**Supplementary Note**

**GWAS analysis**

Individuals were included in analysis based on selection for having >97% European ancestry, as determined by analysis of local ancestry [3]. Briefly, our algorithm first partitions phased genomic data into short windows of about 100 SNPs. Within each window, we use a support vector machine (SVM) to classify individual haplotypes into one of 31 reference populations. The SVM classifications are then fed into a hidden Markov model (HMM) that accounts for switch errors and incorrect assignments, and gives probabilities for each reference population in each window. Finally, we used simulated admixed individuals to recalibrate the HMM probabilities so that the reported assignments are consistent with the simulated admixture proportions. The reference population data is derived from public datasets (the Human Genome Diversity Project, HapMap, and 1000 Genomes), as well as 23andMe research participants who have reported having four grandparents from the same country.

A maximal set of unrelated individuals was chosen for each analysis using a segmental identity-by-descent (IBD) estimation algorithm [5]. Individuals were defined as related if they shared more than 700 cM IBD, including regions where the two individuals share either one or both genomic segments identical-by-descent. This level of relatedness (roughly 20% of the genome) corresponds approximately to the minimal expected sharing between first cousins in an outbred population. All individuals included in the analyses provided informed consent and answered surveys online according to 23andMe’s human subjects protocol, which was reviewed and approved by Ethical & Independent Review Services, an Association for the Accreditation of Human Research Protection Programs accredited institutional review board. All participants were over the age of 18.

DNA extraction and genotyping were performed on saliva samples by National Genetics Institute (NGI), a Clinical Laboratory Improvement Amendments of 1988- licensed clinical laboratory and a subsidiary of Laboratory Corporation of America. Samples have been genotyped on one of four genotyping platforms. The V1 and V2 platforms were variants of the Illumina HumanHap550+ BeadChip, including about 25,000 custom SNPs selected by 23andMe, with a total of about 560,000 SNPs. The V3 platform was based on the Illumina OmniExpress+ BeadChip, with custom content to improve the overlap with our V2 array, with a total of about 950,000 SNPs. The V4 platform in current use is a fully custom array, including a lower redundancy subset of V2 and V3 SNPs with additional coverage of lower-frequency coding variation, and about 570,000 SNPs. Samples that failed to reach 98.5% call rate was re-analyzed. Individuals whose analyses failed repeatedly were re-contacted by 23andMe customer service to provide additional samples.

Participant genotype data were imputed against the September 2013 release of 1000 Genomes Phase1 reference haplotypes, phased with ShapeIt2 [1]. We phased and imputed data for each genotyping platform separately. We phased using an internally developed phasing tool, Finch, which implements the Beagle haplotype graph-based phasing algorithm [2], modified to separate the haplotype graph construction and phasing steps. Finch extends the Beagle model to accommodate genotyping error and recombination, to handle cases where there are no consistent paths through the haplotype graph for the individual being phased. We constructed haplotype graphs for European and non-European samples on each 23andMe genotyping platform from a representative sample of genotyped individuals, and then performed out-of-sample phasing of all genotyped individuals against the appropriate graph.

In preparation for imputation, we split phased chromosomes into segments of no more than 10,000 genotyped SNPs, with overlaps of 200 SNPs. We excluded SNPs with Hardy-Weinberg equilibrium P<10−20, call rate < 95%, or with large allele frequency discrepancies compared to European 1000 Genomes reference data. Frequency discrepancies were identified by computing a 2x2 table of allele counts for European 1000 Genomes samples and 2000 randomly sampled 23andMe participants with European ancestry, and identifying SNPs with a chi squared P<10−15. We imputed each phased segment against all-ethnicity 1000 Genomes haplotypes (excluding monomorphic and singleton sites) using Minimac2 [4], using 5 rounds and 200 states for parameter estimation.

For the X chromosome, we built separate haplotype graphs for the non-pseudoautosomal region and each pseudoautosomal region, and these regions were phased separately. We then imputed males and females together using Minimac2, as with the autosomes, treating males as homozygous pseudo-diploids for the non-pseudoautosomal region.

We computed association test results by linear regression assuming additive allelic effects. For tests using imputed data, we use the imputed dosages rather than best-guess genotypes. We included covariates for age, gender, and the top five principal components to account for residual population structure. Results for the X chromosome were computed similarly, with male genotypes coded as if they were homozygous diploid for the observed allele.

