

A Variant in *FTO* shows association with melanoma risk not due to BMI

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Supplementary Table 1 Numbers of cases and controls from each study and numbers of cases and controls with BMI data from each study.

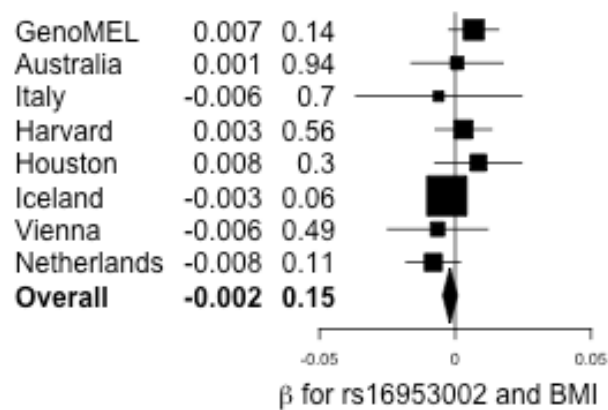
	cases	controls	cases with BMI	controls with BMI
GenoMEL Phase 1	1,353	3,566	144	1,355
GenoMEL Phase 2	1,449	4,043	466	1,541
Leeds case-control*	680	1,785	664	302
Harvard*	≥421	≥2,349	421	2,349
Australia	2,168	4,385	413	1210
Italy	537	430	143	122
Houston	1,802	1,025	929	891
Iceland	926	34,656	679	25,189
the Netherlands	729	1,651	711	1,613
Vienna	1,174	929	542	406
Milan	555	368	0	0
Sweden	1,010	499	0	0
Valencia	576	1,769	0	0
Zaragoza	287	1,778	0	0
Total	13,667	59,233	5,112	34,978

* 421 cases and 2,349 controls were genotyped for rs16953002 and 494 cases and 5,627 controls imputed for rs8050136. Leeds case-control sample genotyped for rs16953002 but not rs8050136. Case/control numbers for rs8050136 are 13,060/60,726.

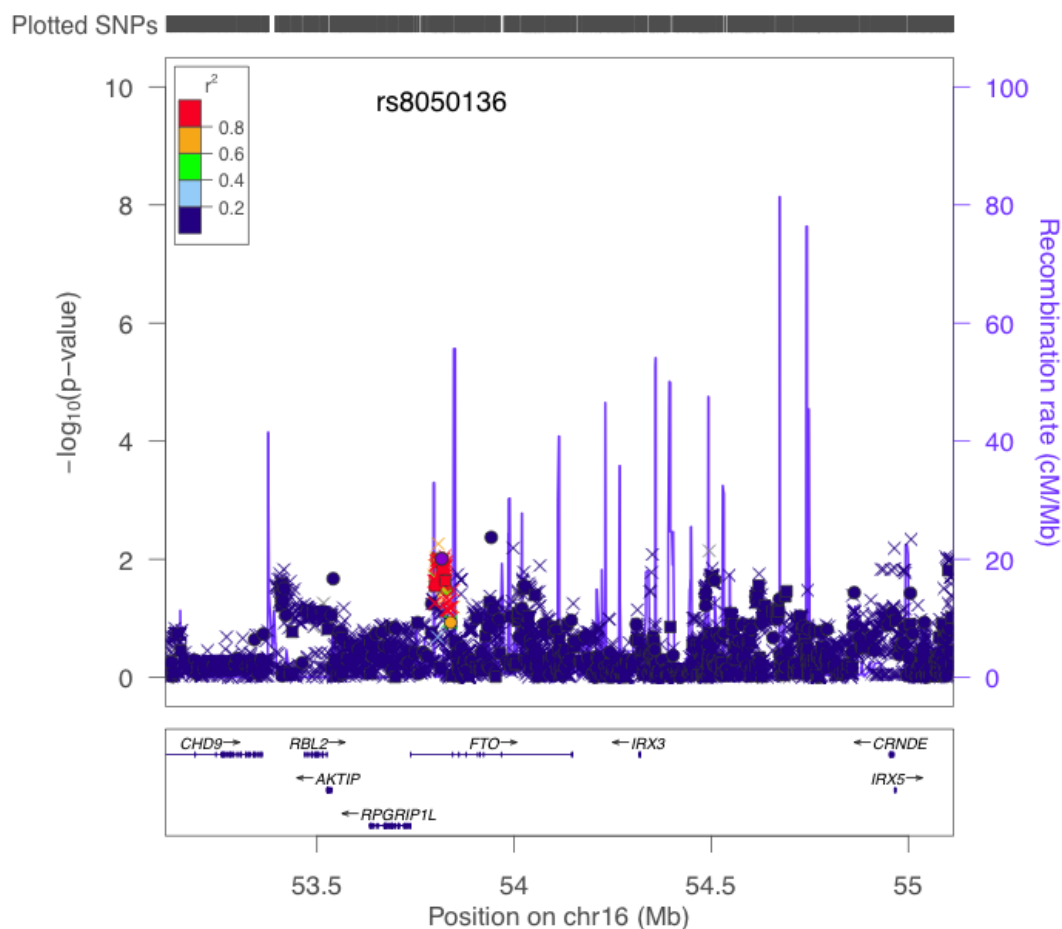
Supplementary Table 2 Results of association between rs16953002 and melanoma, including results for genotyped subjects only, those with BMI only and adjusting for BMI (split into quartiles) as a categorical covariate.

