Supplementary Information

Genome-wide association analyses identifies a susceptibility locus for tuberculosis on chromosome 18q11.2

The African TB Genetics Consortium and the Wellcome Trust Case Control Consortium

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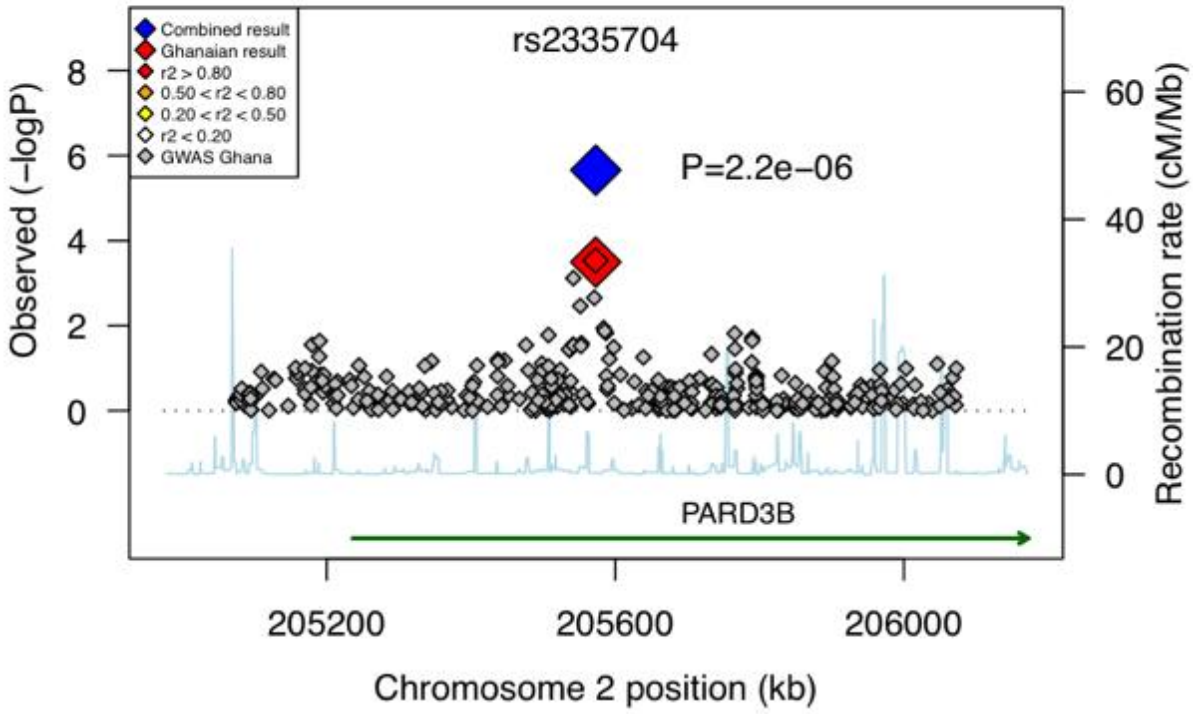


Supplementary Figure 1. Association plot of hits with fine mapping markers on chromosome 2 in the combined analysis (r^2 values between rs2335704 and adjacent SNPs derived from the Ghanaian population uncorrected for λ_{GC}).

Supplementary Table 1. Association statistics for the top 17 SNPs in the Ghana-Gambia analysis.

Chr	SNP	Position	Major allele/ Minor allele	MAF	The Gambia GWA study			Ghana GWA study			Combined GWA study			Replication I			GWA study plus Replication I		
					N	OR [95%CI]	P	N	OR [95%CI]	P	N	OR [95%CI]	P	N	OR [95%CI]	P	N	OR [95%CI]	P
1	rs10493412	66855347	G/C	0.11	2655	1.24 [1.1-1.4]	0.005	2661	1.36 [1.1-1.7]	0.003	5317	1.28 [1.1 1.4]	5.58E-05	2432	1.0 [0.8-1.2]	0.98	7775	1.19 [1.1-1.3]	0.002
1	rs17436311	66856380	A/G	0.12	2665	1.25 [1.1-1.5]	0.004	2660	1.35 [1.1-1.6]	0.003	5326	1.28 [1.1 1.4]	5.17E-05	2367	0.99 [0.8-1.2]	0.94	7725	1.19 [1.1-1.3]	0.001
2	rs10490534	154646176	T/G	0.42	2643	1.18 [1.1-1.3]	0.004	2660	1.18 [1.1-1.3]	0.006	5304	1.18 [1.1 1.3]	9.08E-05	2671	0.94 [0.8-1.1]	0.31	7998	1.09 [1.0-1.2]	0.01
2	rs2335704	205573077	A/C	0.20	2683	1.23 [1.1-1.4]	0.003	2661	1.27 [1.1-1.5]	0.0004	5322	1.26 [1.1 1.4]	4.63E-06	2679	1.19 [1.0-1.4]	0.01	8023	1.23 [1.1-1.3]	3.00E-07
6	rs7769812	38846812	T/G	0.21	2665	0.82 [0.7-0.9]	0.005	2654	0.82 [0.7-0.9]	0.005	5321	0.82 [0.7 0.9]	9.13E-05	2681	1.0 [0.9-1.2]	0.97	8033	0.87 [0.8-0.9]	0.001
6	rs4896905	147713687	A/G	0.12	2651	0.76 [0.6-0.9]	0.002	2660	0.77 [0.6-0.9]	0.006	5312	0.76 [0.7 0.9]	3.22E-05	2452	0.99 [0.8-1.2]	0.9	7788	0.83 [0.7-0.9]	5.10E-04
10	rs1875148	61011997	C/T	0.13	2654	1.28 [1.1-1.5]	0.003	2660	1.28 [1.1-1.5]	0.003	5315	1.29 [1.1 1.5]	2.02E-05	2413	0.95 [0.8-1.1]	0.54	7755	1.16 [1.1-1.3]	0.003
11	rs1503442	16382358	T/C	0.22	2650	0.81 [0.7-0.9]	0.004	2659	0.82 [0.7-0.9]	0.004	5311	0.82 [0.7 0.9]	4.78E-05	2683	0.96 [0.8-1.1]	0.54	8022	0.88 [0.8-1.0]	0.001
12	rs11173067	58203089	A/G	0.27	2634	0.84 [0.7-1.0]	0.006	2660	0.82 [0.7-0.9]	0.003	5296	0.83 [0.8 0.9]	3.32E-05	2394	1.11 [1.0-1.3]	0.13	7721	0.92 [0.9-1.0]	0.033
16	rs7190310	17179363	A/G	0.21	2662	1.19 [1.0-1.4]	0.0096	2657	1.24 [1.1-1.4]	0.003	5321	1.21 [1.1 1.3]	7.61E-05	2413	0.94 [0.8-1.1]	0.44	7766	1.12 [1.0-1.2]	0.009
16	rs1353690	74576356	C/A	0.05	2667	1.50 [1.2-1.9]	0.002	2661	1.49 [1.1-2.0]	0.005	5329	1.50 [1.2 1.8]	1.83E-05	2454	1.12 [0.8-1.5]	0.47	7810	1.40 [1.2-1.6]	4.54E-05
18	rs4331426	18444793	A/G	0.48	2686	1.18 [1.1-1.3]	0.003	2661	1.19 [1.1-1.3]	0.004	5323	1.18 [1.1 1.3]	2.20E-05	2685	1.19 [1.1-13]	0.003	8032	1.19 [1.1-1.3]	1.14E-07
18	rs1943238	56266216	C/A	0.04	2651	1.43 [1.1-1.9]	0.006	2657	1.72 [1.2-2.4]	0.002	5309	1.52 [1.2 1.9]	8.70E-05	2662	1.34 [1.0-1.9]	0.07	8005	1.41 [1.2-1.7]	1.17E-04
18	rs1943240	56267422	G/A	0.04	2664	1.50 [1.2-1.9]	0.001	2661	1.79 [1.3-2.5]	0.001	5326	1.58 [1.3 1.9]	8.39E-06	2684	1.37 [1.0-1.9]	0.04	8038	1.47 [1.2-1.7]	8.68E-06
18	rs3937015	65750496	C/T	0.37	2662	0.83 [0.7-0.9]	0.001	2660	0.84 [0.7-0.9]	0.004	5323	0.83 [0.8 0.9]	1.17E-05	2659	1.07 [0.9-1.2]	0.28	8009	0.90 [0.8-1.0]	0.002
19	rs35387445	59141468	C/T	0.06	2648	1.42 [1.1-1.8]	0.001	2659	1.46 [1.1-1.9]	0.003	5308	1.41 [1.2 1.7]	3.66E-05	2684	1.05 [0.8-1.3]	0.71	8020	1.32 [1.1-1.5]	7.80E-05
21	rs9981165	22262330	A/T	0.04	2657	0.73 [0.6-0.9]	0.0096	2659	0.48 [0.3-0.8]	0.002	5319	0.66 [0.5 0.8]	9.06E-05	2451	1.18 [0.8-1.7]	0.41	7800	0.78 [0.7-0.9]	0.009

Chr, chromosome; Position, chromosomal position (bp); MAF, minor allele frequency; N, number of samples; OR, odds ratio; CI, confidence interval; P, P value calculated with logistic regression analyses adjusted for MDS components in the GWAS data sets and for gender and ethnicity in the replication analyses (uncorrected for λ_{GC}).