For quality control of genotyped GWAS results, we excluded SNPs that were only genotyped on our “V1” and/or “V2” platforms due to small sample size, and SNPs on chrM or chrY because many of these are not genotyped reliably. Using trio data, we excluded SNPs that failed a test for parent-offspring transmission; specifically, we regressed the child’s allele count against the mean parental allele count and flagged SNPs with fitted β<0.6 and P<10−20 for a test of β<1. We excluded SNPs with a Hardy-Weinberg *P*<10−20 in Europeans; or a call rate of <90%. We also tested genotyped SNPs for genotype date effects, and excluded SNPs with P<10−50 by ANOVA of SNP genotypes against a factor dividing genotyping date into 20 roughly equal-sized buckets.

For imputed GWAS results, we excluded SNPs with average r2<0.5 or minimum r2<0.3 in any imputation batch, as well as SNPs that had strong evidence of an imputation batch effect. The batch effect test is an F test from an ANOVA of the SNP dosages against a factor representing imputation batch; we excluded results with P<10−50. Prior to GWAS, we identified, for each SNP, the largest subset of the data passing these criteria, based on their original genotyping platform -- either v2+v3+v4, v3+v4, v3, or v4 only -- and computed association test results for whatever was the largest passing set.

When both imputed and genotyped association test results were available, we used the imputed result. Across all results, we excluded linear regression results for SNPs with MAF < 0.1% because tests of low frequency variants are sensitive to violations of the regression assumption of normally distributed residuals. After applying all filters, we obtained association test results for 11942402 distinct SNPs.

**Survey questions**

23andMe participants were able to fill out web-based questionnaires whenever they logged into their 23andMe accounts. 23andMe currently deploys dozens of surveys to its users covering general health as well as disease specific topics. Since 23andMe asks similar questions in multiple surveys, data is combined across surveys to define a single phenotype end point for each participant. By asking similar question in different surveys, 23andMe is able to identify inconsistent answers and omit them from the final analysis. Many participants in the dysmenorrhea pain survey have also answered other 23andMe surveys and thus it was possible to define co-morbid phenotypes in some cases. The following section shows excerpts from the surveys used to define cases and controls for each phenotype in the 23andMe cohort.

**Survey: Dysmenorrhea pain severity**

[Q1] On average, how painful would you rate your menstrual period pains either before you first gave birth, or now if you haven’t given birth? (Research participants answered one of the following):

* Not painful
* Little painful
* Moderately painful
* Extremely painful
* I’m not sure

**Survey: Endometriosis**

[Q2] Have you ever been diagnosed by a doctor with any of the following *female reproductive* conditions?

Q: Endometriosis

A:

* Yes
* No
* I’m not sure

[Q3] Have you ever been diagnosed with endometriosis?

A:

* Yes
* No
* I'm not sure

[Q4] What was your diagnosis? Please check all that apply.

A:

* Polycystic ovarian syndrome (PCOS)
* Endometriosis
* Primary ovarian insufficiency (POI, also known as premature ovarian failure, premature menopause, or early menopause)
* Advanced maternal age
* Tubal obstruction
* Male factor
* Unexplained infertility
* Combination of male and female factors
* Other
* I'm not sure
* None of the above

**Survey: Uterine fibroids**

[Q5] Have you ever been diagnosed with uterine fibroids?

A:

* Yes
* No
* I'm not sure

[Q6] Has a doctor ever told you that you have any of these conditions?

Q: Uterine fibroids

A:

* Yes
* No
* I'm not sure

**Survey: PCOS**

[Q7] Have you ever been diagnosed with PCOS (polycystic ovary syndrome)?

A:

* Yes
* No
* I'm not sure

[Q8] What was your diagnosis? Please check all that apply.

A:

* Polycystic ovarian syndrome (PCOS)
* Endometriosis
* Primary ovarian insufficiency (POI, also known as premature ovarian failure, premature menopause, or early menopause)
* Advanced maternal age
* Tubal obstruction
* Male factor
* Unexplained infertility
* Combination of male and female factors
* Other
* I'm not sure
* None of the above

[Q9] Have you been diagnosed with any of the following? Please check all that apply.

