SUPPLEMENTS

Tedja M.S. et al. Large genome-wide meta-analysis highlights light-induced signaling as a driver for refractive error.

Supplementary Note:

1: Study Populations and Acknowledgements

2: Methods per subfields of prioritization

3: Dopamine pathway look-ups

4: Phenotyping in CREAM and 23andMe

5: Gene-based test - fgwas

Supplementary Figures:

Supplementary Figure 1: Study design flow-chart

Supplementary Figure 2.1: EasyQC plots per cohort – CREAM-ASN

Supplementary Figure 2.1.1: EasyQC QQ, P-Z, AF-plots per cohort in CREAM-ASN

Supplementary Figure 2.1.2: EasyQC λ-N and SE-N plots per cohort in CREAM-ASN

Supplementary Figure 2.2: EasyQC plots per cohort – CREAM-EUR

Supplementary Figure 2.2.1: EasyQC QQ-plots per cohort in CREAM-EUR

Supplementary Figure 2.2.2: EasyQC PZ-plots per cohort in CREAM-EUR

Supplementary Figure 2.2.3: EasyQC AF-plots per cohort in CREAM-EUR

Supplementary Figure 2.2.4: EasyQC λ-N plots per cohort in CREAM-EUR

Supplementary Figure 2.2.5: EasyQC SE-N plots per cohort in CREAM-EUR

Supplementary Figure 2.3: EasyQC plots per cohort – 23andMe

Supplementary Figure 2.3.1: EasyQC QQ, P-Z, AF-plots per cohort in 23andMe

Supplementary Figure 2.3.2: EasyQC λ-N and SE-N plots per cohort in 23andMe

Supplementary Figure 3: Boxplot of effect sizes per cohort

Supplementary Figure 4: Imputation Quality of genetic variants of Stage 3

Supplementary Figure 5: Manhattan plots and QQ plots per stage (1-3)

Supplementary Figure 6: Lambdas of all cohorts and meta-analyses

Supplementary Figure 7: LD-score regressions per ancestry of CREAM and 23andMe

Supplementary Figure 8: Effects comparison SE and AODM using different p-value thresholds

Supplementary Figure 9: Top canonical pathways of Ingenuity Pathway Analysis

Supplementary Figure 10: Locus Zoom plots of RNA gene regions

Supplementary Figure 11: Locus Zoom plots of dopamine pathway regions

Supplementary Figure 12: GWAS catalog comparison of refractive error genes with other diseases

Supplementary Tables:

Supplementary Table 1a: Descriptives per cohort

Supplementary Table 1b: Phenotyping and imputation methods per cohort

Supplementary Table 2: Stage 1 – 3 Meta-Analyses and Conditional Analysis (separate file)

Supplementary Table 3: Index Variants of FE and RE meta-analyses (separate file)

Supplementary Table 4: HWE P value per cohort TopSNPs Stage 3 (separate file)

Supplementary Table 5: Index SNPs HapMap II from CREAM and 23andMe

Supplementary Table 6: LD score regression analysis and heritability explained by common SNPs

Supplementary Table 7: Exonic genetic variants - protein altering

Supplementary Table 8: Post-GWAS analyses - additional genes

Supplementary Table 9: Predictive power of the polygenic score in Rotterdam Studies (I, II, III)

Supplementary Table 10: DEPICT analysis - gene-set enrichment (separate file)

Supplementary Table 11: Ranking of associated genes according to biological plausibility (separate file)

Supplementary Table 12: RNA genes – region look-ups

Supplementary Table 13: Genes with Human Ocular Phenotypes (separate file)

Supplementary Table 14: Genes with Mice Ocular Phenotypes (separate file)

Supplementary Table 15: Expression of Candidate Genes in Ocular Tissues (separate file)

Supplementary Table 16: Genetic variants harboring known drug target(s) (separate file)

Supplementary Table 17: Genes in Dopamine pathway – region look-ups

Supplementary Data

Supplementary Data 1: Locus Zoom Plots (separate file)

Supplementary Data 2: Forest Plots Stage 3 and Conditional Loci (separate file)

Supplementary Data 3: Summary Statistics Stage 3 Meta-analysis (separate file; SNPs $P < 0.005$)

Supplementary Note

1: Study Populations and Acknowledgements

CREAM cohort

CREAM (Consortium for Refractive Error and Myopia) was established in 2011 as a collaboration between studies with data on refractive error which had performed genome-wide association analysis based on SNP arrays. Details of each study cohort and their group-specific acknowledgements are provided below.

1958 British Birth Cohort

The 1958 British Birth Cohort[1] is a prospective population-based cohort study that initially included 17,000 newborn children whose birth was within the first week of March 1958. All participants gave informed written consent to participate in genetic association studies, and the study was approved by the South East Multi Centre Research Ethics Committee (MREC) and the Oversight Committee for the biomedical examination of the British 1958 British birth cohort. Biomedical examination protocols were approved by the South East MREC.

1958 British Birth Cohort acknowledgements: Phenotyping was funded by the Medical Research Council's Health of the Public grant (PIs Power and Strachan); the genetic studies by the Wellcome Trust (083478 to J.S.R.); some of the analysis by the National Institute for Health Research as Specialist Biomedical Research Centres in Paediatrics and Ophthalmology, partnering respectively with Great Ormond Street and Moorfields Hospitals; with additional personal funding (P.M.C) by the Ulverscroft Vision Research Group.

ALIENOR

The Alienor study is a population-based study in residents of Bordeaux, France[2]. The 963 participants, aged 73 years or more, were recruited from an ongoing population-based study (3C Study)[3]. They underwent an ophthalmological examination, including a recording of ophthalmological history, measures of visual acuity, refraction, two 45° non mydriatic colour retinal photographs (one centred on the macula, the other centred on the optic disc), measures of intraocular pressure and central corneal thickness and break-up time test. Refraction was measured first using autorefractometer (Speedy K, Luneau, France) and secondly by measuring subjective measurement, which was used in the analysis. This research followed the tenets of the Declaration of Helsinki. Participants gave written consent for the participation

in the study. The design of this study has been approved by the Ethical Committee of Bordeaux (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III) in May 2006. After exclusion of subjects operated for cataract and other eye procedures and diseases that could alter refraction, 618 subjects were available, among which 529 were genotyped at the French national centre for genotyping (CNG) using Illumina Human 610-Quad BeadChip. Among them, 509 individuals had good genotype QC (individuals of European ancestry, unrelated with other individuals, without discrepancy between clinical and genetic gender and with missingness < 5%) and had imputation data. In addition, 2 subjects had missing education data, leaving 507 subjects in the statistical analysis. Imputation was performed in two steps: prephasing with SHAPEIT2, followed by imputation with IMPUTE2 using 1000 Genomes(March 2012, MACGT1) as reference panel. SNPs were used in the imputation process if call rate > 98%, HWE p-value > 1 x 10-6 , MAF> 1%. Analysis was performed using Quicktest, with adjustment on age, gender, education, PC1 and PC2 and modelling of interaction between SNP and education, using robust variance estimates. No SNP exclusion was applied on imputed SNPs.

ALIENOR acknowledgements: The Alienor study is supported by laboratoires Théa (Clermont-Ferrand, France). The Three-City study is conducted under a partnership agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM), the University of Bordeaux and Sanofi-Aventis. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The Three-City study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Caisse Nationale de Solidarité pour l'Autonomie, Direction Générale de la Santé, MGEN, Institut de la Longévité, Conseils Régionaux d'Aquitaine et Bourgogne, Fondation de France, Ministry of Research-INSERM Programme "Cohortes et collections de données biologiques", Agence Nationale de la Recherche ANR PNRA 2006 and LongVie 2007, and the "Fondation Plan Alzheimer" (FCS 2009-2012). Laboratoires Théa participated in the design of the Alienor study, but none of the sponsors participated in the collection, management, statistical analysis and interpretation of the data, not in the preparation, review or approval of the present manuscript.

ALSPAC (Avon Longitudinal Study of Parents and Children)

The research adhered to the tenets of the Declaration of Helsinki. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Pregnant women with an expected date of delivery between 1st April 1991 and 31st December 1992, resident in the former Avon health authority area in Southwest England, were eligible to participate in this birth cohort study. 14,541 women were recruited. Data collection has been via various methods including self-completion questionnaires sent to the mother, to her partner and after age 5 to the child; direct

assessments and interviews in a research clinic. As well as investigating the health and well-being of the of the children in the birth cohort, the health of the mothers is also an important area of investigation[4,5]. DNA has been extracted from blood samples collected as part of routine antenatal care, during attendance at ALSPAC research clinics, or from immortalized lymphoblastoid cell lines, for a total of 10,321 of the mothers. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary: http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/.