	rs16953002 and melanoma				rs16953002 and melanoma genotyped only			rs16953002 and melanoma BMI only			rs16953002 and melanoma BMI adjusted		
	MAF	No of cases/controls	OR (95% CI)	P	No of cases/controls	OR (95% CI)	P	No of cases/controls	OR (95% CI)	P	No of cases/controls	OR (95% CI)	P
GenoMEL Phase I	0.16	1,353 / 3,566	1.32 (1.17,1.50)	1.3×10 ⁻⁵	687 / 3,461	1.28 (1.09,1.51)	0.003	144 / 1,355	1.16 (1.03,1.31)	0.02	144 / 1,355	1.16 (1.03,1.31)	0.02
All replicates	0.17	12,314 / 55,667	1.14 (1.09,1.19)	4.8×10 ⁻⁹	12,314 / 55,667	1.14 (1.09,1.19)	4.8×10 ⁻⁹	4,968 / 33,623	1.09 (1.02,1.17)	0.02	4,968 / 33,623	1.06 (0.99,1.13)	0.08
Overall	0.17	13,667 / 59,233	1.16 (1.11,1.20)	3.6×10 ⁻¹²	13,001 / 59,128	1.15 (1.10,1.19)	1.48×10 ⁻¹⁰	5,112 / 34,978	1.11 (1.04,1.18)	0.001	5,112 / 34,978	1.08 (1.02,1.14)	0.01