Supplementary Table 2. Association statistics for additional SNPs genotyped in hit regions on chromosome 2 and 18.

	SNP, allele of minor frequency	Combined data		GWA study samples				Replication I		Replication II				Trios/Duos	
				Ghana case/control		The Gambia case/control		Ghana case/control		Ghana case/control		Malawi case/control		Ghana	
		OR [95%CI]	*P*	OR [95%CI]	*P*	OR [95%CI]	*P*	OR [95%CI]	*P*	OR [95%CI]	*P*	OR [95%CI]	*P*	OR [95%CI]	*P*
Chromosome	2q33.2														
GWA Study	rs2335704,C	1.19 [1.1-1.3]	2.2E-06	1.28 [1.1-1.5]	0.0004	1.23 [1.1-1.4]	0.003	1.14 [1.0-1.4]	0.01	0.93 [0.7-1.3]	0.63	1.02 [0.8-1.4]	0.91	0.78 [0.6-1.0]	0.08
Additional	rs2335705,C	1.17 [1.1-1.3]	6.2E-05	1.32 [1.1-1.5]	0.0002	1.19 [1.0-1.4]	0.045	1.15 [1.0-1.3]	0.05	0.93 [0.7-1.3]	0.67	1.04 [0.8-1.4]	0.82	0.82 [0.6-1.1]	0.16
Chromosome	18q11.2														
GWA Study	rs4331426,G	1.19 [1.1-1.3]	6.8E-09	1.18 [1.1-0.3]	0.004	1.18 [1.1-1.3]	0.003	1.19 [1.1-1.3]	0.003	1.18 [0.9-1.5]	0.19	1.15 [0.9-1.4]	0.23	1.33 [1.1-1.7]	0.016
Additional	rs11874936,C	1.17 [1.1-1.3]	7.3E-07	1.21 [1.1-1.4]	0.001	1.11 [1.0-1.3]	0.14	1.21 [1.1-1.4]	0.001	1.20 [0.9-1.6]	0.15	n.d.	n.d.	1.33 [1.0-1.7]	0.019
Additional	rs11877287,T	1.18 [1.1-1.3]	1.1E-07	1.20 [1.1-1.4]	0.002	1.12 [1.0-1.3]	0.073	1.18 [1.0-0.3]	0.005	1.14 [0.9-1.5]	0.32	1.40 [1.0-2.0]	0.045	n.d.	n.d.
Additional	rs7231506, A	0.85 [0.8-0.9]	3.5E-07	0.84 [0.7-0.9]	0.002	0.90 [0.8-1.0]	0.11	0.86 [0.8-1.0]	0.009	0.81 [0.6-1.0]	0.09	0.83 [0.6-1.2]	0.31	0.69 [0.5-0.9]	0.003

OR, odds ratio; CI, confidence interval; P, P value of logistic regression analyses adjusted by gender and ethnicity for GWA studies and replication I and II**.** P value of the family based data set was computed with the algorithm implemented in the UNPHASED

Supplementary Table 3: Association statistics of SNP rs2337504 in the overall study

rs2335704 – C allele	**Controls**	**Controls**	**Cases**	**Cases**	**OR 95% CI**	***P* value**
GWA study scan	*N*	*Freq*	*N*	*Freq*		
Ghana	1740	0.192	921	0.232	1.28 (1.12-1.47)	4.3E-04
The Gambia (WTCCC)	1378	0.172	1305	0.206	1.23 (1.07-1.42)	3.2E-03
Replication I						
Ghana	1607	0.204	1072	0.230	1.19 (1.04-1.37)	1.4E-02
Replication II						
Ghana	2200	0.202	149	0.188	0.92 (0.68-1.26)	6.3E-01
Malawi	524	0.163	187	0.166	1.02 (0.75-1.38)	9.1E-01
Combined analysis	7449		3634		1.29 (1.11-1.28)	2.1E-06
λ_{GC} corrected combined *P* value						3.9E-06
Ghanaian nuclear families*					0.78 (0.60-1.03)	8.2E-02

* Cases from nuclear families were part of the Ghanaian GWA case-control study; the TDT statistic is not included in the combined analysis.

Supplementary Table 4. Association results of imputed SNPs of the Ghanaian, the Gambian and the combined samples.

Chromosome	rs#	Position	Alleles	MAF	Ghana			The Gambia			Ghana / The Gambia			Rsq
					OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	
1	rs10889630	66807377	T/C	0.11	1.36	1.1 - 1.7	0.0029	1.26	1.1 - 1.5	0.0033	1.3	1.1 - 1.5	3.74E-05	0.89
1	rs6699200	66813897	C/T	0.11	1.36	1.1 - 1.7	0.0029	1.27	1.1 - 1.5	0.0029	1.3	1.1 - 1.5	3.28E-05	0.89
1	rs4147266	66821331	G/T	0.11	1.35	1.1 - 1.7	0.004	1.26	1.1 - 1.5	0.0037	1.29	1.1 - 1.5	5.58E-05	0.95
1	rs12117202	66835157	T/C	0.11	1.35	1.1 - 1.7	0.004	1.26	1.1 - 1.5	0.0037	1.29	1.1 - 1.5	5.54E-05	0.95
1	rs11208921	66848642	G/C	0.12	1.35	1.1 - 1.6	0.0034	1.24	1.1 - 1.5	0.005	1.28	1.1 - 1.4	6.81E-05	0.97
1	rs12141816	66854606	A/G	0.12	1.36	1.1 - 1.7	0.0028	1.25	1.1 - 1.5	0.005	1.28	1.1 - 1.4	5.73E-05	1
1	rs324870	96576439	C/T	0.04	0.63	0.5 - 0.9	0.0062	0.7	0.5 - 0.9	0.0084	0.66	0.5 - 0.8	1.00E-04	0.98
1	rs2150037	106634119	C/G	0.33	1.18	1 - 1.3	0.0082	1.19	1.1 - 1.3	0.0039	1.18	1.1 - 1.3	9.27E-05	0.77
1	rs2210094	106635133	C/G	0.33	1.18	1 - 1.3	0.0073	1.19	1.1 - 1.3	0.0038	1.18	1.1 - 1.3	7.77E-05	0.77
2	rs6545883	61625761	G/A	0.48	0.82	0.7 - 0.9	0.0008	0.85	0.8 - 0.9	0.0037	0.83	0.8 - 0.9	5.29E-06	1
2	rs778753	61633704	A/T	0.47	0.82	0.7 - 0.9	0.0009	0.86	0.8 - 1	0.007	0.84	0.8 - 0.9	1.16E-05	1
2	rs778764	61639184	T/C	0.44	0.84	0.7 - 0.9	0.0036	0.84	0.8 - 0.9	0.0023	0.84	0.8 - 0.9	1.25E-05	0.94
2	rs13390761	205518183	G/T	0.12	1.33	1.1 - 1.6	0.0016	1.26	1.1 - 1.5	0.0077	1.3	1.1 - 1.5	2.73E-05	0.74
2	rs2335705	205572777	C/A	0.17	1.33	1.2 - 1.5	0.0001	1.21	1 - 1.4	0.0089	1.27	1.1 - 1.4	4.59E-06	0.86
2	rs12616462	212198517	C/A	0.33	1.21	1.1 - 1.4	0.0019	1.18	1 - 1.3	0.0063	1.19	1.1 - 1.3	3.65E-05	0.96
3	rs9823492	143893977	G/A	0.14	0.79	0.7 - 0.9	0.0032	0.79	0.7 - 0.9	0.0077	0.78	0.7 - 0.9	2.98E-05	0.85
3	rs6780978	163600044	G/A	0.23	0.82	0.7 - 0.9	0.0044	0.83	0.7 - 0.9	0.0046	0.83	0.8 - 0.9	6.17E-05	0.82
4	rs10005603	106063722	G/T	0.35	0.82	0.7 - 0.9	0.0008	0.85	0.8 - 1	0.0066	0.83	0.8 - 0.9	7.23E-06	0.9
6	rs2560812	13580621	T/C	0.44	1.17	1 - 1.3	0.0085	1.23	1.1 - 1.4	0.0002	1.19	1.1 - 1.3	1.35E-05	0.82
6	rs12211963	38875428	C/T	0.23	0.82	0.7 - 0.9	0.0042	0.84	0.7 - 1	0.0086	0.83	0.8 - 0.9	9.14E-05	0.99
6	rs6933055	43433771	G/A	0.13	0.78	0.7 - 0.9	0.0032	0.77	0.7 - 0.9	0.0022	0.78	0.7 - 0.9	5.14E-05	0.91
6	rs7750647	43467243	T/C	0.13	0.77	0.7 - 0.9	0.0028	0.77	0.7 - 0.9	0.0021	0.78	0.7 - 0.9	4.45E-05	0.93
6	rs175360	72448948	T/C	0.16	1.23	1.1 - 1.4	0.0094	1.31	1.1 - 1.5	0.0005	1.26	1.1 - 1.4	2.10E-05	0.8
6	rs17448801	87806344	A/T	0.05	0.6	0.4 - 0.9	0.0039	0.73	0.6 - 0.9	0.0066	0.69	0.6 - 0.8	9.30E-05	0.98
6	rs17448899	87807285	G/A	0.05	0.6	0.4 - 0.9	0.0039	0.73	0.6 - 0.9	0.0066	0.69	0.6 - 0.8	9.30E-05	0.99
6	rs17448940	87807562	C/T	0.05	0.6	0.4 - 0.9	0.0039	0.73	0.6 - 0.9	0.0066	0.69	0.6 - 0.8	9.30E-05	0.98
6	rs17546090	87807766	C/A	0.05	0.6	0.4 - 0.9	0.0039	0.73	0.6 - 0.9	0.0066	0.69	0.6 - 0.8	9.30E-05	0.98
6	rs9373523	147742826	T/G	0.19	0.75	0.6 - 0.9	0.0002	0.8	0.7 - 0.9	0.0018	0.77	0.7 - 0.9	1.23E-06	0.7
7	rs10267586	43021029	C/T	0.18	1.25	1.1 - 1.4	0.0026	1.22	1.1 - 1.4	0.0057	1.23	1.1 - 1.4	5.61E-05	0.77
7	rs7787531	128810833	C/T	0.29	1.22	1.1 - 1.4	0.0022	1.22	1.1 - 1.4	0.0013	1.22	1.1 - 1.3	8.51E-06	0.86
8	rs4873534	52350766	A/G	0.39	0.84	0.7 - 1	0.0053	0.81	0.7 - 0.9	0.0002	0.84	0.8 - 0.9	1.17E-05	0.96
8	rs16915954	52352025	G/A	0.46	0.82	0.7 - 0.9	0.0008	0.85	0.8 - 0.9	0.0026	0.84	0.8 - 0.9	1.56E-05	0.96