ALSPAC acknowledgements: Core support for ALSPAC was provided by the UK Medical Research Council and Wellcome Trust (Grant 102215/2/13/2) and the University of Bristol; this research specifically was funded by Wellcome Trust ISSF Populations Pilot Award (508353/509506); C.W. is supported by an NIHR Fellowship (CDF-2009-02-35). We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

AREDS

The Age-Related Eye Disease Study (AREDS) was initially designed as a long-term multicenter, prospective study of the clinical course of age-related macular degeneration (AMD) and age-related cataract[6,7]. In addition to collecting natural history data, AREDS included a randomized clinical trial of high-dose vitamin and mineral supplements for AMD and a clinical trial of high-dose vitamin supplements for cataract[6-8]. Prior to study initiation, the protocol was approved by an independent data and safety monitoring committee and by the institutional review board for each clinical center. Written informed consent was obtained from all participants before enrollment in accordance with the Declaration of Helsinki. AREDS participants were 55 to 80 years of age at enrollment and had to be free of any illness or condition that would make long-term follow-up or compliance with study medications unlikely or difficult. On the basis of fundus photographs graded by a central reading center, best-corrected visual acuity and ophthalmologic evaluations, 4,757 participants were enrolled in one of several AMD categories, including persons with no AMD (control group). Visual acuity measurement of all participants was performed with the standard procedure developed for the Early Treatment of Diabetic Retinopathy Study (ETDRS). A refraction measurement was performed for participants at the randomization visit and each annual visit. For those who experience a decrease of 10 letters from baseline visual acuity, refractions were also conducted at the non-annual visits. Blood samples were collected at baseline and longitudinally as participants were send, and cell lines were established. DNA was extracted from cell

lines according to standard protocols. For the current analysis, 816 participants aged 60 and older were included from the AREDS 1a-1b population and 1506 from the AREDS 1c population. Refractive error measured by a refraction protocol at baseline enrollment into the AREDS study[6-9] was analyzed, taking the mean measured spherical equivalent (SE) across both eyes (or SE in a single eye when both eyes were not measured) as the trait of interest. Age, gender and the first two principal components (to adjust for significant population stratification) were also included as covariates.

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AREDS1c was supported by contracts from National Eye Institute/National Institutes of Health, Bethesda, MD, with additional support from Bausch & Lomb Inc, Rochester, NY. The genotyping costs were supported by the National Eye Institute (R01EY020483 to D.S.) and some of the analyses were supported by the Intramural Research Program of the National Human Genome Research Institute, National Institutes of Health, USA. AREDS acknowledges Frederick Ferris, National Eye Institute, National Institutes of Health, Bethesda, MD; and the Center for Inherited Disease Research, Baltimore, MD where SNP genotyping was carried out. The investigators gratefully acknowledge the advice and guidance of Hemin Chin of the National Eye Institute.

Blue Mountains Eye Study (BMES)

The Blue Mountains Eye Study (BMES) is a population-based cohort of a predominantly white population in west of Sydney, Australia. At baseline (1992-94), 3,654 permanent residents aged 49 years or older participated (participation rate of 82.4%[11]. During 1997-99 (BMES II A), 2,335 participants (75.1% of survivors) returned for examinations after 5 years. During 1999-2000, 1,174 (85.2%) new participants took part in an Extension Study of the BMES (BMES IIB). BMES cross-section II thus includes BMES IIA (66.5%) and BMES IIB (33.5%) participants (n=3,509)[12]. From the BMES cross section II who had blood samples collected, DNA was extracted for 3,189 (90.1 %) participants. Over 98% of BMES participants were European ancestry. All BMES examinations were approved by the Human Ethics Committees of the Western Sydney Area Health Service and University of Sydney. Signed informed consent was obtained from participants at each examination.

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CROATIA-Korčula Study

The CROATIA-Korčula study, Croatia, is a population-based, cross-sectional study in the island of Korčula that includes a total of 969 adult examinees, aged 18-98 (mean=56.3), and most (N=930) underwent a complete eye examination[13]. The study received approval from relevant ethics committees in Scotland and Croatia and followed the tenets of the Declaration of Helsinki.

CROATIA-Split Study

The CROATIA-Split study, Croatia, is a population-based, cross-sectional study in the Dalmatian City of Split that includes 1000 examinees aged 18-95. The study received approval from relevant ethics committees in Scotland and Croatia and followed the tenets of the Declaration of Helsinki.

CROATIA-Vis Study

The CROATIA-Vis study, Croatia, is a population-based, cross-sectional study in the island of Vis including adult participants, aged 18–93 years (mean = 56), a subset of which (N=640) underwent a complete eye examination in summer 2007 and provided their ophthalmologic history[13]. The study received approval from relevant ethics committees in Scotland and Croatia and followed the tenets of the Declaration of Helsinki.

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Diabetes Control and Complications Trial (DCCT)

DCCT (1982-1993) was a multi-center randomized clinical trial to compare the effectiveness of intensive (≥3 daily insulin injections or insulin pump) and conventional (<3 daily insulin injections) diabetic treatments at the time in preventing development and progression of microvascular complications of type 1 diabetes. Subjective refraction was measured following the standard protocols using a letter chart at 10 to 20 feet, at baseline visit and annually thereafter during DCCT. Refraction measurement was attempted at 1 meter for the subjects with poor visual acuity. In these cases the 4 meter refraction was estimated by subtracting +0.75 sphere from the 1 m measurement[14]. In the current study measurements at baseline were analyzed.

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Estonian Genome Center, University of Tartu (EGCUT)

The Estonian cohort is from the population-based biobank of the Estonian Genome Center of the University of Tartu (EGCUT). The whole project is conducted according to the Estonian Gene Research Act and all participants have signed the broad informed consent (http://www.biobank.ee[16]). The current cohort size is over 51,515, from 18 years of age and up, which reflects closely the age distribution in the adult Estonian population. Subjects are recruited by the general practitioners (GP), physicians in the hospitals,and special recruitment offices of the EGCUT. They were randomly selected from the individuals visiting GP offices or hospitals. Computer Assisted Personal interviews were conducted by primary care providers and nurses during 1-2 hours at a doctor's office to collect information that includes personal data (place of birth, place(s) of living, nationality etc.), genealogical data (family history, three generations), educational and occupational history and lifestyle data (physical activity, dietary habits, smoking, alcohol consumption, women's health, quality of life) etc. Anthropometric and physiological measurements were also taken. All diseases are defined according to the ICD10 coding[17].

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European Prospective Investigation into Cancer (EPIC-Norfolk)

The European Prospective Investigation into Cancer (**EPIC**) study is a pan-European prospective cohort study designed to investigate the aetiology of major chronic diseases[18]. EPIC-Norfolk, one of the UK arms of EPIC, recruited and examined 25,639 participants aged 40-79 years between 1993 and 1997 for the baseline examination[19]. Recruitment was via general practices in the city of Norwich and the surrounding small towns and rural areas, and methods have been described in detail previously[20]. Since virtually all residents in the UK are registered with a general practitioner through the National Health Service, general practice lists serve as population registers. Ophthalmic assessment formed part of the third health examination and this has been termed the EPIC-Norfolk Eye Study[21]. In total, 8,623 participants were seen for the ophthalmic examination, between 2004 and 2011. Refractive error was measured using a Humphrey Auto-Refractor 500 (Humphrey Instruments, San Leandro, California, USA). Genotyping was undertaken using the Affymetrix GeneChip Human Mapping 500K Array Set. Data were pre-phased with SHAPEIT version 2 and imputed to the March 2012 build of the 1000 Genomes project using IMPUTE version 2.2.2. The EPIC-Norfolk Eye Study was carried out following the principles of the Declaration of Helsinki and the Research Governance Framework for Health and Social Care. The study was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk & Waveney NHS Research Governance Committee (2005EC07L). All participants gave written, informed consent.

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Erasmus Rucphen Family Study (ERF)

The Erasmus Rucphen Family (ERF) Study is a family-based cohort in a genetically isolated population in the southwest of the Netherlands with over 3,000 participants aged between 18 and 86 years. Cross-sectional examination took place between 2002 and 2005. The rationale and study design of this study have been described elsewhere[22,23]. Cross-sectional examination took place between 2002 and 2005, including a non-dilated automated measurement of refractive error using a Topcon RM-A2000 autorefractor. All measurements in these studies were conducted after the Medical Ethics Committee of the Erasmus University had approved the study protocols and all participants had given a written informed consent in accordance with the Declaration of Helsinki.

Acknowledgements ERF: see Rotterdam Study.