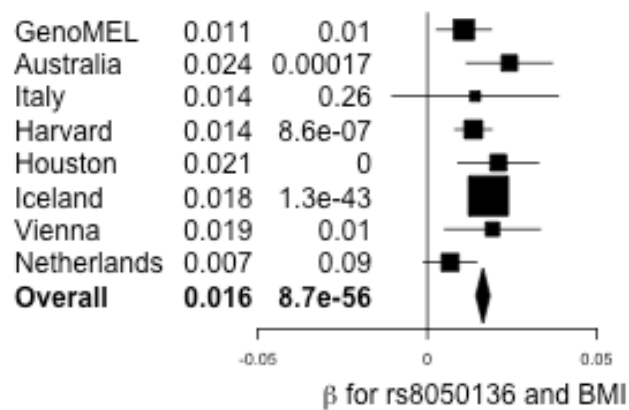
Supplementary Figures



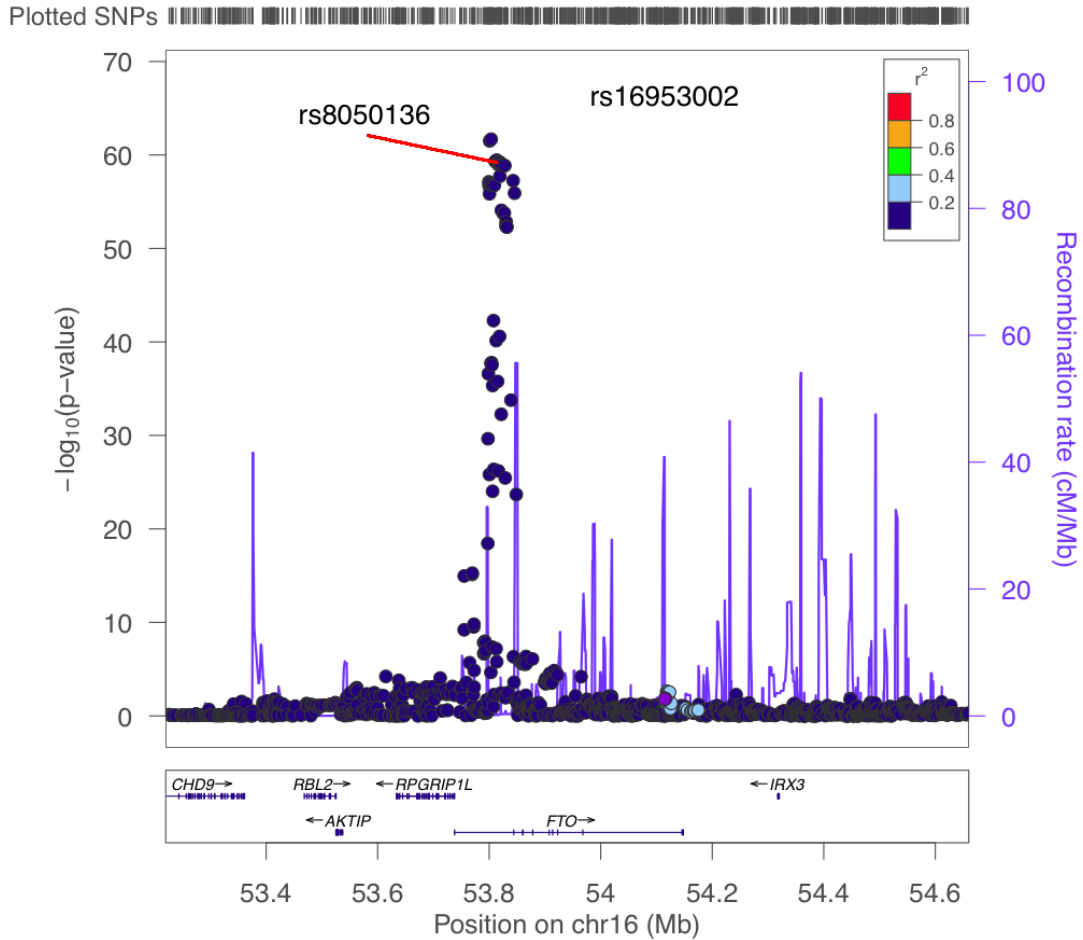
Supplementary Figure 1 Forest plot of estimated beta coefficients and p-values for effect of rs16953002 [A] on log adjusted BMI. Horizontal bars indicate 95% confidence intervals. Results shown for combined GenoMEL Phase 1, Phase 2 and Leeds cohort data combined (GenoMEL) followed by subsequent non-UK replication data and meta-analysis for all data combined.