Supplementary Table 4 (continued)

Chromosome	rs#	Position	Alleles	MAF	Ghana			The Gambia			Ghana / The Gambia			Rsq
					OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	
8	rs7821565	52379315	T/C	0.39	0.84	0.7 - 1	0.0053	0.81	0.7 - 0.9	0.0001	0.83	0.8 - 0.9	7.80E-06	0.97
8	rs6986651	52381670	G/A	0.39	0.85	0.8 - 1	0.0058	0.81	0.7 - 0.9	0.0001	0.83	0.8 - 0.9	8.45E-06	0.97
8	rs7844531	52382184	T/A	0.39	0.85	0.8 - 1	0.0058	0.81	0.7 - 0.9	0.0001	0.83	0.8 - 0.9	8.45E-06	0.97
8	rs1837087	52389016	G/T	0.4	0.85	0.8 - 1	0.008	0.81	0.7 - 0.9	0.0002	0.84	0.8 - 0.9	1.52E-05	0.95
8	rs10110193	52389303	C/T	0.4	0.85	0.8 - 1	0.008	0.81	0.7 - 0.9	0.0002	0.84	0.8 - 0.9	1.52E-05	0.95
8	rs160441	90726108	C/T	0.41	1.24	1.1 - 1.4	0.0003	1.17	1.1 - 1.3	0.0045	1.2	1.1 - 1.3	8.41E-06	0.98
9	rs7019478	124105244	C/A	0.2	0.82	0.7 - 0.9	0.0066	0.81	0.7 - 0.9	0.0036	0.82	0.7 - 0.9	8.02E-05	1
10	rs10788068	122092412	T/C	0.17	1.26	1.1 - 1.5	0.0031	1.23	1.1 - 1.4	0.004	1.24	1.1 - 1.4	5.43E-05	0.91
11	rs7107287	13269545	T/G	0.27	0.82	0.7 - 0.9	0.0058	0.85	0.8 - 1	0.006	0.84	0.8 - 0.9	9.40E-05	0.99
12	rs11173018	58060297	G/A	0.26	0.82	0.7 - 0.9	0.0041	0.83	0.7 - 0.9	0.0031	0.82	0.7 - 0.9	1.99E-05	0.77
12	rs10877268	58062330	C/A	0.25	0.83	0.7 - 0.9	0.0063	0.84	0.7 - 1	0.0086	0.83	0.8 - 0.9	8.54E-05	0.75
12	rs10877301	58199293	A/T	0.27	0.81	0.7 - 0.9	0.0027	0.85	0.7 - 1	0.0066	0.82	0.8 - 0.9	2.58E-05	0.98
12	rs12369542	58204533	C/T	0.27	0.81	0.7 - 0.9	0.0027	0.85	0.7 - 1	0.0066	0.82	0.8 - 0.9	2.58E-05	0.98
12	rs2175950	58206649	A/G	0.27	0.81	0.7 - 0.9	0.0025	0.84	0.7 - 0.9	0.0048	0.82	0.8 - 0.9	1.79E-05	0.95
12	rs1146110	61985359	G/A	0.07	1.34	1.1 - 1.7	0.0078	1.36	1.1 - 1.7	0.0029	1.35	1.2 - 1.6	6.62E-05	0.87
13	rs1323565	75344483	A/G	0.48	0.85	0.8 - 1	0.0054	0.85	0.8 - 0.9	0.0031	0.85	0.8 - 0.9	6.56E-05	0.85
13	rs9544058	75345197	T/C	0.48	0.85	0.8 - 1	0.005	0.85	0.8 - 0.9	0.0034	0.85	0.8 - 0.9	6.65E-05	0.85
13	rs1323566	75349241	A/G	0.48	0.85	0.8 - 0.9	0.0042	0.86	0.8 - 1	0.0058	0.85	0.8 - 0.9	8.28E-05	0.89
14	rs9323270	54310799	C/A	0.49	0.84	0.7 - 0.9	0.0045	1.18	1.1 - 1.3	0.0024	0.84	0.8 - 0.9	2.69E-05	0.75
14	rs9323271	54311395	C/G	0.49	0.84	0.7 - 0.9	0.0041	1.18	1.1 - 1.3	0.0024	0.84	0.8 - 0.9	2.56E-05	0.75
14	rs12890882	68170371	T/C	0.15	1.25	1.1 - 1.5	0.0063	1.28	1.1 - 1.5	0.0017	1.25	1.1 - 1.4	6.91E-05	0.95
14	rs11624680	95096203	G/A	0.37	0.8	0.7 - 0.9	0.0003	0.85	0.8 - 1	0.0047	0.83	0.8 - 0.9	1.13E-05	0.79
14	rs8005962	95096906	C/T	0.37	0.8	0.7 - 0.9	0.0002	0.85	0.8 - 0.9	0.004	0.83	0.8 - 0.9	8.33E-06	0.79
14	rs2887395	95098967	G/A	0.42	0.84	0.7 - 0.9	0.0035	0.84	0.8 - 0.9	0.0025	0.85	0.8 - 0.9	4.57E-05	0.83
14	rs2369019	95099341	G/A	0.42	0.84	0.8 - 0.9	0.0039	0.85	0.8 - 0.9	0.0033	0.85	0.8 - 0.9	6.81E-05	0.84
14	rs7152619	95100195	C/T	0.27	0.79	0.7 - 0.9	0.0002	0.82	0.7 - 0.9	0.0035	0.8	0.7 - 0.9	1.96E-06	0.83
14	rs8014367	95100516	T/C	0.25	0.79	0.7 - 0.9	0.0002	0.81	0.7 - 0.9	0.0018	0.8	0.7 - 0.9	1.15E-06	0.81
14	rs9323929	95101710	T/C	0.25	0.79	0.7 - 0.9	0.0002	0.8	0.7 - 0.9	0.0016	0.79	0.7 - 0.9	1.07E-06	0.82
14	rs8011929	95119605	T/C	0.25	0.84	0.7 - 1	0.0084	0.81	0.7 - 0.9	0.0019	0.83	0.8 - 0.9	4.43E-05	0.76
16	rs1542421	17178445	A/G	0.2	1.24	1.1 - 1.4	0.0032	1.22	1.1 - 1.4	0.003	1.22	1.1 - 1.3	5.43E-05	0.88
16	rs7195149	17179490	G/A	0.2	1.25	1.1 - 1.4	0.0025	1.21	1.1 - 1.4	0.0037	1.22	1.1 - 1.3	5.54E-05	0.89
16	rs7197587	17179743	A/G	0.2	1.24	1.1 - 1.4	0.0029	1.22	1.1 - 1.4	0.003	1.22	1.1 - 1.3	4.95E-05	0.89
16	rs7197476	17180044	C/T	0.2	1.24	1.1 - 1.4	0.0029	1.22	1.1 - 1.4	0.0027	1.22	1.1 - 1.3	4.46E-05	0.89
16	rs7198185	17180061	A/G	0.2	1.24	1.1 - 1.4	0.0029	1.22	1.1 - 1.4	0.003	1.22	1.1 - 1.3	5.05E-05	0.89