Fuchs' Endothelial Corneal Dystrophy Controls (FECD)

We utilized control subjects who were part of a larger study on the genetics of Fuchs' Endothelial Corneal Dystrophy (FECD)[10]. All control subjects were of European descent and were at least 60 years of age and matched according to age, gender, and ancestry to the enrolled index cases. To qualify, each control subject was required to be grade 0 on the FECD grading scale, have no family history of a possibly inherited corneal disorder (eg, FECD, keratoconus, stromal dystrophy), and have normal corneas with no abnormalities on slit-lamp examination apart from certain conditions judged not to affect FECD[10]. Subjects were excluded from participation as controls if they displayed any signs of corneal dystrophy or degeneration or had previous/active interstitial keratitis or anterior uveitis, or active/previous infectious keratitis, or vascularization of the epithelium and/or stroma. Subjects were also excluded if they had previously undergone bilateral corneal surgery or had experienced perforating corneal trauma resulting in scarring. Measurements of refractive error, central corneal thickness and absence of FECD were obtained at baseline, along with recorded age, and gender. This work was performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. Data were collected under multi-center Institutional Review Board (IRB) approval.

Acknowledgements FECD: see BMES

Finnish Twin Study on Aging (FITSA)

Finnish Twin Study on Aging (FITSA) is a study of genetic and environmental effects on the disablement process in older female twins[24]. The study cohort of 13 888 adult twin pairs started in 1975. Altogether 103 MZ and 114 DZ twin pairs (424 individuals, all women of European ancestry) aged 63-76 years living in Finland took part in multiple laboratory examinations in 2000 and 2003, and responded in

questionnaires in 2011. Before the examinations, the subjects provided a written informed consent according to the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Central Hospital District of Central Finland.

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Framingham Eye Study

The Framingham Eye Study[25] (FES) was nested within the Framingham Heart Study (FHS, http://www.framinghamheartstudy.org), which began its first round of extensive physical examinations in 1948 by recruiting 5,209 men and women from the town of Framingham, MA, USA. Surviving participants from the original cohort returned for biennial exams, which continue to the present. A total of 2675 FHS participants were also examined as part of the FES between 1973 and 1975. The FES was designed to evaluate ocular characteristics of examinees such as: senile cataract; age-related macular disease; glaucoma; and retinopathy. Between 1989 and 1991, 1603 offspring of original cohort participants also received ocular examinations[26]. The analyses in the current study are limited 1497 (42.5% men) participants from both the original and the offspring cohorts for whom genotype data were available. Most individuals in this analysis set are unrelated but a small number of related pairs remain. All data--including refractive error, demographics and genotypes--were retrieved from the database of Genotypes and Phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/gap) after approval for controlled access to individual-level data. All study protocols are in compliance with the World Medical Association Declaration of Helsinki. Since 1971, written consent has been obtained from participants before each examination. The research protocols of the Framingham Heart Study are reviewed annually by the Institutional Review Board of the Boston University Medical Center and by the Observational Studies Monitoring Board of the National Heart, Lung and Blood Institute.

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Gutenberg Health Study (GHS1, GHS2)

The **Gutenberg Health Study** is a population-based, prospective, observational cohort study in mid-western Germany that includes consecutive follow-ups every five years. The primary study aim is to evaluate and improve cardiovascular risk stratification and the general health status of the population. The baseline examination included a total of 15,010 participants aged 35 to 74 years and took place from 2007 to 2012. The participants were randomly drawn and equally stratified for sex, residence (urban or rural) and for each decade of age. Exclusion criteria were the following: insufficient knowledge of German and physical or mental inability to participate in the examinations in the study center. The ophthalmic examination was based on standard operating procedures and included without limitation autorefraction and visual acuity testing (Humphrey® Automated Refractor/Keratometer (HARK) 599™, Carl Zeiss Meditec AG, Jena, Germany). The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.020.07; original vote: 22.3.2007, latest update: 20.10.2015). According to the tenets of the Declaration of Helsinki, written informed consent was obtained from all participants prior to their entry into the study.

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KORA

KORA ("Kooperative Gesundheitsforschung in der Region Augsburg" which translates as “Cooperative Health Research in the Region of Augsburg”) is a population based study of adults randomly selected from 430,000 inhabitants living in Augsburg and 16 surrounding counties in Germany[27-29]. The collection was done in 4 separate groups from 1984-2001 (S1-S4). All survey participants are residents of German nationality identified through the registration office. In the KORA S3 and S4 studies 4,856 and 4,261 subjects have been examined implying response rates of 75% and 67%, respectively. 3,006 subjects participated in a 10-year follow-up examination of S3 in 2004/05 (KORA F3), and 3080 of S4 in 2006/2008 (KORA F4). The age range of the participants was 25 to 74 years at recruitment. The study

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OGP Ogliastra Genetic Park, Talana study (OGP Talana)

A cross-sectional ophthalmic study was performed in Talana, Perdasdefogu and Urzulei within the Ogliastra Project, a large epidemiological survey conducted in a geographically, culturally and genetically isolated population living in an eastern-central region of Sardinia[30]. In Talana the study was carried out between October 2001 and October 2002 and adhered to the tenets of the declaration of Helsinki. Talana is a village situated at an altitude of 700 m above sea level in one of the most secluded areas of Sardinia, Ogliastra; it has about 1200 inhabitants and, importantly, archival records are available from 1589 and genealogical trees have been reconstructed from 1640. 789 volunteers gave their written informed consent and were invited to the local medical centre, which was equipped with a complete set of ophthalmic instruments for this survey. Participants underwent a complete eye examination including visual acuity (Snellen charts, 5 m) and refraction status assessment (autorefractor RK-8100 Topcon, Tokyo, Japan)

Acknowledgements OGP Ogliastra Genetic Park, Talana study (OGP Talana): **OGP Talana** was supported by grants from the Italian Ministry of Education, University and Research (5571DSPAR2002, 718Ric2005). OGP Talana thanks the Ogliastra population and the municipal administrators for their collaboration to the project and for economic and logistic support.

Orkney Complex Disease Study (ORCADES)

The Orkney Complex Disease Study (ORCADES) is a population-based, cross-sectional study in the Scottish archipelago of Orkney, including 1,285 individuals with eye measurements. The study received approval from relevant ethics committees in Scotland and followed the tenets of the Declaration of Helsinki.

Acknowledgements ORCADES: **ORCADES** recruitment and genotyping were supported by the Chief Scientist Office of the Scottish Government, the Royal Society, the UK Medical Research Council Human Genetics Unit and the European Union framework program 6 EUROSPAN project (LSHGCT2006018947). ORCADES acknowledges the invaluable contributions of Lorraine Anderson and the research nurses in Orkney, in particular Margaret Pratt who performed the eye measurements, as well as the administrative team in Edinburgh University, the Wellcome Trust Clinical facility (Edinburgh, United Kingdom) for DNA extraction, Peter Lichner and the Helmholtz Zentrum Munchen (Munich, Germany) for genotyping, and Mirna Kirin, Pau Navarro and Peter Joshi for the genetic data imputation. Genetic analyses were supported by the MRC HGU "QTL in Health and Disease" core programme.

Rotterdam Study (RS1, RS2, RS3)

The Rotterdam Study is a prospective population-based cohort study in the elderly living in Ommoord, a suburb of Rotterdam, the Netherlands. Details of the study are described elsewhere[31]. In brief, the Rotterdam Study consists of 3 independent cohorts: RS1, RS2, and RS3. For the current analysis, 5,328 residents aged 55 years and older were included from RS1, 2,009 participants aged 55 and older from RS2, and 1,970 aged 45 and older from RS 3. 99% of subjects were of European ancestry. Participants underwent multiple physical examinations with regular intervals from 1991 to present, including a non-dilated automated measurement of refractive error using a Topcon RM-A2000 autorefractor. All measurements in RS-1–3 were conducted after the Medical Ethics Committee of the Erasmus University had approved the study protocols and all participants had given a written informed consent in accordance with the Declaration of Helsinki.