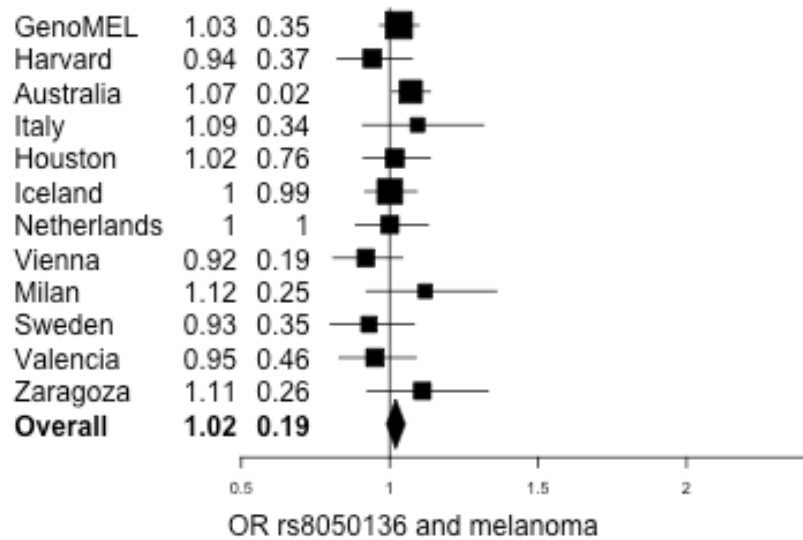
Supplementary Figure 2 Results of stratified trend tests of imputed data for association with BMI in region around *FTO* in GenoMEL Phase 1 and 2 data combined. $-\log_{10}p$ values for association between SNPs in the region of *FTO* and $\log(\text{BMI})$ (adjusted for age and age^2) with sex and case-control status as covariates are shown adjusted for geographic region. Colour of points indicates degree of LD with rs8050136 (indicated by purple circle) the most strongly-associated genotyped SNP. SNPs genotyped in all GenoMEL samples are plotted as circles, SNPs imputed in all samples as crosses and SNPs genotyped in some samples and imputed in others (as a result of chip differences) as squares. Positions of genes are given underneath the graph and estimated recombination rates also given by the blue line along the bottom, with scale on the right hand axis. Plot produced using LocusZoom¹.



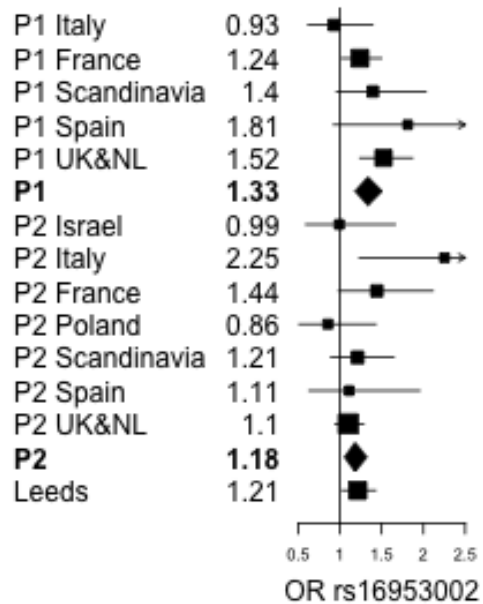
Supplementary Figure 3 Forest plot of estimated beta coefficients and p-values for effect of rs8050136 on log adjusted BMI. Horizontal bars indicate 95% confidence intervals. Results shown for combined GenoMEL Phase 1, Phase 2 and Leeds cohort data combined (GenoMEL) followed by subsequent non-UK replication data and meta-analysis for all data combined.