Supplementary Table 4 (continued)

Chromosome	rs#	Position	Alleles	MAF	The Ghana			The Gambia			Ghana / The Gambia			Rsq
					OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	
16	rs7198350	17180132	A/T	0.2	1.25	1.1 - 1.4	0.0026	1.22	1.1 - 1.4	0.003	1.22	1.1 - 1.3	4.64E-05	0.89
16	rs7205152	17183562	T/C	0.11	1.38	1.2 - 1.7	0.0004	1.26	1.1 - 1.5	0.0071	1.31	1.2 - 1.5	2.33E-05	0.83
16	rs11863514	17184792	G/A	0.29	1.2	1.1 - 1.4	0.0054	1.21	1.1 - 1.4	0.002	1.2	1.1 - 1.3	5.10E-05	0.76
16	rs1948632	74548947	G/A	0.04	1.64	1.2 - 2.2	0.0006	1.48	1.1 - 1.9	0.0028	1.55	1.3 - 1.9	7.53E-06	0.92
16	rs7196289	74552000	A/G	0.04	1.62	1.2 - 2.2	0.0008	1.48	1.1 - 1.9	0.0028	1.54	1.3 - 1.9	9.17E-06	0.93
16	rs904264	74569388	C/T	0.05	1.5	1.1 - 2	0.0046	1.48	1.2 - 1.9	0.0013	1.5	1.3 - 1.8	1.14E-05	0.96
16	rs904263	74569690	A/G	0.04	1.57	1.2 - 2.1	0.0037	1.41	1.1 - 1.8	0.0061	1.48	1.2 - 1.8	5.43E-05	0.94
16	rs7191424	74576951	T/G	0.05	1.49	1.1 - 2	0.0047	1.48	1.2 - 1.9	0.0013	1.5	1.3 - 1.8	1.14E-05	0.97
16	rs7184868	74577088	G/C	0.05	1.49	1.1 - 2	0.0047	1.48	1.2 - 1.9	0.0013	1.5	1.3 - 1.8	1.14E-05	0.97
16	rs12386026	81375092	T/C	0.04	1.59	1.2 - 2	0.0003	1.75	1.2 - 2.6	0.0047	1.66	1.3 - 2	2.32E-06	0.77
17	rs8082190	32822980	T/C	0.05	1.53	1.2 - 2	0.0034	1.36	1.1 - 1.7	0.0068	1.44	1.2 - 1.7	5.16E-05	0.94
17	rs712039	32924666	C/T	0.49	1.21	1.1 - 1.4	0.001	0.85	0.8 - 0.9	0.0024	1.21	1.1 - 1.3	3.30E-06	0.9
17	rs16976206	66243685	C/T	0.35	0.83	0.7 - 0.9	0.0019	0.85	0.8 - 1	0.0053	0.84	0.8 - 0.9	2.15E-05	0.89
18	rs11874936	18457951	C/T	0.43	1.21	1.1 - 1.4	0.0012	1.17	1 - 1.3	0.0057	1.19	1.1 - 1.3	1.61E-05	0.96
18	rs4257308	56260170	C/T	0.04	1.7	1.2 - 2.3	0.0009	1.45	1.1 - 1.8	0.0022	1.55	1.3 - 1.9	5.56E-06	0.8
18	rs7236588	56261863	T/C	0.04	1.7	1.2 - 2.4	0.0031	1.49	1.2 - 1.9	0.0018	1.58	1.3 - 1.9	1.36E-05	0.99
18	rs12970649	65756787	C/T	0.43	0.85	0.8 - 1	0.0068	0.83	0.7 - 0.9	0.0007	0.84	0.8 - 0.9	1.87E-05	0.97
19	rs1434579	49624812	T/C	0.06	1.41	1.1 - 1.8	0.0045	1.52	1.2 - 1.9	0.0003	1.46	1.2 - 1.7	4.33E-06	0.94

Association results were filtered for those SNPs having a P value of < 0.01 in both studies and an imputation quality score of R-squared >= 0.7 as calculated by the MACH software. rs#, reference SNP number; Position, chromosomal position (bp); MAF, minor allele frequency of the combined Ghanaian and Gambian data set; OR, odds ratio; CI, 95% confidence interval; Rsq, R-squared imputation quality value computed by the MACH software; P, P values calculated using logistic regression analysis adjusted by the first 3 MDS components for each, the Ghanaian and the Gambian study, and the first 6 MDS components for the combined data set.

Supplementary Table 5. Associations of the best SNPs in the present combined GWA studies of candidate genes previously found to associate with TB.

Chr	Gene	Size (kb)	No of SNPs	Best SNP ID	OR	95%CI	*P*-value
1	*IL10*	4.9	21	rs3024505	1.23	1.00-1.51	0.052
2	*NRAMP1*	14.9	5	rs11904786	1.18	0.96-1.44	0.119
3	*PTX3*	6.8	19	rs1014855	1.12	1.01-1.24	0.025
4	*TLR2*	21.8	19	rs10517578	1.19	0.98-1.44	0.082
5	*IL12B*	15.7	21	rs6874870	1.23	0.97-1.56	0.094
6	*HLA-DQA1*	6.2	9	rs9469220	1.15	1.05-1.25	0.002
6	*HLA-DRB1*	11.0	5	rs9272346	1.10	1.01-1.19	0.022
6	*IFNGR1*	21.9	17	rs9373180	1.57	1.16-2.13	0.004
6	*TNF*	2.9	5	rs1052248	0.96	0.87-1.06	0.401
10	*MBL2*	6.3	32	rs12573117	1.18	1.04-1.35	0.013
12	*IFNG*	5.0	29	rs2193047	1.09	1.00-1.18	0.038
12	*VDR*	63.5	23	rs11168312	0.86	0.72-1.02	0.082
15	*UBE3A*	101.7	27	rs7169070	1.12	0.96-1.30	0.158
16	*NOD2*	35.9	16	rs2066849	1.07	0.99-1.16	0.077
17	*CCL18*	7.2	20	rs1614133	1.11	1.02-1.19	0.012
17	*MCP1*	1.9	19	rs3917891	0.90	0.81-1.00	0.047
17	*CCL4*	1.8	11	rs1614133	1.11	1.02-1.19	0.012
17	*NOS2A*	43.8	12	rs3729508	0.90	0.81-1.00	0.042
17	*STAT5B*	77.2	7	rs9912576	1.05	0.96-1.14	0.283
19	*CD209*	7.5	10	rs11260030	0.93	0.84-1.03	0.164
19	*IL12RB1*	27.3	4	rs7255589	0.92	0.85-1.01	0.071
20	*MC3R*	1.1	35	rs6014657	0.88	0.79-0.97	0.012

Chr, chromosome; rs#, reference SNP number; OR, odds ratio; CI, confidence interval; P, uncorrected P values of the combined Ghanaian and Gambian association analysis using logistic regression tests.

Supplementary Methods

Ghanaian study group and population structure

TB patients were consecutively enrolled in Ghana, West Africa, between September 2001 and July 2004 at Korle Bu Teaching Hospital in Accra, Komfo Anokye Teaching Hospital in Kumasi, and at additional 15 hospitals and polyclinics in Accra and Kumasi and at regional district hospitals. The case group consisted of 2147 individuals with a median age of 32 years and a proportion of males of 66.7%. Phenotyping of patients included medical histories and documentation of major symptoms on structured questionnaires, physical examination, HIV-1/2 testing (Capillus, Trinity Biotech, Bray, Co Wicklow, Ireland), posterior-anterior chest X-rays, Ziehl-Neelsen staining of two independent sputum smears, and culturing of *M. tuberculosis* complex isolates on solid Loewenstein-Jensen medium. Cases were HIV-negative and had characteristic radiological lesions of pulmonary TB. All patients were treated in the framework of the DOTS programme (Directly Observed Treatment Short-Course strategy) organized by the Ghanaian National Tuberculosis Programme.