A:

* Alopecia areata
* Androgenic alopecia
* Anemia (low blood iron levels)
* Hyperandrogenism (elevated androgens)
* Hyperthyroidism (overactive thyroid)
* Hypothyroidism (underactive thyroid)
* Polycystic ovary syndrome (PCOS)
* I'm not sure
* None of the above

**Survey: Some psychiatric disease**

[Q10] In the last 2 years, have you been newly diagnosed with or newly prescribed treatment for any of the following conditions by a medical professional?

Q: Schizophrenia

A:

* Yes
* No

Q: Bipolar disorder/Manic depression

A:

* Yes
* No

Q: Depression

A:

* Yes
* No

Q: Obsessive-compulsive disorder (OCD)

A:

* Yes
* No

Q: Attention deficit disorder (ADD)

A:

* Yes
* No

Q: Anxiety

A:

* Yes
* No

[Q11] Have you ever been diagnosed with or treated for any of the following conditions?

Q: Obsessive-compulsive disorder (OCD)

A:

* Yes
* No
* I'm not sure

Q: Schizophrenia

A:

* Yes
* No
* I'm not sure

Q: Autism

A:

* Yes
* No
* I'm not sure

Q: Attention deficit hyperactivity disorder (ADHD)

A:

* Yes
* No
* I'm not sure

Q: Anxiety

A:

* Yes
* No
* I'm not sure

Q: Depression

A:

* Yes
* No
* I'm not sure

Q: Bipolar disorder/Manic depression

A:

* Yes
* No
* I'm not sure

[Q12] In the last 2 years, have you been newly diagnosed with or started treatment for any of the following conditions?

Q: Attention deficit disorder (ADD)

A:

* Yes
* No

Q: Bipolar disorder/Manic depression

A:

* Yes
* No

Q: Schizophrenia

A:

* Yes
* No

Q: Obsessive-compulsive disorder (OCD)

A:

* Yes
* No

Q: Depression

A:

* Yes
* No

Q: Anxiety

A:

* Yes
* No

[Q13] Have you ever been diagnosed by a doctor with any of the following psychiatric conditions?

Q: Attention deficit disorder (ADD) or Attention deficit hyperactivity disorder (ADHD)

A:

* Yes
* No
* I don't know

Q: Schizophrenia

A:

* Yes
* No
* I don't know

Q: Dissociative identity disorder (multiple personality disorder)

A:

* Yes
* No
* I don't know

Q: Obsessive-compulsive disorder

A:

* Yes
* No
* I don't know

Q: Bipolar disorder (manic depression)

A:

* Yes
* No
* I don't know

Q: Depression

A:

* Yes
* No
* I don't know

Q: Mental retardation or other learning difficulties

A:

* Yes
* No
* I don't know

Q: Anxiety disorder

A:

* Yes
* No
* I don't know

Q: Autism-spectrum disorder (for example, Asperger syndrome, pervasive developmental disorder, or autism)

A:

* Yes
* No
* I don't know

[Q14] What mental health problems have you had? Please check all that apply.

A:

* Depression
* Anxiety
* Bipolar disorder/Manic depression
* Schizophrenia
* Attention deficit disorder (ADD)
* Attention deficit hyperactivity disorder (ADHD)
* Post-traumatic stress disorder (PTSD)
* Autism
* Panic attacks
* Phobia
* Asperger's
* Obsessive-compulsive disorder (OCD)
* An eating disorder (e.g. anorexia, bulimia)
* Other, please specify

[Q15] Have you ever been diagnosed with anxiety?

A:

* Yes
* No
* I'm not sure

[Q16] Have you ever been diagnosed with obsessive-compulsive disorder (OCD)?

A:

* Yes
* No
* I'm not sure

[Q17] Have you ever been diagnosed with autism?

A:

* Yes
* No
* I'm not sure

[Q18] Have you ever been diagnosed with bipolar disorder?

A:

* Yes
* No
* I'm not sure

[Q19] Have you ever been diagnosed with attention-deficit hyperactivity disorder (ADHD)?

A:

* Yes
* No
* I'm not sure

[Q20] Have you ever been diagnosed with schizophrenia?