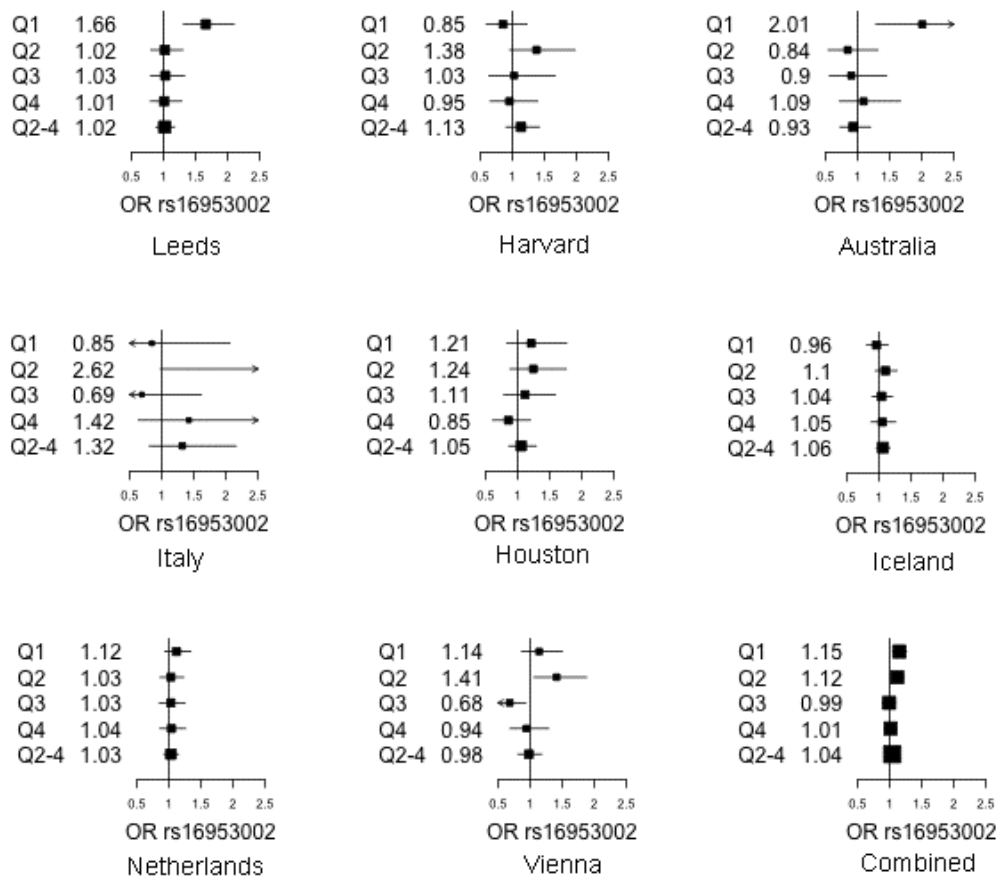
Supplementary Figure 4 Association between SNPs in FTO region and BMI in GIANT data². $-\log_{10}P$ values for association between SNPs in the region and BMI. Colour of points indicates degree of LD with rs16953002 (indicated by purple circle) the most strongly melanoma-associated genotyped SNP. rs8050136 indicated by red line. Positions of genes are given underneath the graph and estimated recombination rates also given by the blue line along the bottom, with scale on the right hand axis. Plot produced using LocusZoom¹.



Supplementary Figure 5 Forest plot of estimated per-allele ORs and p-values for effect of rs8050136 on melanoma risk. Horizontal bars indicate 95% confidence intervals. Results shown for combined GenoMEL Phase 1, Phase 2 and Leeds cohort data combined (GenoMEL) followed by subsequent non-UK replication data and meta-analysis for all data combined.



Supplementary Figure 6 Forest plot for original GenoMEL data split by region (Italy, France, Scandinavia, Spain, UK&NL (UK and Netherlands), Israel and Poland) and Phase (P1 - Phase 1, P2 - Phase 2). Estimated per-allele ORs given for each region as well as combined in a meta analysis for the Phase 1 and Phase 2 data. Horizontal bars indicate 95% confidence intervals.



Supplementary Figure 7 Forest plot of estimated per-allele ORs and p-values for effect of rs16953002 on melanoma risk within each quartile of BMI and quartiles 2-4 combined. Horizontal bars indicate 95% confidence intervals. Results plotted separately for each data set followed by results for a meta-analysis of all data sets by quartile.