Acknowledgements Rotterdam Study and ERF: **The Rotterdam Study** and **ERF** were supported by European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant 648268), Netherlands Organisation for Scientific Research (NWO, grant 91815655), Erasmus Medical Center and Erasmus University, Rotterdam, The Netherlands; Netherlands Organization for Health Research and Development (ZonMw); UitZicht; Netherlands Organisation for Scientific Research (NWO Veni 91617076 to V.J.M.V.); the Research Institute for Diseases in the Elderly; the Ministry of Education, Culture and Science; the Ministry for Health, Welfare and Sports; the European Commission (DG XII); the Municipality of Rotterdam; the Netherlands Genomics Initiative/NWO; Center for Medical Systems Biology of NGI; Lijf en Leven; M.D. Fonds; Henkes Stichting; Stichting Nederlands Oogheelkundig Onderzoek; Swart van Essen; Bevordering van Volkskracht; Blindenhulp; Landelijke Stichting voor Blinden en Slechtzienden; Rotterdamse Vereniging voor Blindenbelangen; Oogfonds; Algemene Nederlandse Vereniging ter Voorkoming van Blindheid; Stichting MaculaFonds;

Combined Ophthalmic Research Rotterdam; Rotterdamse Oogheelkundig Onderzoek Stichting; Erasmus MC Vriendenfonds, Topcon Europe; Novartis; Ada Hooghart, Corina Brussee, Riet Bernaerts-Biskop, Patricia van Hilten, Pascal Arp, Jeanette Vergeer, Marijn Verkerk; Sander Bervoets.

TEST/BATS

The Australian Twin Eye Study comprises participants examined as part of the Twins Eye Study in Tasmania or the Brisbane Adolescent Twins Study. Details of the study are described elsewhere[32]. Ethical approval was obtained from the Royal Victorian Eye and Ear Hospital, the University of Tasmania, the Australian Twin Registry and the Queensland Institute of Medical Research.

Acknowledgements TEST/BATS: **TEST** and **BATS** (Australian Twins) were supported by an Australian National Health and Medical Research Council (NHMRC) Enabling Grant (2004-2009, 350415, 2005-2007); Clifford Craig Medical Research Trust; Ophthalmic Research Institute of Australia; American Health Assistance Foundation; Peggy and Leslie Cranbourne Foundation; Foundation for Children; Jack Brockhoff Foundation; National Institutes of Health/National Eye Institute (RO1EY01824601 (2007-2010)); Pfizer Australia Senior Research Fellowship (to D.A.M.); and Australian NHMRC Career Development Award (to S.M.). Genotyping was funded by an NHMRC Medical Genomics Grant; US National Institutes of Health/National Eye Institute (1RO1EY018246), Australian sample imputation analyses were carried out on the Genetic Cluster Computer which is financially supported by the Netherlands Scientific Organization (NWO48005003). Australian Twins thanks Grant Montgomery, Scott Gordon, Dale Nyholt, Sarah Medland, Brian McEvoy, Margaret Wright, Anjali Henders, Megan Campbell for ascertaining and processing genotyping data; Jane MacKinnon, Shayne Brown, Lisa Kearns, Jonathan Ruddle, Paul Sanfilippo, Sandra Staffieri, Olivia Bigault, Colleen Wilkinson, Yaling Ma, Julie Barbour for assisting with clinical examinations; and Dr Camilla Day and staff at the Center for Inherited Disease Research.

TwinsUK

The TwinsUK adult twin registry based at St. Thomas' Hospital in London is a volunteer cohort of over 10,000 twins from the general population[33]. Twins largely volunteered unaware of the eye studies, gave fully informed consent under a protocol reviewed by the St. Thomas' Hospital Local Research Ethics Committee.

Acknowledgements TwinsUK: **TwinsUK** received funding from the Wellcome Trust; the European Union MyEuropia Marie Curie Research Training Network; Guide Dogs for the Blind Association; the European

Community's FP7 (HEALTHF22008201865GEFOS); ENGAGE (HEALTHF42007201413); the FP-5 GenomEUtwin Project (QLG2CT200201254); US National Institutes of Health/National Eye Institute (1RO1EY018246); NIH Center for Inherited Disease Research; the National Institute for Health Research comprehensive Biomedical Research Centre award to Guy's and St. Thomas' National Health Service Foundation Trust partnering with King's College London. P.G.H. is the recipient of a Fight for Sight ECI award. We acknowledge the contribution of Drs Toby Andrew, Margarida Lopes, Samantha Fahy and Diana Kozareva.

Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)

WESDR is an observational cohort study of diabetes complications (1979-2007)[34]. Subjective refraction, measured following standard protocols at first visit, was analyzed in the current study (n=589).

Acknowledgements WESDR: **WESDR** was supported by NEI (grants R01EY03083 and EY016379) and a Research to Prevent Blindness Senior Scientific Investigator Award.

Young Finns Study (YFS)

The YFS cohort is a Finnish longitudinal population study sample on the evolution of cardiovascular risk factors from childhood to adulthood[35]. The first cross-sectional study was conducted in the year 1980 in five different centers. It included 3,596 participants in the age groups of 3, 6, 9, 12, 15, and 18, who were randomly chosen from the national population register. After the baseline in 1980 these subjects have been re-examined in 1983 and 1986 as young individuals, and in 2001, 2007 and 2011 as older individuals. For the current analysis a subsample from the newest (2011) follow-up was used from four centers (N=1479) where the refractive error measurements data from both eyes were available.

This study was carried out in accordance with the recommendations of the Declaration of Helsinki. All participants provided written informed consent and the study protocol was approved by the Ethics Committee.

Acknowledgements Young Finns Study (YFS): The Young Finns Study has been financially supported by the Academy of Finland: grants 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research ; Finnish Cultural Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation;

Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; and Diabetes Research Foundation of Finnish Diabetes Association.

Beijing Eye Study (BES)

The BES is a population-based cohort of Han Chinese in the rural region and in the urban region of Beijing in North China. The Medical Ethics Committee of the Beijing Tongren Hospital approved the study protocol and all participants gave informed consent, according to the Declaration of Helsinki. At baseline (2001), 4439 individuals out of 5324 eligible individuals aged 40 years or older participated (response rate: 83.4%). In the years 2006 and 2011, the study was repeated by re-inviting all participants from the survey from 2001 to be re-examined. Out of the 4439 subjects examined in 2001, 3251 (73.2%) subjects returned for the follow-up examination in 2006, and 2695 (60.7%) subjects returned for the follow-up examination in 2011.

Acknowledgements Beijing Eye Study: **Beijing Eye Study** was supported by National Natural Science Foundation of China (grant 81170890).

Nagahama

Nagahama Prospective Cohort for Comprehensive Human Bioscience (the Nagahama Study) is a community-based cohort consisted of 9,804 healthy Japanese volunteers recruited between 2008 and 2010 from the general population of Nagahama City in Japan. Community residents from 30–74 years of age, living independently and without physical impairment or dysfunction were eligible. The Kyoto University Graduate School and Faculty of Medicine Ethics Committee and the Nagahama Municipal Review Board of Personal Information Protection approved the study protocol and procedures used to obtain informed consent. All the study procedures adhered to the tenets of the Declaration of Helsinki. All participants were fully informed about the purpose and procedures of the study, and written consent was obtained from each subject.

Acknowledgements Nagahama: Nagaham Study was financially supported by Comprehensive Research on Aging and Health Science Research Grants for Dementia R&D from Japan Agency for Medical Research and Development (AMED) and the Centre of Innovation Program, the Global University Project from Japan Science and Technology Agency.

Singapore Studies

All Singapore studies adhere to the Declaration of Helsinki. Ethics approvals have been obtained from the Institutional Review Boards of the Singapore Eye Research Institute, Singapore General hospital, National University of Singapore and National Healthcare Group, Singapore. In all cohorts, participants provided written, informed consent at the recruitment into the studies.

Singapore Prospective Study Program (SP2)

Samples of SP2 were from a revisit of two previously conducted population-based surveys carried out in Singapore between 1992 and 1998, including the National Health Survey 1992 and the National Health Survey 1998[36]. These studies comprise random samplings of individuals stratified by ancestry from the entire Singapore population. A total of 8266 subjects were invited in this follow-up survey and 6301 (76.1% response rate) subjects completed the questionnaire, of which 4056 (64.4% of those who completed the questionnaire) also attended the health examination and donated blood specimens.

Acknowledgements Singapore Prospective Study Program (SP2): See "Acknowledgements Singapore Studies"

Singapore Malay Eye Study (SiMES)

SiMES is a population-based prevalence survey of Malay adults aged 40 to 79 years living in Singapore that was conducted between August of 2004 and June of 2006[37]. From a Ministry of Home Affairs random sample of 16,069 Malay adults in the Southwestern area, an age-stratified random sampling strategy was used in selecting 1400 from each decade from age 40 years onward (40–49, 50–59, 60–69, and 70–79 years).The 4,168 eligible participants from the sampling frame, while 3280 (78.7%) participated.

Acknowledgements Singapore Malay Eye Study (SiMES)**:** *See "Acknowledgements Singapore Studies"*

Singapore Indian Eye Study (SINDI)

SINDI is a population-based survey of major eye diseases[38] in ethnic Indians aged 40 to 80 years living in the South-Western part of Singapore and was conducted from August 2007 to December 2009. In brief, 4,497 Indian adults were eligible and 3,400 participated.

