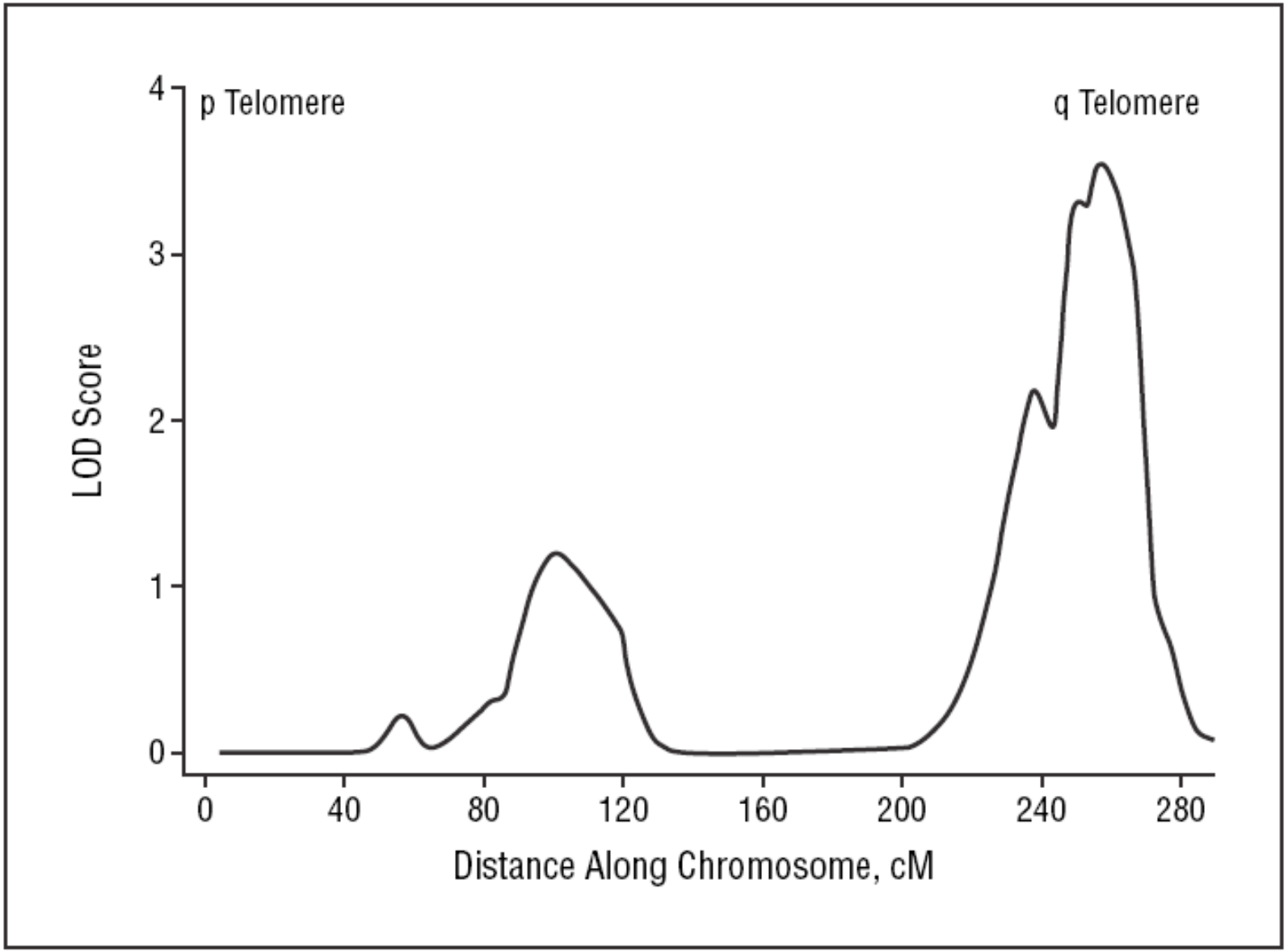
ORIGINAL ARTICLE

Genomewide Linkage Scan in Schizoaffective Disorder

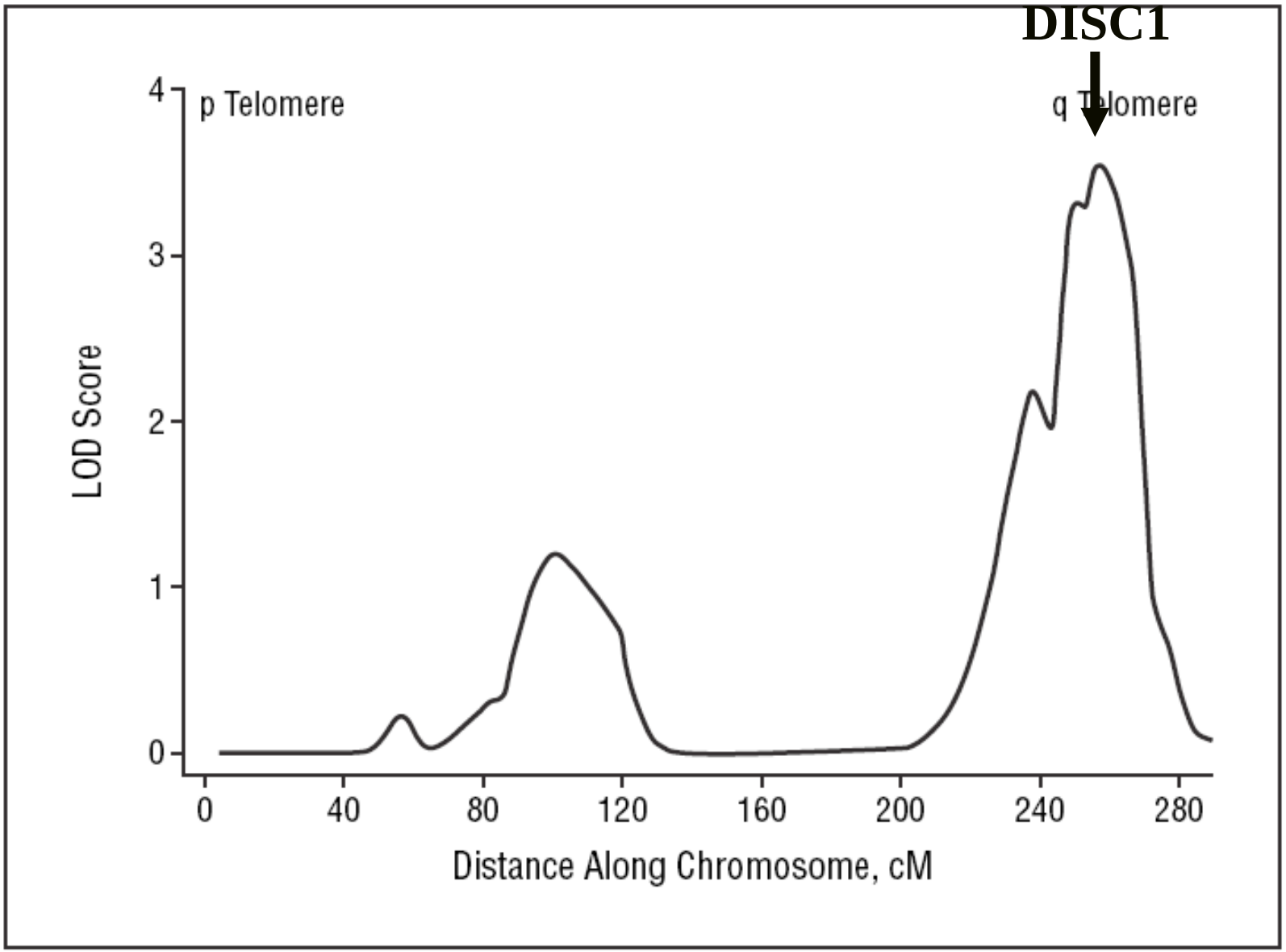
Significant Evidence for Linkage at 1q42 Close to DISC1, *and Suggestive Evidence at 22q11 and 19p13*

Marian L. Hamshere, PhD; Phil Bennett, PhD; Nigel Williams, PhD; Ricardo Segurado, PhD; Alastair Cardno, PhD, MRCPsych; Nadine Norton, PhD; David Lambert, PhD; Hywel Williams, PhD; George Kirov, MD, MRCPsych; Aiden Corvin, MD, MRCPsych; Peter Holmans, PhD; Lisa Jones, PhD; Ian Jones, PhD, MRCPsych; Michael Gill, MD, MRCPsych; Michael C. O'Donovan, PhD, FRCPsych; Michael J. Owen, PhD, FRCPsych; Nick Craddock, PhD, FRCPsych