Supplementary Note

Supplementary analyses and results

Analysis only of genotyped data

We have established that the imputation of rs16953002 is of high quality, given the strong concordance we see between the genotypes and their imputed predictions in the 3,694 GenoMEL samples (see main paper). However, to be certain, we have also analysed just those data that have been genotyped at rs16953002. This excludes about half of the cases in the GenoMEL Phase I data. When we do this we see that the estimated effect size is very slightly (but not significantly) reduced and the association is somewhat less significant overall (increasing from 3.6×10^{-12} to 1.48×10^{-10}) as might be expected when the sample size is thus reduced (see Supplementary Table 2).

We further reanalysed both the association between rs16953002 and melanoma and between rs8050136 and melanoma, using only samples that were genotyped for both SNPs. In addition to the Phase I GenoMEL samples that were removed, we also excluded the Leeds case-control samples and the Harvard samples, neither of which were genotyped at rs8050136. This results in an overall 13% reduction in cases compared to the initial analysis of rs16953002 and a 7% reduction in controls. The effect size of the association between rs16953002 and melanoma is reduced, but not significantly (OR=1.16 95%CI:(1.11,1.21)) and the p-value sees a further moderate increase to 3.1×10^{-9} . Similarly rs8050136 has a virtually unchanged effect size on melanoma risk (OR=1.03 95%CI:(0.99,1.06)) with, once again, a non-significant p-value of 0.12.

Analysis only of data with BMI information

The GIANT data² in particular establish beyond reasonable doubt that while rs8050136 is very strongly associated with BMI, there is no strong association between rs16953002 and BMI. However our own data have far smaller numbers of individuals with BMI recorded. For comparison we look at the association between rs16953002 and melanoma only in those individuals with BMI recorded. The results of this can be seen in Supplementary Table 2.

Despite losing 63% of cases and 40% of controls by excluding those without BMI, we find that the association between between rs16953002 and melanoma risk persists although, with $p=0.001$, no longer reaches genome-wide significance, perhaps not surprisingly.

When we include BMI itself as a categorical covariate (with categories based on quartiles) the association remains nominally significant at $p=0.01$. In GenoMEL genome-wide genotyped subjects were preferentially selected to have either family history, multiple primaries or early onset. Those with BMI recorded are largely from the Leeds case-control study, most of whom do not have any of the preferential characteristics listed above. It has previously been observed^{3,4} that those with family history and, to a lesser extent, those with multiple primaries have a larger estimated

effect size at disease-associated loci, as might be expected given their genetic enhancement. Thus when we see here that in the GenoMEL samples the estimated effect size is lower in those with BMI, this is most likely due to the lack of any genetic enhancement in those subjects with BMI recorded.

It was also noted in the Icelandic samples that those with BMI information had a significantly lower effect size for the association with melanoma than did those without BMI recorded. This was due to a lower risk allele frequency in cases with BMI information than in cases without BMI information. No difference in allele frequency was observed between controls with and without BMI information. It was noticed that cases with BMI information were more likely to be male and have an earlier age at onset, which may explain the difference observed.

Functional evidence

SNPs overlapping regulatory elements, such as transcription factor binding sites can be identified using the recent ENCODE data as well other data sources^{5,6}. The score is based on the data types available at that coordinate. So a score of 2a requires TF binding + matched TF motif + matched DNase Footprint + DNase peak. To score more highly than this requires supporting eQTL data. Looking up the *FTO* gene (at RegulomeDB, <http://RegulomeDB.org/>), 2,148 SNPs are identified, only 8 of which reach the highest score possible without eQTL data (score 2a - “Likely to affect binding”). The 8 SNPs are rs7186637, rs73612011, rs16952525, rs75390518, rs77931547, rs79028504, rs116959378 and rs16953002.

Six of these are in intron 1, the location of most of the BMI-associated SNPs, 5 of these in a 5.4kb region less than 1kb from rs8050136. The other two SNPs are 13kb apart from one another in intron 8 and, interestingly, one of these is rs16953002, the melanoma-associated SNP (see Supplementary material for further details).