Acknowledgements Singapore Indian Eye Study (SINDI): *See "Acknowledgements Singapore Studies"*

Singapore Chinese Eye Study (SCES)

Similar to SINDI, the Singapore Chinese Eye Study (SCES) is a population-based cross-sectional study of eye diseases in Chinese adults 40 years of age or older residing in the southwestern part of Singapore. The methodology of the SCES study has been described in details previously. Between 2009 and 2011, 3,353 (72.8%) of 4,605 eligible individuals underwent a comprehensive ophthalmologic examination, using the same protocol as SINDI[37].

Acknowledgements Singapore Chinese Eye Study (SCES): see "Acknowledgements Singapore Studies" STARS

Acknowledgements Singapore Studies: The Singapore studies (**SP2, SIMES, SINDI, SCES, STARS**) were supported by the National Medical Research Council, Singapore (NMRC 0796/2003, NMRC 1176/2008, STaR/0003/2008; CG/SERI/2010), Biomedical Research Council, Singapore (06/1/21/19/466, 09/1/35/19/616 and 08/1/35/19/550). The Singapore Tissue Network and the Genome Institute of Singapore, Agency for Science, Technology and Research, Singapore provided services. National supercomputing centre (NSCC) provided high performance computing resources to support GWAS analysis.

Acknowledgements UK Biobank: This research was facilitated by data from the UK Biobank Resource. UK Biobank was established by the Wellcome Trust medical charity, Medical Research Council (UK), Department of Health (UK), Scottish Government, and Northwest Regional Development Agency. It also had funding from the Welsh Assembly Government, British Heart Foundation, and Diabetes UK. The eye and vision dataset has been developed with additional funding from The NIHR Biomedical Research Centre at Moorfields Eye Hospital and the UCL Institute of Ophthalmology, Fight for Sight charity (UK), Moorfields Eye Charity (UK), The Macula Society (UK), The International Glaucoma Association (UK) and Alcon Research Institute (USA). This research has been conducted using the UK Biobank Resource (applications #17351 and #17615).

Acknowledgements expression study Young TL et al: This study was funded by the National Institutes of Health R01 EY014685, the Research to Prevent Blindness Inc. Lew R. Wasserman Award, and the University of Wisconsin Centennial Scholars Award (T.L. Young).

2: methods per subfields of prioritization

Internal replication of index genetic variants in the individual cohort GWAS'es (CREAM-ASN, CREAM-EUR and 23andMe)

Internal replication of the index genetic variants from Stage 3 were checked in Stage 1 and 2 using the Bonferroni corrected p-value of $0.05/(140*3) = 1.19x10^{-4}$.

Evidence for eQTL

We used FUMA[39] for eQTL look-ups which was based on eQTLs and gene expression used in the pipeline were obtained from GTEx v6[40], eQTLs of blood cells from the Blood eQTL Browser[41] (cis-eQTLs with FDR ≤ 0.05), eQTLs of blood cells in Dutch population from the BIOS QTL Browser (cis-eQTLs on gene-level with FDR ≤ 0.05), eQTLs of 10 brain regions from BRAINEAC ((http://www.braineac.org/,; sis-eQTLs with nominal *P* value < 0.05) and additional extensive look-ups in GtEx.

Evidence of expression in the eye in developmental and adult ocular tissues

Bergen AA et al:

Gene expression of myopia candidate genes in laser dissected, freshy frozen retinal tissues: human RPE, photoreceptors and choroid. Cellular expression was measured using validated 44K microarray data on an Agilent platform in multiple samples, and RNA levels were ranked in percentiles, with 100,00 indicating the highest expression, and 0 the lowest, according to methodology described by Booij et al (2009).

Young TL et al:

Expression of genes annotated to the index variants was studied in human ocular tissue using various methods: expression profiles in laser dissected freshly frozen RPE, photoreceptors and choroid of healthy human adult donor eyes[42]; whole-transcriptome expression analysis of macular and peripheral retina, choroid, and sclera from eight adult normal human ocular eyes[43]; and whole genome expression in retina, retinal pigment epithelium, choroid, sclera, optic nerve, and cornea from 15 normal fetal (24 weeks gestational age) and 6 adult donor eyes[44]. Human fetal and adult gene expression data for retina, RPE, choroid, sclera, optic nerve and cornea were obtained as described in Young TL, et al. (2013)[44]. In brief, 9 fetal eyes at 12-weeks' gestation and 6 fetal eyes at 24-weeks' gestation were obtained from Advanced Biosciences Resources (Alameda, CA, USA), while 6 adult eyes were obtained from the North Carolina

Eye Bank (Winston–Salem, North Carolina, USA). Whole globes with a 2mm equatorial incision were immersed in RNAlater (Qiagen, Hilden, Germany) shortly after collection to preserve RNA integrity, and shipped overnight on ice. The retina, RPE, choroid and scleral tissues were isolated at the posterior pole using round biopsy punches. Some fetal tissues, such as RPE and retina could not be separated, and were collected in combination. Central corneal samples were isolated using a biopsy punch, and optic nerve was collected using clean dissection scissors. Tissue samples were homogenized at 4°C in Ambion lysis buffer using a Bead Ruptor Tissue Homogenizer (Omni, Kennesaw, Georgia, USA) with 2.38 mm metal beads, and RNA was extracted using the mirVanaTM total RNA extraction kit (Ambion, Austin, Texas, USA) following the manufacturer's protocol. The RNA samples were labeled and amplified using the Illumina Total Prep kit (Ambion, Austin, Texas, USA), and hybridized to Illumina HumanHT-12 v4 Expression BeadChips (San Diego, California, USA). All protocols were performed following the manufacturer's recommendations. Twelve tissue samples were processed on each chip. Microarray data background noise was subtracted from the intensity values using Illumina's GenomeStudio software, exported and log2 transformed.

Presence of an eye phenotype in knock-out mice

The Mouse Genome Informatics database (MGI, www.informatics.jax.org) and the International Mouse Phenotyping Consortium (IMPC, http://www.mousephenotype.org) were checked for entries matching an eye-phenotype. Genes were listed and their human equivalents were looked up in NCBI (www.ncbi.nlm.nih.gov).

Presence of an eye phenotype in humans

All genes were checked in Online Mendelian Inheritance in Man (OMIM, http://omim.org) and DisGeNET (http://www.disgenet.org) for the involvement of a human ocular phenotype.

Presence of gene in a significant enriched functional pathway (DEPICT)

We first clumped the SNPs with *p*-value $<1x10^{-5}$ or lower from the meta-analysis of stage III using 500kb as physical distance threshold and an $R^2 > 0.1$ with PLINK, resulting in 534 clumps. Secondly, we performed gene set, cell type, and tissue enrichment analyses using DEPICT[45]. The Affinity Propagation tool[46-49] was used for clustering, and clusters were named by their 'representative' gene set, which was automatically chosen by the Affinity Propagation clustering method. The pairwise Pearson correlation between significant gene sets was calculated and then the AP algorithm was used to cluster similar

pathways into meta gene sets. Clusters were named by their representative gene set, which was automatically selected by the AP algorithm. In addition, correlation between the meta gene sets was calculated to create a network. The visualizations of the gene set enrichment analysis were created in Cytoscape[50].

Presence of gene in a significant canonical pathway (IPA)

IPA is a subscription based manually curated knowledge archive. Bioinformatic analysis according to Ingenuity protocol and data sets containing RefSeq identifiers were uploaded into the application IPA. Each RefSeq identifier was mapped to its corresponding human splicing variant in the Ingenuity® Knowledge Base. Canonical pathway analysis identified the 5 canonical pathways from the IPA library that were most significant to the data set. The significance of the association between the data set and the canonical pathway was measured in two ways: 1) A ratio of the number of molecules from the data set that map to the pathway divided by the total number of molecules that map to the canonical pathway. 2) Fisher's Exact test was used to calculate a P-value determining the probability that the association between the genes in the data set and the canonical pathway is explained by chance alone.

3: Dopamine pathway look-ups

To further investigate the association of genes playing a key role in the dopamine pathway, we we looked up the regions coding for dopamine receptors (*DRD1, DRD2, DRD3, DRD4, DRD5*), genes involved in synthesis & degradation (*COMT, DBH, DDC, MAOA, TH*) and transporters: (*SLC6A3/DAT, SLC6A4/SERT*) in the Stage 3 meta-analysis[51-53]. An overview of the results are provided in Supplementary Table 10 and Locus Zoom regional plots are provided in Supplementary Figure 12.