Green et al, *Arch Gen Psychiatry. 2005;62:1081-1088*

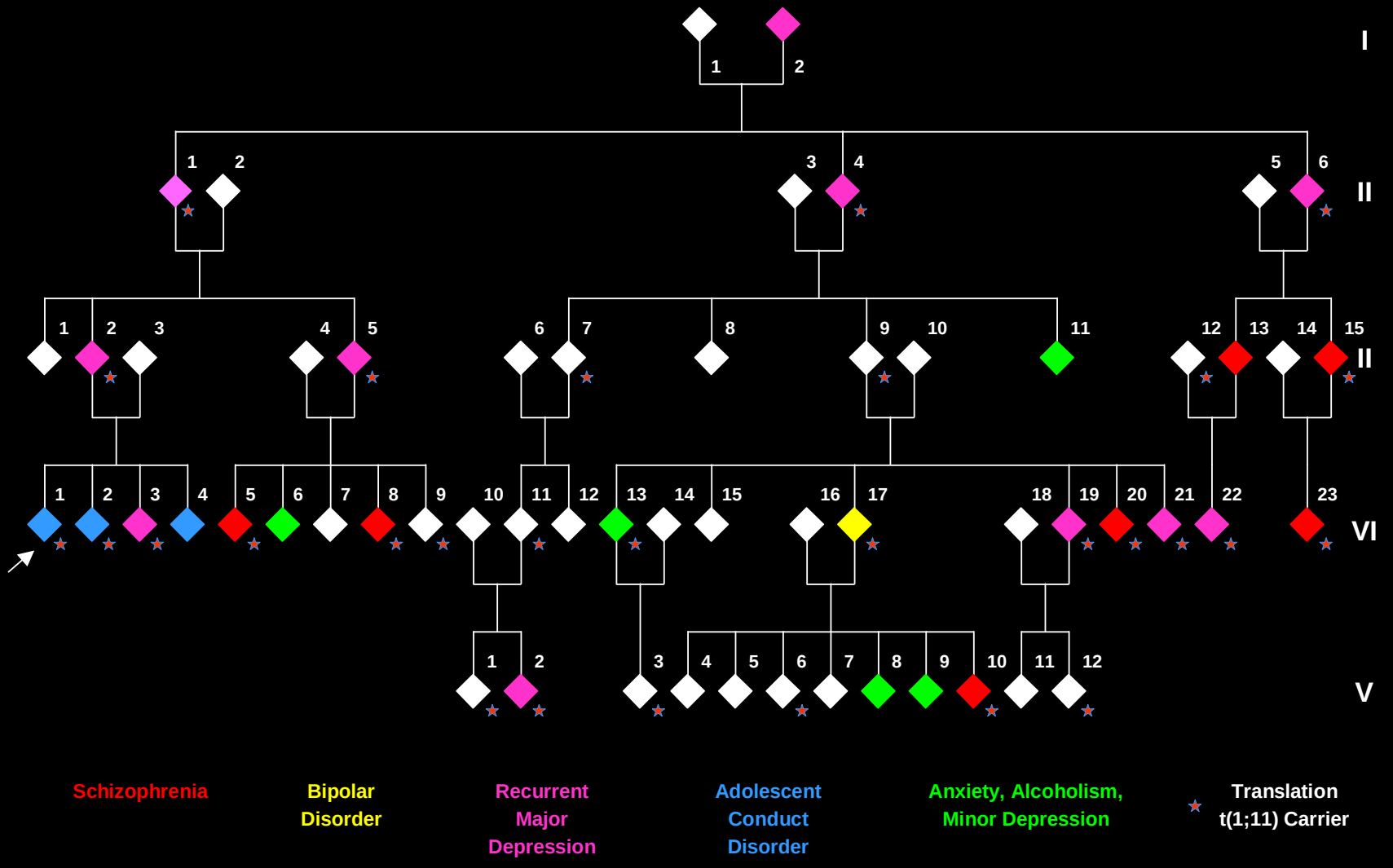


Green et al, *Arch Gen Psychiatry. 2005;62:1081-1088*



Green et al, *Arch Gen Psychiatry. 2005;62:1081-1088*

ASSOCIATION OF A BALANCED AUTOSOMAL TRANSLOCATION t(1;11) WITH MAJOR MENTAL ILLNESS



St Clair et al. Lancet 1990; 336:13-6; Blackwood et al. Am J Hum Genet. 2001; 69:428-33

Am. J. Hum. Genet. 75:862–872, 2004

Disrupted in Schizophrenia 1 (DISC1): Association with Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder

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Table 1

Allele-Based and Genotype-Based Association with Schizophrenia, Schizoaffective Disorder, and Bipolar Disorder, Showing the Celera SNP and dbSNP Identifiers for Each Genotyping Marker

		Association *P* Value[a]			Allele Frequency		
Celera SNP	dbSNP	Allelic	Genotypic	Coding Change	Controls	Cases	Risk Ratio
hCV27474272	*rs3738400*	...	...	Gly5Met	...	...	...
hCV12001977	*rs1895225*	...	...	...	...	...	...
hCV12001946	*rs1572899*	...	.048[c]	...	.298	.397	1.185
hCV12001945	*rs1538975*	...	...	...	...	...	...
hCV25641899	*rs3738401*	...	...	Gln264Arg	...	...	...
hCV12001940	*rs1954175*	...	...	...	...	...	...
hCV9626784	*rs1340982*	...	...	...	...	...	...
hCV16113533	*rs2812379*	...	...	...	...	...	...
hCV16114160	*rs2793094*	...	...	...	...	...	...
hCV12001932	*rs1538977*	...	...	...	...	...	...
hCV16114126	*rs2793101*	...	...	...	...	...	...
hCV16113570	*rs2812393*	.048[b]	...	...	.336	.404	1.203
hCV12001930	*rs1322784*	.013[b]	.008[b]	...	.680	.759	1.117
hCV12001929	*rs1322783*	.047[b]	...	...	.849	.899	1.059
hCV1650649	*rs2255340*	.006[b]	.016[b]	...	.702	.787	1.121
hCV1650650	*rs2738864*	.005[b]	.012[b]	...	.700	.787	1.125
hCV1650657	*rs1407598*	...	.046[d]	...	.198	.227	1.150
hCV1650667	*rs6675281*	.0000023[c]	.000056[c]	Leu607Phe	.132	.319	2.417
hCV1650669	*rs1407598*	...	.039[a]	...	.195	.221	1.133
hCV9627536	*rs1535529*	...	.035[d]	...	.200	.221	1.106
hCV1650688	*rs1000731*						