The region surrounding rs16953002 that scores 2a is only 26bp long (54114807-54114833). DNase footprinting indicates that rs16953002 overlaps a potential AR binding site in multiple cell types. 24 unique proteins bind to the rs16953002 region in a variety of cells. 10 of these are in the *FOXA1* pathway (of a total of 43 in the genome, hypergeometric test $p=3\times 10^{-15}$) and 10 are in the *SMAD2/3* pathway (of a total of 81 in the genome, hypergeometric test $p=2.8\times 10^{-12}$) (from ToppGene⁷ <http://toppgene.cchmc.org/>), suggesting possible hypotheses for further functional analysis.

Replication samples

Australia

The combined 2,168 cases represents 1,619 collected through the Queensland study of Melanoma: Environment and Genetic Associations (Q-MEGA)⁸ and 549 cases collected by the Australian Melanoma Family Study (AMFS)⁹. The combined 4,385 controls represent 3 control sets: 1,799 unrelated individuals from the Brisbane Adolescent Twin Study^{10,11}, 2,155 endometriosis patients recruited by The Queensland Institute of Medical Research (QIMR) from 1995 to 2002¹² and 431 controls collected by the AMFS study⁹.

Q-MEGA – Australian melanoma cases of European descent (n=1,697) were ascertained from four population-based studies of melanoma conducted between 1987 and 1995. There were two control sets. One was a sample of 1,799 unrelated individuals recruited through schools. 20% were taken from twins or siblings and 80% from the parents of participants in the Brisbane Adolescent Twin Study^{10,11}. The second control set was of 2,155 endometriosis patients recruited by The Queensland Institute of Medical Research (QIMR) from 1995 to 2002¹². AMFS - Recruitment occurred from 2001-2005 and case probands identified from population-based state cancer registries. Control probands were selected from the electoral roll and frequency-matched to cases by city, age and sex. Blood was requested from all probands. A 20ml blood sample was collected in EDTA tubes by local pathology services and transported to a central laboratory in Sydney within 48h of collection. White blood cells were separated on a Ficoll gradient and plasma obtained by centrifugation, and stored at -70°C. Guthrie Spots were obtained from 1ml blood. Remaining blood was used for DNA extraction. Buccal swabs were collected from participants who did not wish to give blood. All AMFS case probands and population control probands were aged between 18-39 years inclusive.

The samples with BMI information were from AMFS. In the AMFS, height and weight were measured only for those participants who attended a clinical skin examination. All case and control probands were invited to attend a clinical skin examination, which were conducted at dermatology clinics in Brisbane, Sydney, and Melbourne by dermatology trainees trained on the study protocol. Attending a skin examination was a preferred but not essential component of participation in the overall study; it was completed by 73% of cases, 55% of population controls and 67% of spouse or friend controls.

Cases were genotyped on Illumina Omni1-Quad or HumanHap610 while controls were genotyped on Illumina Omni1-Quad or HumanHap610 or HumanHap670¹⁰

Principal component analysis was used for outlier removal and correction for population stratification using the first 10 principal components. Following these quality control steps lambda was 1.04. A more detailed description of the QC procedures applied to these data can be found in a previous publication¹⁰.

Houston (M.D. Anderson)

931 cutaneous melanoma (CM) non-Hispanic white patients were recruited together with 1,026 cancer-free controls (friends or acquaintances of patients reporting to other clinics at M.D. Anderson) frequency matched on age and sex. The majority of these also had BMI measured. These were supplemented with an additional 873 individuals presenting for treatment for CM at MD Anderson which did not have BMI recorded. All samples were collected between March 1998 and August 2008.

Samples were genotyped using the Illumina HumanOmni1-Quad_v1-0_B array and called using the BeadStudio algorithm. No adjustment was made for ethnicity as the genomic inflation factor was 1.02. Data were analysed by regressing case-control status on genotype (coded according to an additive model). This study has been previously published¹³ and a more detailed description of the QC procedures applied to these data can be found there.