4: Phenotyping in CREAM and 23andMe

CREAM

Phenotyping of the CREAM cohorts has been described in detail previously[54]. Eligible participants underwent a complete ophthalmic examination, including a non-dilated measurement of refractive error for both eyes using a similar protocol (Supplementary Excel Table 1a). Inclusion criteria were individuals over the age of 25 years, of European or Asian descent, with available data on refractive error and with available genotype data. As previously described[54], exclusion criteria were all refraction altering conditions and ocular syndromes or systemic syndromes. Spherical equivalent (SE) was calculated according to the standard formula (SE = sphere + ½ cylinder); the mean SE of two eyes was used for analyses. When SE was only available for one eye, the SE of this eye was used.

23andMe

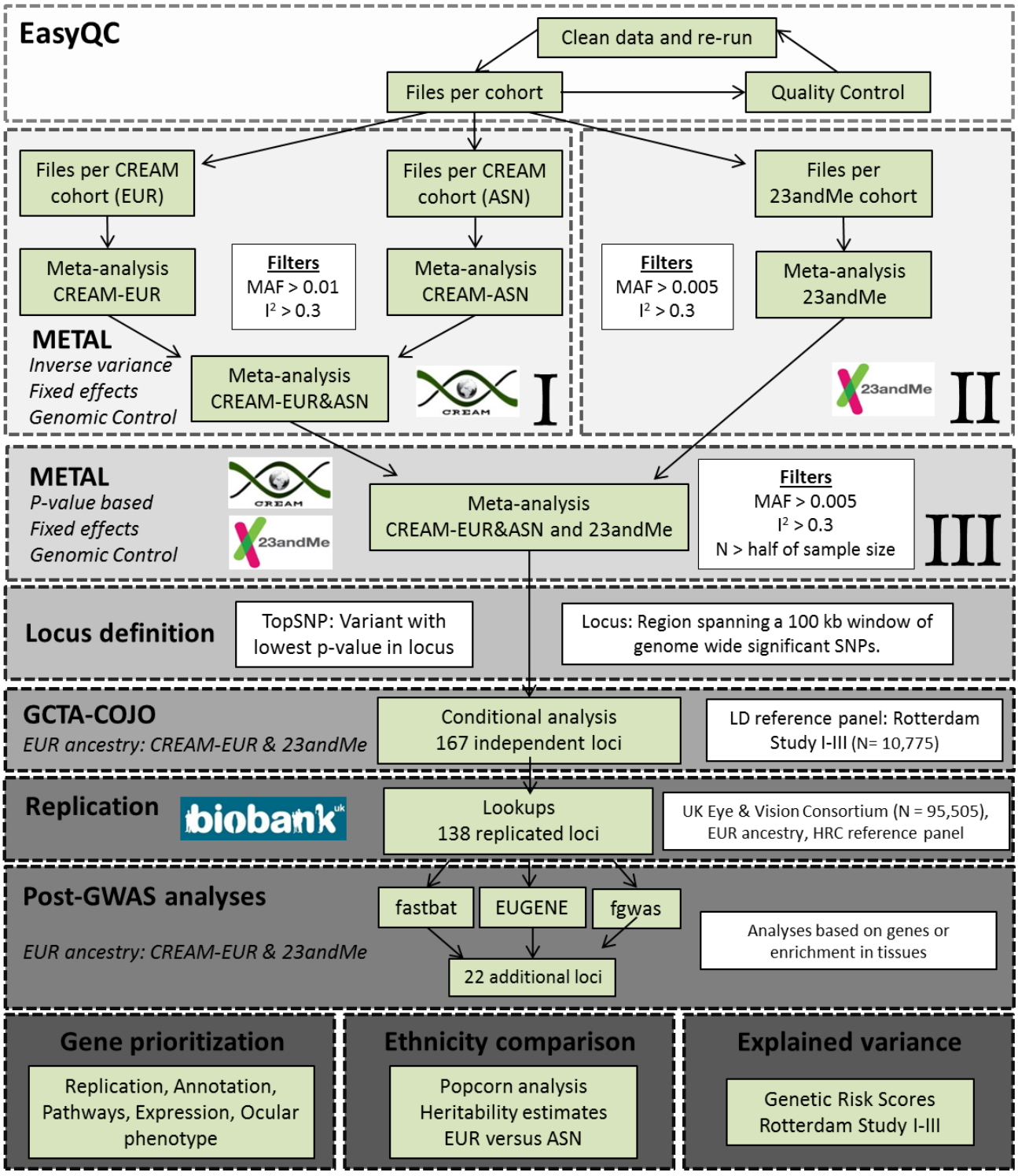
All participants were drawn from the customer database of 23andMe, Inc., a direct-to-consumer genetic testing company. Phenotyping of this cohort has been described in detail previously[55,56]. Participants were asked online whether they had myopia (yes or no), and at what age they were diagnosed with myopia. Inclusion criteria were individuals of European ancestry, age at diagnosis between five and 30 years of age, and available genotype data.

Participants provided informed consent and participated in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services (E&I Review).