A:

* Yes
* No
* I'm not sure

[Q21] Have you ever been diagnosed with attention-deficit disorder without hyperactivity (ADD)?

A:

* Yes
* No
* I'm not sure

[Q22] Have you ever been diagnosed with mania (been told by a medical professional that you were having a manic episode)?

A:

* Yes
* No
* I'm not sure

[Q23] Have you ever been diagnosed with attention deficit disorder (ADD) or attention deficit hyperactive disorder (ADHD)?

A:

* Yes
* No
* I'm not sure

[Q24] A mental health or psychiatric condition

A:

* Yes
* No
* I'm not sure

**Survey: Depression**

[Q25] Have you ever been diagnosed with clinical depression?

A:

* Yes
* No
* I'm not sure

[Q26] Have you ever been diagnosed with depression?

A:

* Yes
* No
* I'm not sure

[Q27] In the last 2 years, have you been **newly** diagnosed with or started treatment for any of the following conditions?

A:

* Yes
* No
* I'm not sure

[Q28] A mental health or psychiatric condition

A:

* Yes
* No
* I'm not sure

[Q29] Have you ever been diagnosed by a doctor with any of the following psychiatric conditions?

Q: Depression

A:

* Yes
* No
* I'm not sure

[Q30] Have you ever been diagnosed with or treated for any of the following conditions?

Q: Depression

A:

* Yes
* No
* I'm not sure

[Q31] What mental health problems have you had? Please check all that apply.

* Depression
* Anxiety
* Bipolar disorder/Manic depression
* Schizophrenia
* Attention deficit disorder (ADD)
* Attention deficit hyperactivity disorder (ADHD)
* Post-traumatic stress disorder (PTSD)
* Autism
* Panic attacks
* Phobia
* Asperger's
* Obsessive-compulsive disorder (OCD)
* An eating disorder (e.g. anorexia, bulimia)
* Other, please specify

[Q32] In the last 2 years, have you been newly diagnosed with or newly prescribed treatment for any of the following conditions by a medical professional?

Q: Depression

A:

* Yes
* No

**Survey: Some hormonal oral contraceptive**

[Q33] Are you currently using any form of hormonal birth control (such as the pill, the patch, or a depo provera shot)?

A:

* Yes
* No
* I'm not sure

[Q34] Are you currently taking birth control pills or other hormonal contraceptives?

A:

* Yes
* No
* I'm not sure

**Logic for defining research participants as positive for relevant co-phenotypes**

*Endometriosis*

* Responders scored as positive if answering ‘Yes’ to Q2 or Q3, or selecting ‘endometriosis’ option for Q4.

*Uterine fibroids*

* Responders scored positive if answering ‘Yes’ to Q5 or Q6.

*PCOS*

* Responders scored positive if answering ‘Yes’ to Q7, or selecting ‘Polycystic ovarian syndrome (PCOS)’ option to Q8 or Q9.

*Some psychiatric disease*

* Responders scored positive if answering ‘Yes’ to any condition except ‘Depression’ for Q10, Q11, Q12, Q13, or selecting any listed condition except ‘depression’ as an answer option for Q14, or selecting ‘Yes’ to Q15, Q16, Q17, Q18, Q19, Q20, Q21, Q22, Q23, or Q24.

*Depression*

* Responders scored positive if answering ‘Yes’ to any answer option for Q25, Q26, Q27, Q28, Q29, Q30, or Q32, or selecting ‘depression’ as an answer option for Q31.

*Some hormonal oral contraceptive*

* Responders scored positive if answering ‘Yes’ to any answer option for Q33 or Q34.

**Supplementary References**

[1] Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA. A map of human genome variation from population-scale sequencing. Nature 2010;467(7319):1061-1073.

[2] Browning SR, Browning BL. Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. American journal of human genetics 2007;81(5):1084-1097.

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[4] Fuchsberger C, Abecasis GR, Hinds DA. minimac2: faster genotype imputation. Bioinformatics (Oxford, England) 2015;31(5):782-784.

[5] Henn BM, Hon L, Macpherson JM, Eriksson N, Saxonov S, Pe'er I, Mountain JL. Cryptic distant relatives are common in both isolated and cosmopolitan genetic samples. PloS one 2012;7(4):e34267.