Out of 5565 control individuals that were included in the present study, 3551 were part of the primary Ghanaian TB study. Of those, 2546 persons were characterized by a medical history and clinical examination as well as posterior-anterior chest X-rays. An additional 1005 clinically healthy control individuals were phenotyped by medical history and clinical examination only. The age range of the 5565 control individuals was 5-76 years, with a median age of 28 years and a male proportion of 51.3%. An additional 2014 Ghanaian population controls were part of a control group recruited for a malaria association study in the Kumasi region. All individuals belonging to this group were children with a median age of 20 month and a proportion of males of 52.7%. Children of this group were healthy as assessed by physical examination.

To validate significant association results, 332 parent child trios/duos were collected for family based association tests. All affected children that were part of this group were added to the Ghanaian case group.

Study participants belonged to the ethnic groups of Akan, Ga-Adangbe, Ewe and several other ethnic groups from northern Ghana (Dagomba, Sissala, Gonja, and Kusasi; herein denoted as Northerners). The study protocol was approved by the Committee on Human Research, Publications and Ethics, School of Medical Sciences, Kwame Nkrumah University of Science

and Technology, Kumasi, Ghana, and the Ethics Committee of the Ghana Health Service, Accra, Ghana. Venous blood samples were taken only after a detailed explanation of the aims of the study, and consent was obtained of individuals enrolled or their parents/guardians by signature or by thumbprint in case of illiteracy.

Ghana GWA study; genotyping

DNA was isolated from venous blood samples of study participants (AGOWA® mag Maxi DNA Isolation Kit, Macherey & Nagel, Germany) according to the manufacturer´s instructions. Genotyping was performed with the Affymetrix SNP 6.0 array at Affymetrix Services Laboratory (South San Francisco, CA 9408, USA) and ATLAS Biolabs GmbH (10117, Berlin, Germany). The genotype calling algorithm Birdseed (software v2) was applied on all samples.

Ghana GWA study; quality control

All CEL files were subjected to a contrast QC analysis that judges the ability of an experiment to resolve SNP signals and assign them to the three genotype clusters. Fifteen samples yielded a contrast QC value below the recommended threshold of 0.4 for the Affymetrix SNP 6.0 array and were excluded from further analyses. Comparing annotated with computed sex identified 56 individuals with discordant results and results of these samples were removed from the data set. Eleven samples with an autosomal heterozygosity rate > 32% or a genome-wide autosomal genotype missing fraction of > 5% were excluded from further analysis.
Genetic outliers were eliminated by the nearest neighbour allele sharing algorithm of PLINK. A total of 49 individuals with $Z < -3$ and 5 subjects with $Z > 1$ were excluded from further analysis. Only one subject of related individuals was kept in the analyses (proportion of identity by descent ≤ 0.125). Two-hundred-sixty individuals of related pairs with the higher SNP missing frequencies were excluded. In total, 376 individuals were excluded from the data set resulting in 921 cases and 1740 controls.

The Gambian WTCCC GWA study; genotyping

DNA for this study was whole-genome amplified using the GenomiPhi (GE Healthcare) technology by Geneservice (Cambridge, U.K.). Genotyping was performed with the Affymetrix GeneChip 500K arrays at the Affymetrix Services Laboratory (South San Francisco, CA 9408, USA). The CHIAMO algorithm was used for genotying calling, which uses a Bayesian hierarchical four-class mixture model to call genotypes for all samples simultaneously. *A posteriori* estimates of the probability of the AA, AB and BB genotypes are calculated, together with a fourth, null genotype class. All CHIAMO genotypes analysed here were based on an *a posteriori* call probability threshold of 90%, which resulted in a discordance rate of 0.48 in this study, based on almost 50 million duplicate genotypes.

The Gambian WTCCC GWA study; quality control

Of samples for which Affymetrix returned CEL files, a total of 396 samples were excluded from analysis. QC filters for call rate and heterozygosity were established via visual inspection of the sample genotype calls. A set of 202 samples were removed due to genome-wide call rates less than 92.5%. One sample with autosomal heterozygosity of less than 23% was removed from the analysis, together with six samples with autosomal heterozygosity greater than 32%. 'Identity-by-state' (IBS) between each pair of samples can be used to identify duplicates and related individuals. A total of 122 pairs of samples had IBS > 98% across 100,715 uncorrelated autosomal SNPs, and were taken here to be duplicates. For each pair, the sample with the lowest call rate was removed from the analysis. A further 54 pairs of samples had IBS > 85%, noticeably higher than would be expected between unrelated individuals. Again, the sample from each pair with the lowest call rate was removed from the analysis. Finally, IBS was also calculated between each sample from this study and 270 individuals from the International HapMap project. The IBS relationships were converted to distances, and projected onto two axes of multi-dimensional scaling. Based on this projection, 5 samples were removed from the analysis as a result of outlying ancestry.

Supplementary Methods. *Study populations; GWA and replication studies*

	Ghana	**The Gambia**	**Malawi**	**Total**
Scan cases	921	1316		2237
Scan controls	1740	1382		3122
Replication I cases	1076			1076
Replication I controls	1611			1611
Replication II cases	150		236	386
Replication II controls	2214		779	2993

The scan genotyping platforms where Affymetrix SNP Array 6.0 (Ghana) and Affymetrix GeneChip 500k (The Gambia). Replication study genotyping platform was LightTyper for Ghanaian samples and Sequenom for The Gambian and Malawian samples. In total 11,425 samples were included in this study.

Supplementary Methods: *Number of GWAS TB cases and controls; Ghanaian and Gambian ethnic groups.*

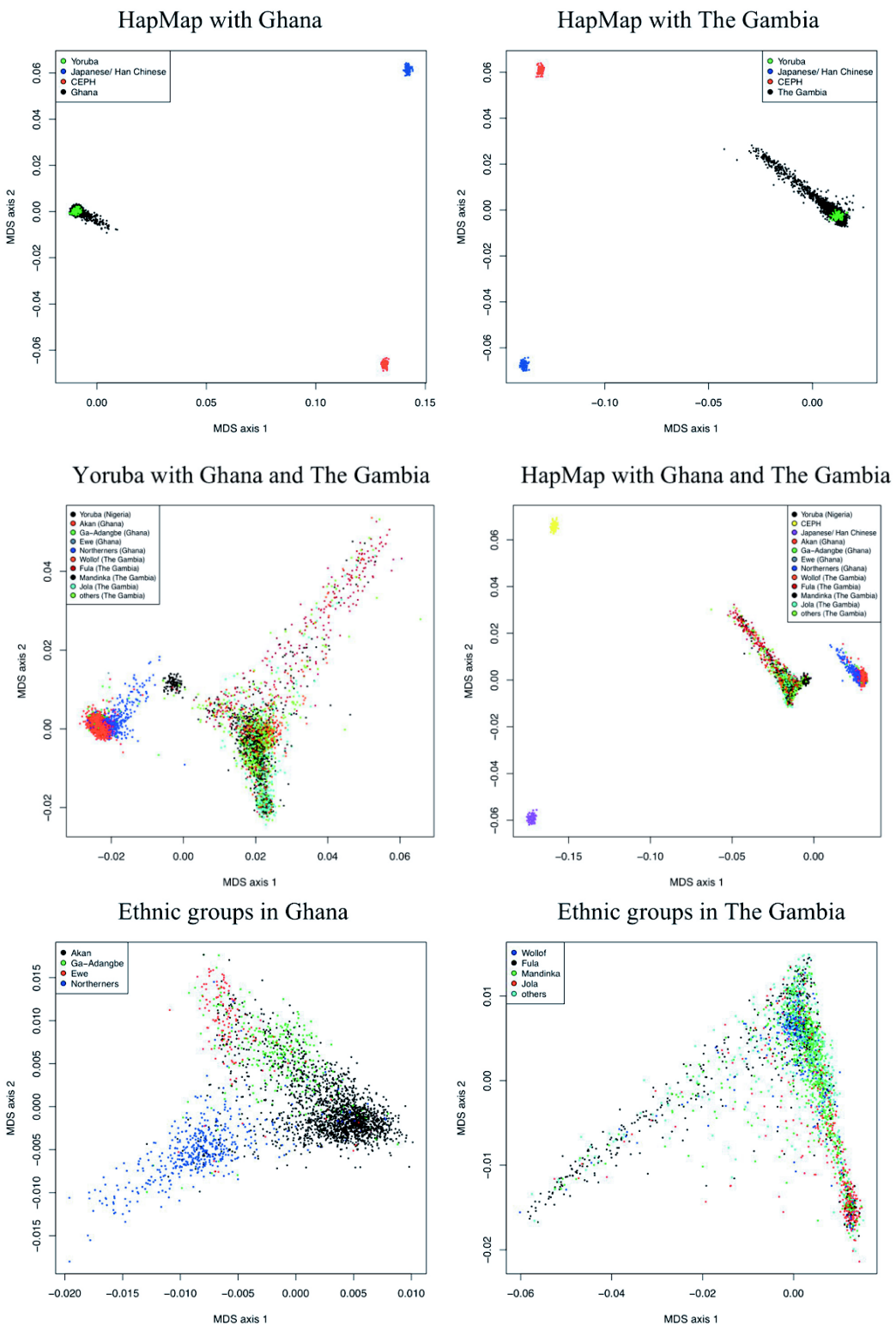
		TB-cases N	Controls N
Ghana	Akan	620	1158
	Ga-Adangbe	132	155
	Ewe	58	78
	Northerners	111	349
The Gambia	Wolloff	190	274
	Jola	190	264
	Fulani	434	424
	Mandinka	411	187
	Yoruba	91	233