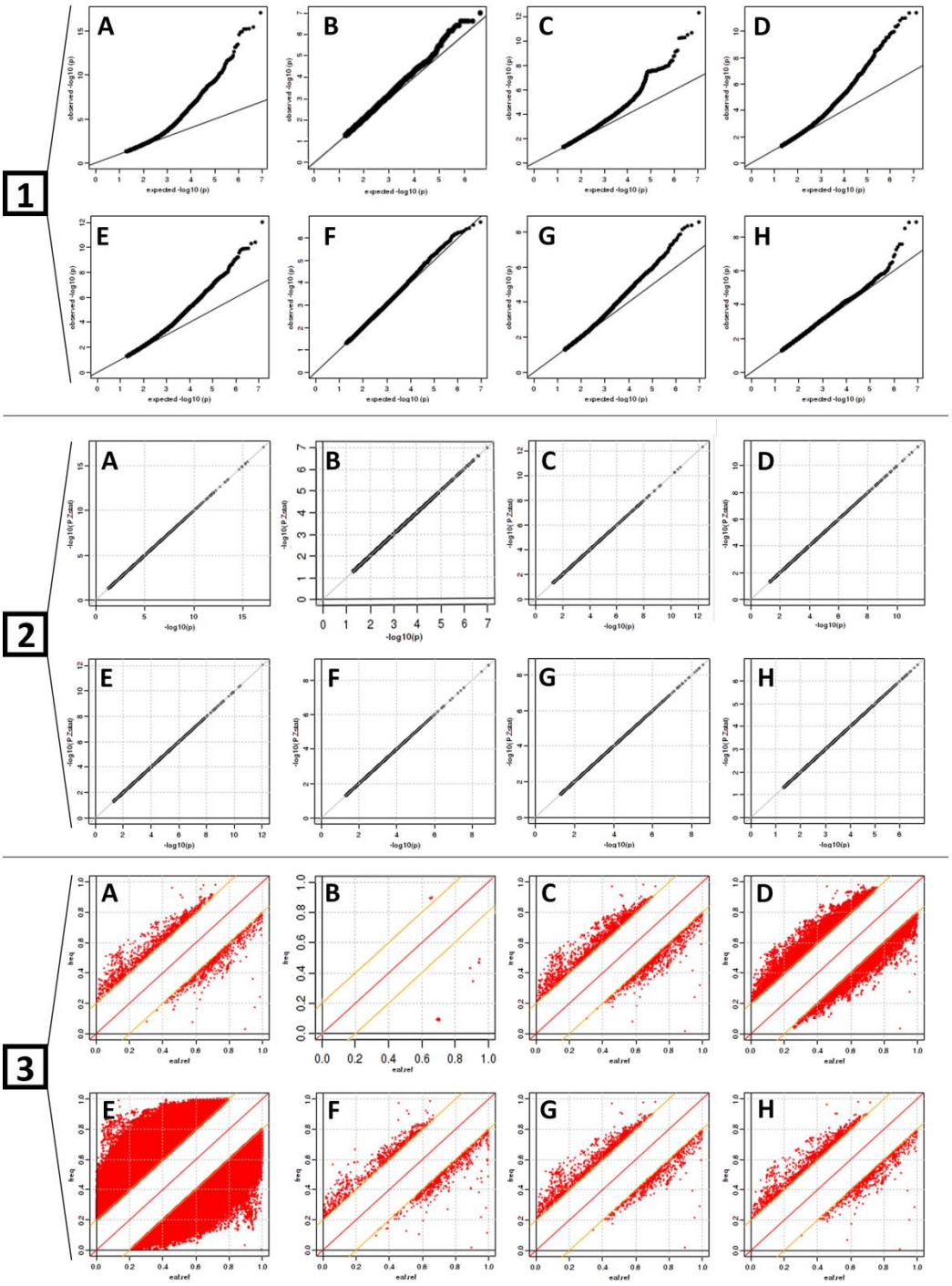
5: Gene-based test - fgwas

We looked at enrichment of 450 genomic annotations as implemented in fgwas with 5000 SNPs per window and . We derived the best annotations from genome-wide significant loci. We first considered annotations separately to see if they were individually significant. Some annotations were correlated and, hence, we built a model by adding terms sequentially in decreasing order of significance. We started with a model with two region based annotations (top one third of the distribution of gene density and bottom one third of the distribution of gene density). We then added two SNP based annotations (SNPs between 0 and 5kb from the transcription start site and SNPs between 5kb and 10kb from the transcription start site) and continued to add annotations until a maximum of 10 SNP based annotations were included in the model (adding further annotations is possible although we had problems with convergence within the fgwas software when a large number of annotations were added so we stopped adding further annotations at 10). We then applied the cross-validation approach implemented in fgwas to ensure no over-fitting in the final model. We used this final Bayesian model to derive a prior distribution for the remainder of the genome. We calculated the posterior probability of association based on the derived prior distribution. A posterior probability greater than 0.9 in this approach performed similarly to the traditional genome-wide significance threshold in genome-wide association studies (p-value$<5 \times 10^{-8}$) based on the analysis of previously published genome-wide association studies.

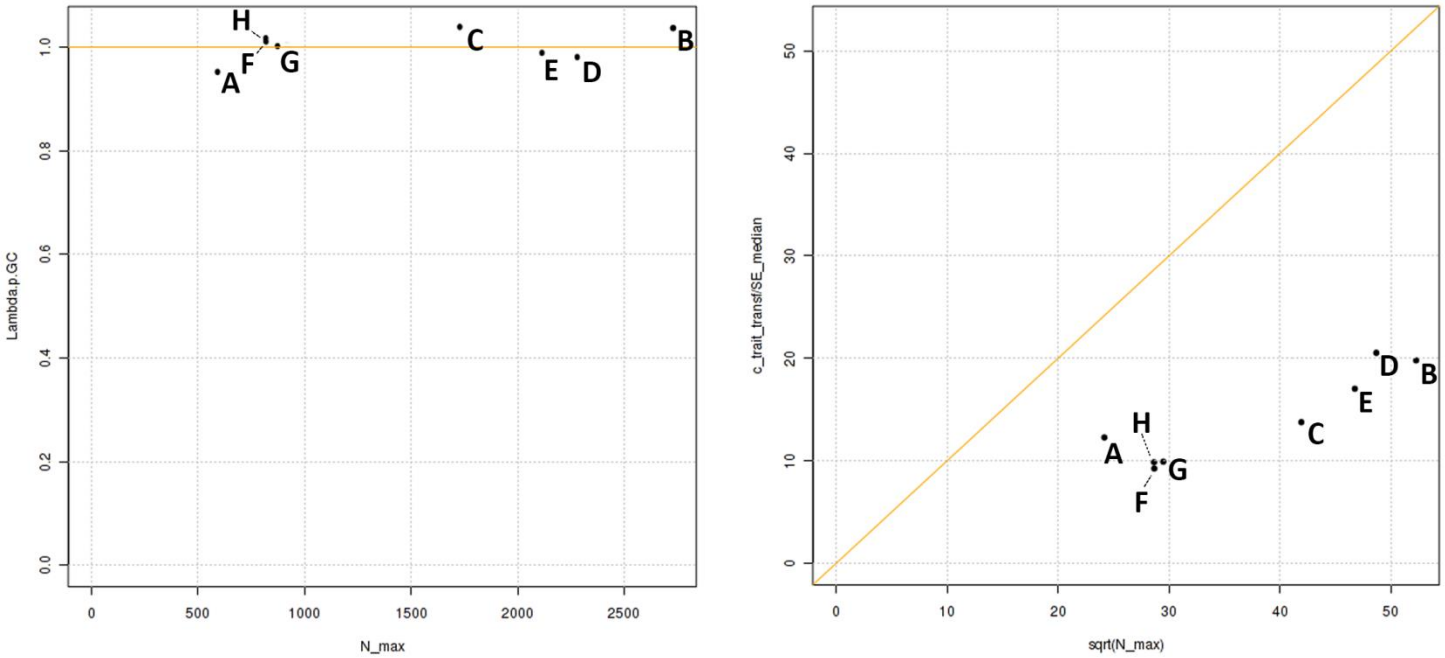
Supplementary Figure 1: Study design flow-chart



Supplementary Figure 2.1: EasyQC plots per cohort – CREAM-ASN



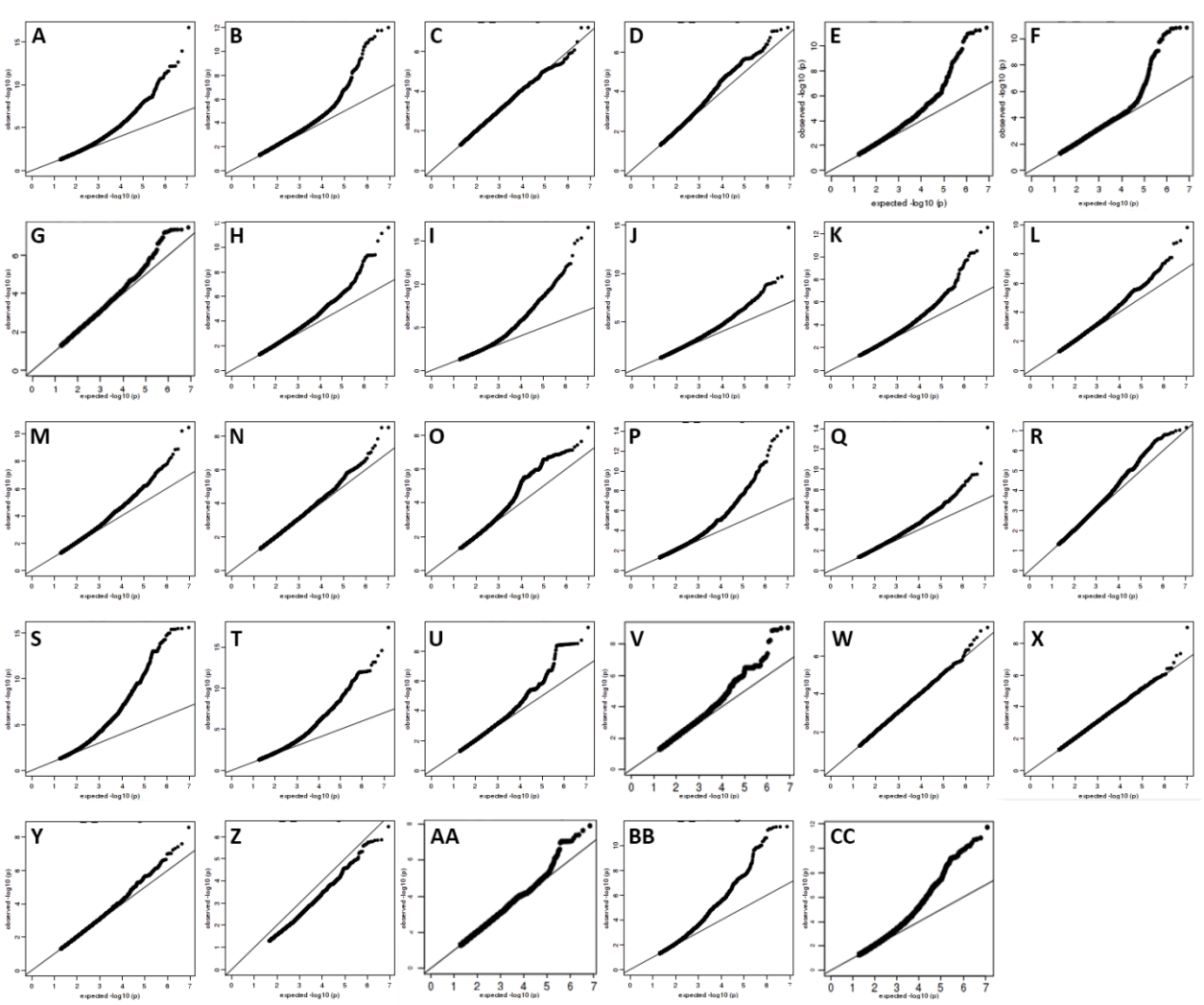
Supplementary Figure 2.1.1: Quality control – Quantile-Quantile (QQ), Pvalue-Z-statistics (P-Z) and Allele Frequency (AF)-plots per cohort in CREAM-ASN generated from EasyQC
Panel 1: QQ-plots per cohort in CREAM-ASN; Panel 2: P-Z plots per cohort in CREAM-ASN; Panel 3: AF plots per cohort in CREAM-ASN; A=BES (n=590), B=Nagahama (n=2730); C=SCES (n=1724), D=SIMES (n=2275), E=SINDI (n=2110), F=STARS (n=817), G=SP2-610 (n=871), H=SP2-1M (n=818).