Harvard

The dataset consisted of 494 melanoma cases and 5,628 controls from the Nurses' Health Study and the Health Professionals Follow-up Study. Cases from both cohorts had a pathologically confirmed invasive melanoma diagnosed any time after baseline up to the 2008 follow-up cycle. All controls were from existing GWAS of other traits in the two cohorts and were not diagnosed for melanoma. All subjects were US non-Hispanic Caucasians. Self-reported BMI was collected in both cohorts.

Samples from existing GWAS were previously genotyped using Illumina and Affymetrix arrays. Additional melanoma cases were genotyped using the Illumina HumanHap610 array. Based on the genotyped SNPs and haplotype information in the NCBI build 35 of phase II Hapmap CEU data, rs8050136 was imputed using MACH^{14,15} (imputation $r^2 = 1$). rs16953002 failed imputation and only the 421 cases and 2349 controls for which the SNP was genotyped were used. Further details of the Harvard data including QC procedures can be found elsewhere¹⁶.

BMI was recorded for all participants.

Italy

The samples come from three case-control studies conducted in Central and Northern Italy (Cesena, L'Aquila and Genoa), all genotyped with an iSelect Illumina Infinium custom array at the NCI Core Genotyping Facility.

276 samples came from the Cesena study^{17,18,19}. Here, cases were incident sporadic melanoma patients, without family history of melanoma, aged 17-77, negative for the CDKN2A/CDK4 mutations, diagnosed between December 1994 and January 1999 at the Dermatology Unit of Maurizio Bufalini Hospital in Cesena. Controls were spouses or close friends of the cases, patients treated at the same hospital for minor accidental trauma or healthy hospital personnel recruited during the same period without a history of melanoma and coming from the same geographical areas as the cases. They were frequency-matched by age and gender to cases. BMI was collected on these samples.

343 samples came from the L'Aquila study¹⁹. Here, sporadic melanoma patients, negative for the CDKN2A/CDK4 mutations, diagnosed at the Departments of Dermatology of the Universities of L'Aquila, Florence or Modena in central Italy, aged 17-82, were recruited between 2000 and 2002. Subjects treated for diseases unrelated to melanoma at the Internal Medicine Departments of the corresponding Universities were recruited as controls for the study. They were frequency matched by sex and age (± 1 year) and study area. BMI was not recorded for these samples.

350 individuals came from the Genoa study of sporadic melanoma cases diagnosed between 2000-2007 at the units of dermatology, medical oncology and plastic surgery of the National Cancer Research Institute and San Martino Hospital, Genoa, in Northern Italy. Melanoma cases were older than 18 years of age, without family history of melanoma and negative for the CDKN2A/CDK4 mutations. Control subjects without history of melanoma, older than 18 years of age were recruited

during the same period. BMI was not recorded for these samples. QC procedures are described in the references given above^{17,18,19,20}.

Valencia

For melanoma patients, the present study utilized data held on the database of the Dermatology Department of the Instituto Valenciano de Oncología, Valencia, Spain. A detailed description of this database can be found in previous reports^{21,22,23}. Briefly, this database includes incident and prevalent melanoma cases definitively treated at this institution, a referral skin cancer center for the provinces of Valencia, Alicante and Castellón, with a catchment population of ~5 million people. Clinical and pathologic data from these patients are prospectively collected since January 2000 by medical history review, personal interview and clinical examination performed by an expert dermatologist.

Disease free and ethnically matched healthy control subjects were recruited at Transfusion Center of Valencia. The phenotypic characteristics were obtained from a self-administered structured questionnaire. All the patients in the study had signed an informed consent and the study protocol was approved by institutional ethics boards.

Other replication data

Sample collections from Iceland, the Netherlands, Vienna, Milan, Sweden and Zaragoza have been described previously^{24,25}. Collection of Icelandic BMI is described elsewhere²⁶, approximately 23% being self-reported and the remainder measured at recruitment. Dutch BMI was self-reported by almost all participants. Viennese BMI was recorded by a nurse at the recruitment interview. As BMI is not an established risk factor, it was not recorded in approximately the first half of the Viennese study recruitment, after which it was systematically recorded.

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