The Gambia population structure

IBS between each pair of samples was calculated across 100,715 uncorrelated autosomal SNPs passing QC filters. The IBS relationships were converted to distances and projected onto multi-dimensional scaling axes. The first three of these axes distinguish the four most common ethnic groups in the study and thus provide a basis for accounting for underlying population structure in the subsequent association analyses.

Malawian study group

The population, basic field methods, and TB case finding and diagnostic procedures of the Karonga Prevention Study (Malawi study) have been described in detail elsewhere[1-3]. TB cases recruited into the study were ascertained largely by passive self-reporting at health centers. A small proportion of cases were identified in the context of other studies. Sputum samples and lymph node aspirates were examined (fluorescence and Ziehl-Neelsen stain) and cultured at project headquarters in Chilumba, with species confirmation by the United Kingdom Public Health Laboratory Service Mycobacterial Reference Unit (Dulwich, U.K.). Biopsy specimens were analysed at St. Thomas' Hospital, London, U.K. Inclusion in this study required confirmation of TB by culture, smear, or histology. The study protocol was reviewed and approved by the National Health Sciences Research Committee of Malawi and by the Ethics Committee of the London School of Hygiene and Tropical Medicine.

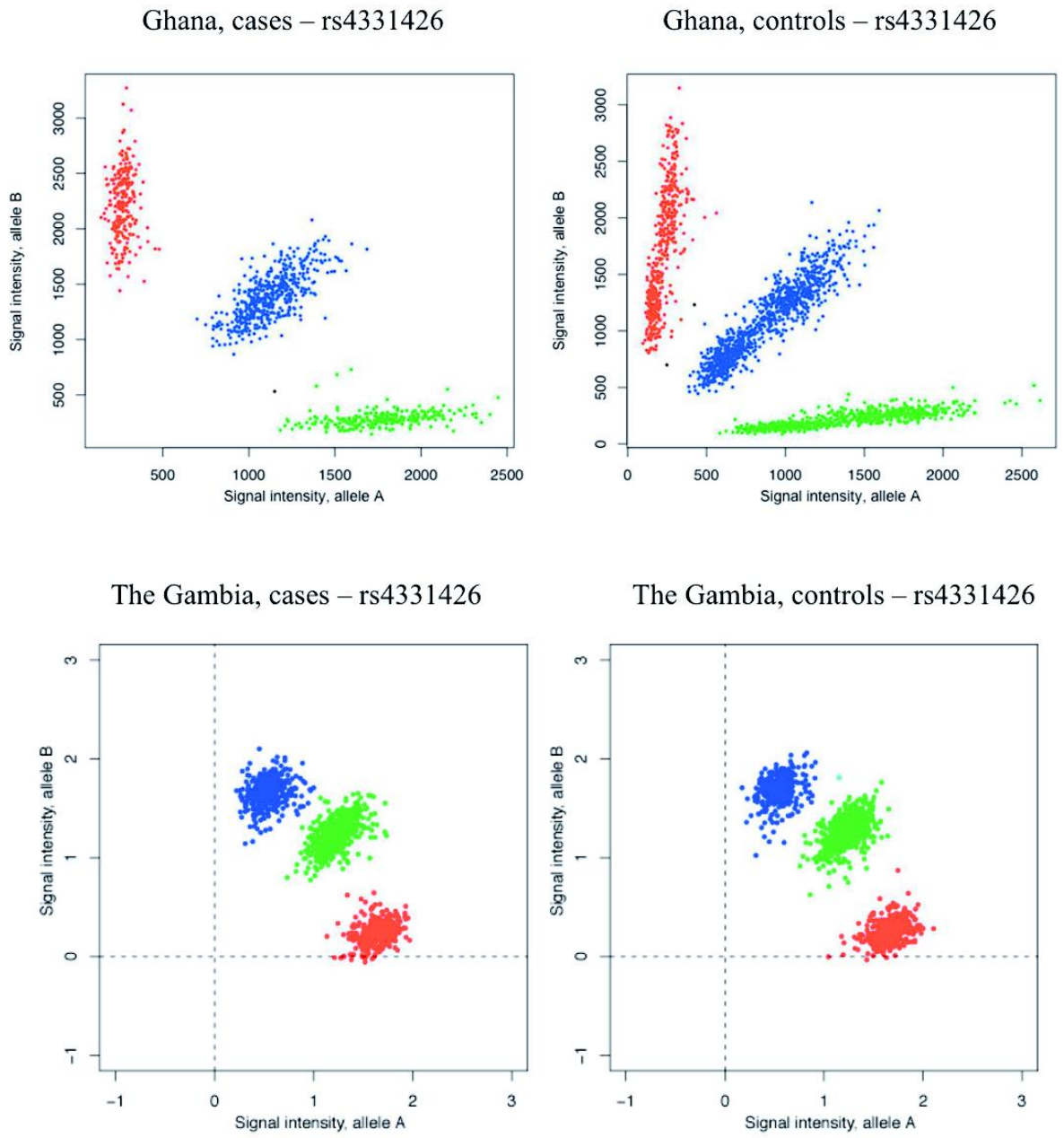


Supplementary Methods: *MDS plots of GWA study samples from Ghana and The Gambia. First panel; Multi-dimensional scaling (MDS) plots of GWA study samples from the Ghanaian,*

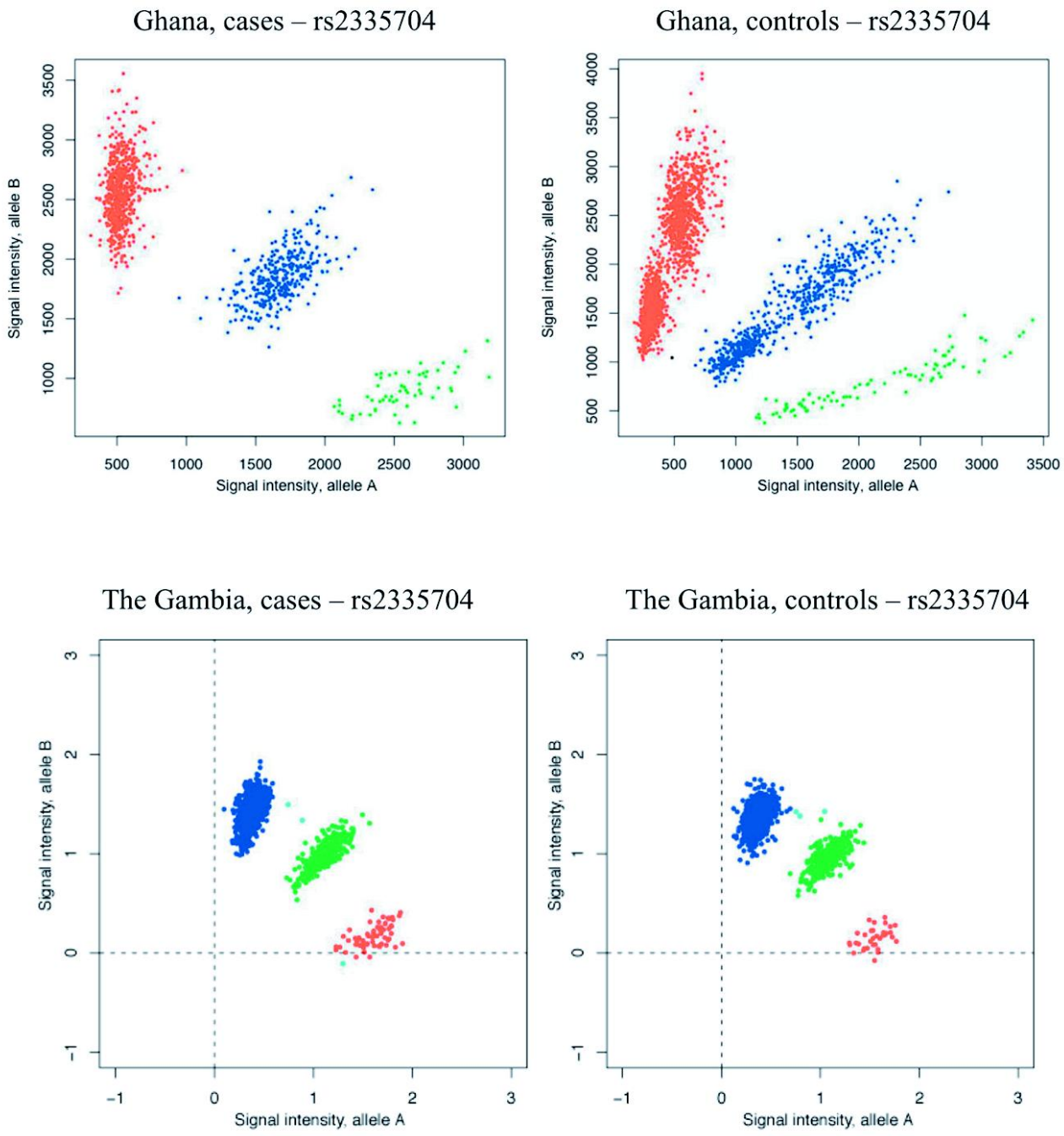
The Gambian and HapMap populations. Second panel; Multi-dimensional scaling (MDS) plots of GWA study samples from Ghana and The Gambia, plotted with the HapMap samples; Third panel; MDS plot stratified according to self-reported ethnic groups

SNP quality control of the Ghanaian and Gambian GWA study groups

Quality metrics were applied for SNPs of both studies equally. SNPs of the Ghanaian and Gambian study groups with minor allele frequencies (MAF) < 1% and deviation from Hardy Weinberg Equilibrium (HWE) as defined by a P value $<10^{-4}$ were removed from the combined and separated data sets. In addition, a SNP-wise genotyping rate <98% was applied. From all SNPs that met these criteria and yielded association signals of $< 10^{-5}$ in the combined analysis, signal intensity plots were visually inspected to exclude SNPs with ambiguous or erroneous calling results.



Supplementary Methods: *Cluster plots from the microarray genotyping of the Ghanaian and The Gambian samples for SNP rs4331426.*



Supplementary Methods: *Cluster plots from the microarray genotyping of the Ghanaian and Gambian samples for SNP rs2335704.*

Sequenom genotyping

Genotyping of the Malawi population was performed using the Sequenom system (Sequenom, San Diego, CA 92121-1331, USA) which uses mass spectrometry (MALDI-TOF) to discriminate products by their absolute masses. Genotyping was performed out at the Wellcome Trust Centre for Human Genetics Core Facility (Oxford, UK). Primer extension was carried out utilising a DNA primer adjacent to the SNP, and a specific reaction mix of polymerase, dNTPs and one ddNTP. Samples were analysed by MALDI-TOF mass spectrometry and the alleles were called by weight (in daltons) of the extension products.

LightTyper genotyping

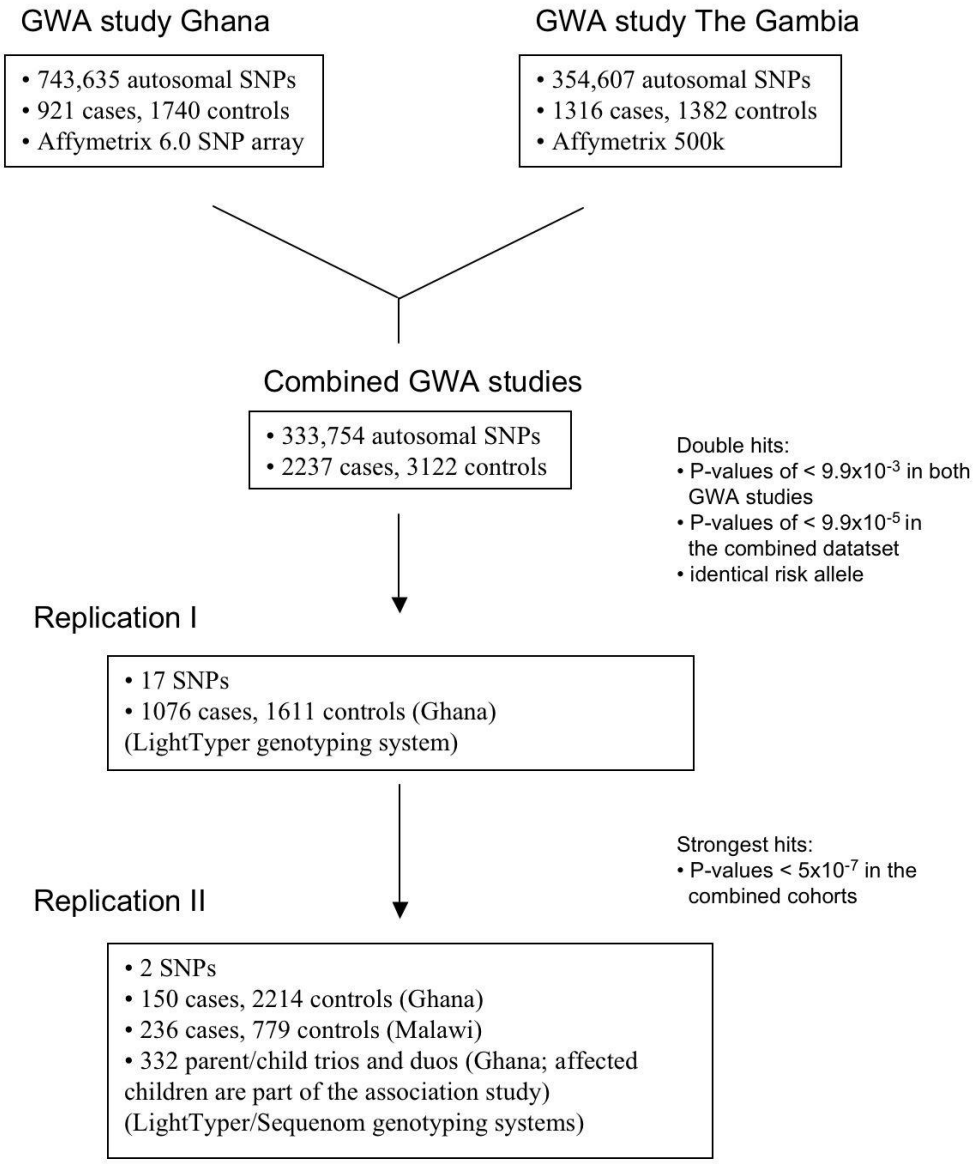
Genotyping of variants in the replication studies and, for confirmation, re-genotyping of the hit SNPs rs4331426 and rs2335704 in all samples was performed by dynamic allele specific hybridization with fluorescence resonance energy transfer (FRET) in a LightTyper device (Roche Diagnostics, Mannheim, Germany).

Statistical Analysis

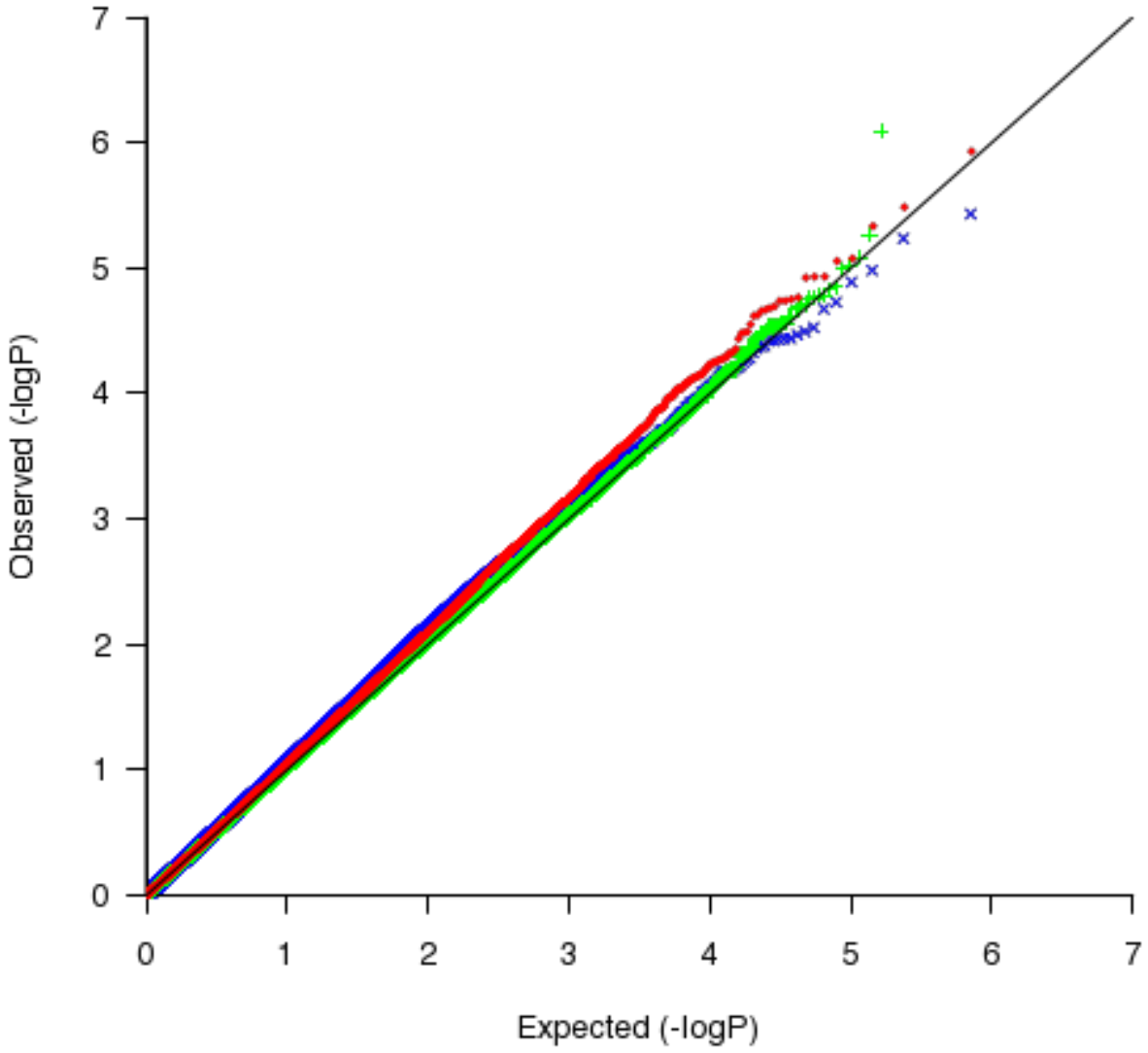
Association analyses

Logistic regression analyses were performed to assess association of autosomal SNP genotypes with the disease status in Ghanaian and Gambian GWA study samples using PLINK v1.06. To control for population stratification, we inferred continuous axes of genetic variation by multidimensional scaling (MDS) and used them as covariates in logistic regression analyses. As strong linkage disequilibria (LD) may bias correct identification of MDS axes, a pruned set of SNPs were generated by removing one SNP of a pair with LD values (R2) > 0.2 within a window of 1500 SNPs and by discarding SNPs of 4 chromosomal regions with known strong LD (chr8:8000000..12000000, chr6:25000000..33500000, chr11:45000000..57000000, chr5:44000000..51500000). We applied the top six MDS coordinates in logistic regression analyses on the combined GWA studies and the top three MDS coordinates on each study

separately. Criteria for Replication I were P-values < $9.9x10^{-3}$ in both GWA studies data sets, P-values of the combined data set < $9.9x10^{-5}$, and identical risk alleles. SNPs fulfilling these criteria were genotyped and statistically evaluated in an additional 2687 Ghanaian replication samples (Replication I). For those SNPs where a joint P-value < $5x10^{-7}$ was determined in the combined results of the GWA studies and of Replication I, Replication II was performed in 2364 and 867 case-control samples of Ghanaian and Malawian ancestry, respectively. Statistical analyses of the replication stages and the entire data set including all 11425 samples were done by logistic regression tests adjusted for gender and ethnicity under an additive mode of inheritance and by Cochrane Mantel Haenszel analyses stratified by ethnic groups. For each SNP that yielded significant replication results, Breslow Day statistics were performed to test for heterogeneity of genetic effects across ethnic groups. To assess the amount of between-study heterogeneity, the I-squared statistic was calculated with odds ratios and standard errors derived from the logistic regression analysis applying a fixed effect model. All statistical analyses on replication data were performed using STATA 10.0 (Stata Corporation, College Station, TX, USA). A likelihood based approach for association analyses of nuclear families implemented in the software UNPHASED v3.1.3 was applied on genotype data of the 332 Ghanaian parent child duos and trios in order to detect allelic transmission distortion in those SNPs that yielded significant association results.



Supplementary Methods: *Study design heuristic of the combined analysis of the Ghanaian and Gambian GWA studies and the replication studies.*



Supplementary Methods: *Quantile-quantile plot of the Ghanaian (green, lambda factor λ = 1.02), the Gambian (blue, λ = 1.07) and the combined GWA studies (red, λ = 1.05); association statistics corrected for the first three (Ghana, The Gambia) or six (combined studies) multidimensional scaling components.*

Imputation and fine mapping experiments

In order to identify additional associated SNPs close to the hits on chromosomes 2 and 18 (rs2335704, rs4331426) and on a genome-wide scale, we imputed SNPs of the Yoruban (YRI) HapMap reference sample (release 22) into the combined Ghanaian and Gambian data set. Imputation accuracy of the West African populations was assessed by masking 2% of the actual Ghanaian and Gambian genotypes for all chromosomes and the hidden genotypes were then re-imputed based on the YRI reference panel. We performed genome wide imputation analyses, applying stringent criteria for selecting only those imputed SNPs with high quality score (Rsq > 0.7) for further association analyses, as the mean imputation genotype error rate across all chromosomes for the combined Ghanaian and Gambian sample were 8.2%.

SNPs were selected for fine typing experiments when LDs between imputed SNPs and the hit SNP were in strong LD and the imputed SNPs yielded similar association results to that of the hit SNP rs4331426. Imputation analyses were calculated with the MACH software (version 1.0.16; r^2 indicated as Rsq; http://www.sph.umich.edu/csg/abecasis/MaCH/index.html).

Fixation index

The Fixation index (Fst) was calculated on the LD pruned data set including only those SNPs having weak LDs with a SNP in 1500 kb windows ($r^2 < 0.2$). Known high LD regions were excluded as well and Fst values were computed with the EIGENSOFT software package (version 3.0; available at http://genepath.med.harvard.edu/~reich/Software.htm).

Supplementary Methods: *Pair-wise Fst values for comparisons of Ghanaian, Gambian and Yoruban (Nigeria) ethnic groups.*

	Ghana				The Gambia				Nigeria
	Akan	Ga-Adangbe	Ewe	Northerners	Wolloff	Jola	Fulani	Mandinka	Yoruba
Akan	0	0	0.001	0.001	0.006	0.007	0.006	0.005	0.004
Ga-Adangbe		0	0	0.001	0.006	0.007	0.006	0.005	0.003
Ewe			0	0.001	0.006	0.007	0.007	0.006	0.003
Northerners				0	0.004	0.005	0.005	0.004	0.003
Wolloff					0	0.001	0.001	0	0.008
Jola						0	0.002	0.001	0.009
Fulani							0	0.001	0.009
Mandinka								0	0.008
Yoruba									0

Supplementary Methods: *Pair-wise Fst values for comparisons of Ghanaian, Gambian and Yoruban (Nigeria) populations.*

	Ghana	The Gambia	Nigeria (Yoruba)
Ghana	0	0.005	0.003
The Gambia		0	0.008
Nigeria (Yoruba)			0

Power Calculations

Power calculations were performed for the combined Ghanaian and Gambian GWA study groups with the CaTS software (http://www.sph.umich.edu/csg/abecasis/CaTS/). An additive model was assumed with a TB prevalence of 0.003, 20 % disease allele frequency, a genotype relative risk of 1.4 and *P* value level of $5x10^{-8}$. Applying the CaTS software on 2237 TB cases and 3122 controls resulted in 90% power to detect existing effects.

Supplementary References

S1. Bennett S, Lienhardt C, Bah-Sow O, Gustafson P, Manneh K, et al. (2002) Investigation of environmental and host-related risk factors for tuberculosis in Africa. II. Investigation of host genetic factors. Am J Epidemiol 155: 1074-1079.

S2. Fitness J, Floyd S, Warndorff DK, Sichali L, Malema S, et al. (2004) Large-scale candidate gene study of tuberculosis susceptibility in the Karonga district of northern Malawi. Am J Trop Med Hyg 71: 341-349.

S3. Lienhardt C, Bennett S, Del Prete G, Bah-Sow O, Newport M, et al. (2002) Investigation of environmental and host-related risk factors for tuberculosis in Africa. I. Methodological aspects of a combined design. Am J Epidemiol 155: 1066-1073.