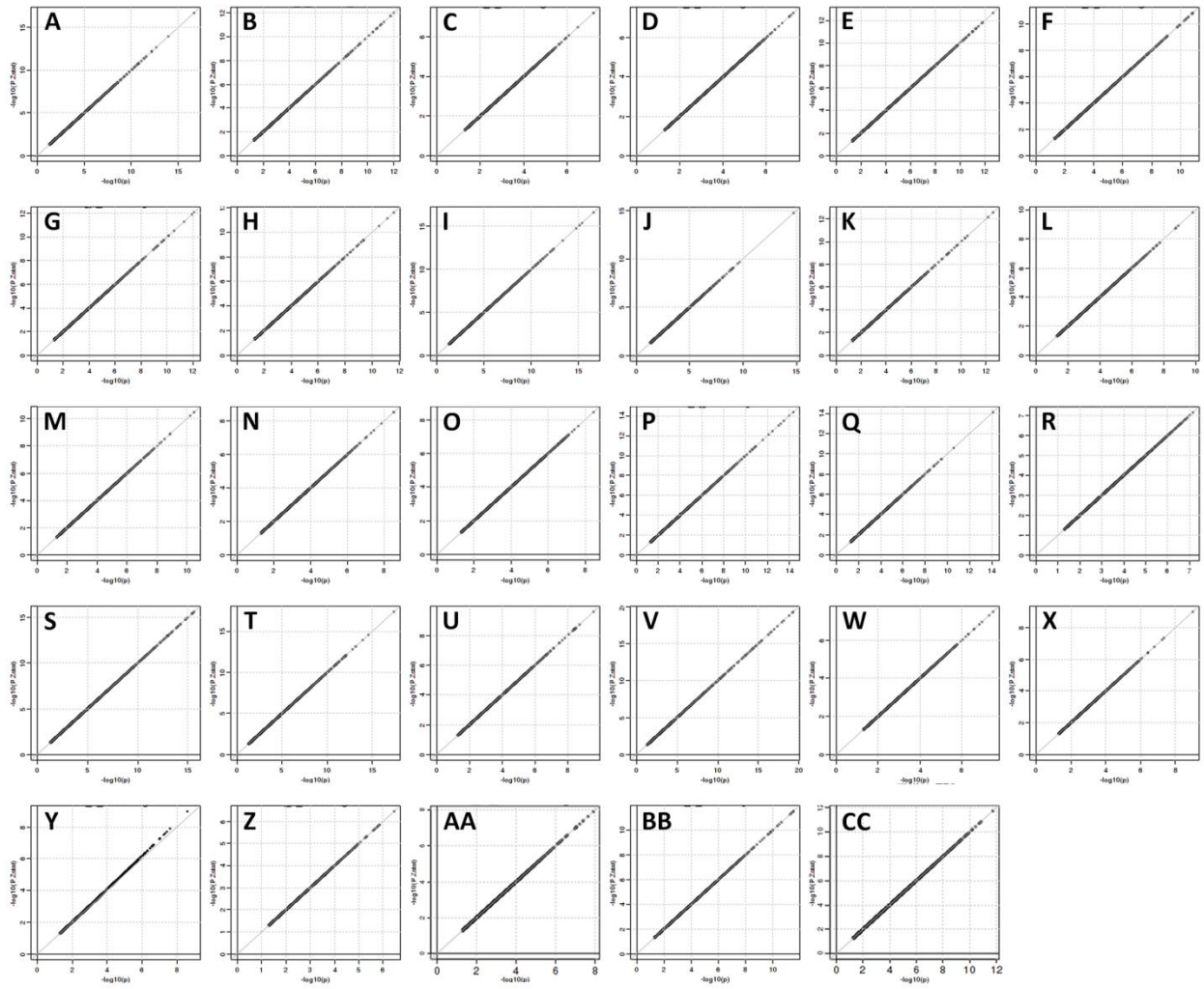
Supplementary Figure 2.1.2: Lambda-N and SE-N plots per cohort in CREAM-ASN generated from EasyQC

A=BES (n=590), B=Nagahama (n=2730); C=SCES (n=1724), D=SIMES (n=2275), E=SINDI (n=2110), F=STARS (n=817), G=SP2-610 (n=871), H=SP2-1M (n=818).

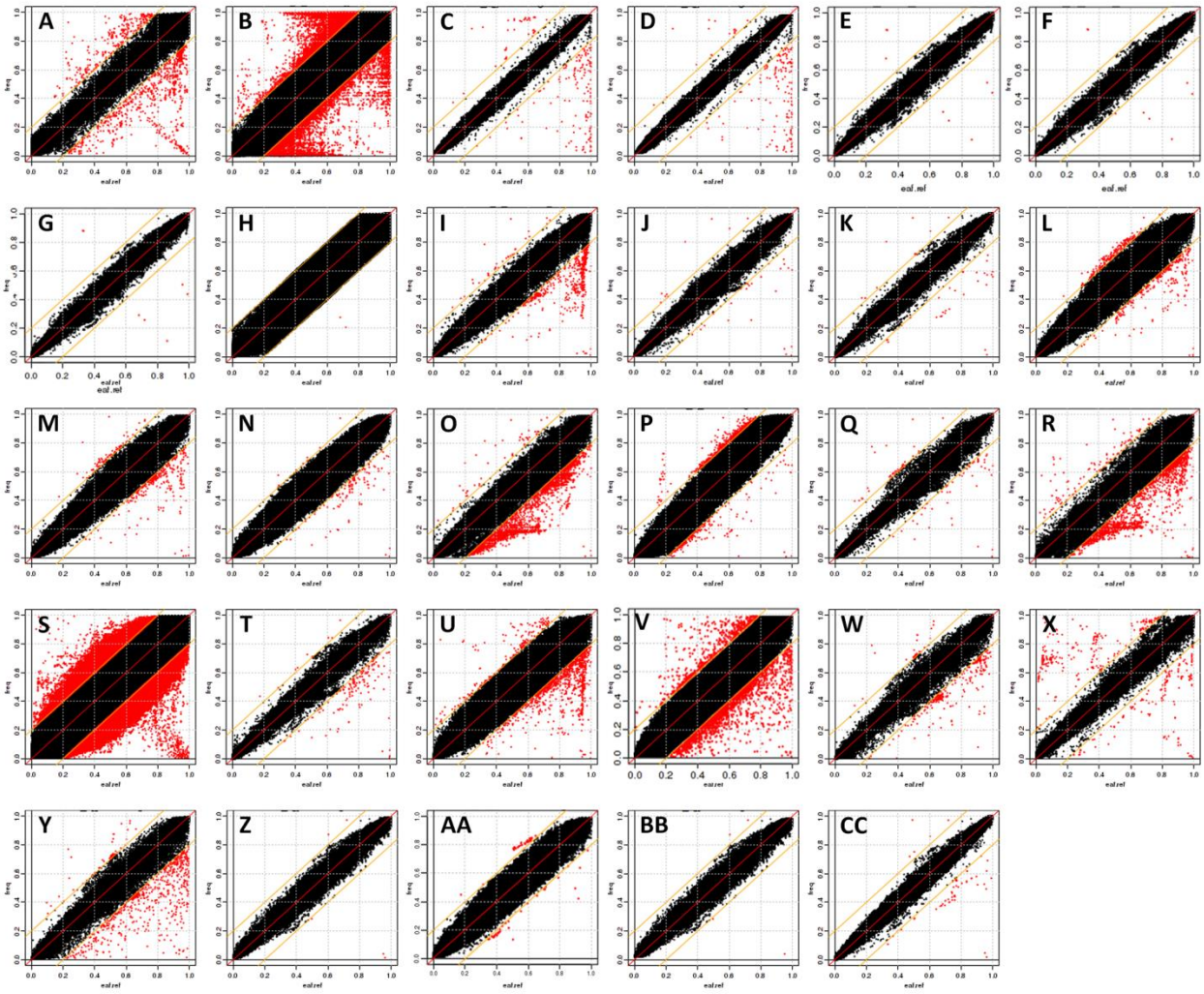
Supplementary Figures 2.2: EasyQC plots per cohort – CREAM-EUR



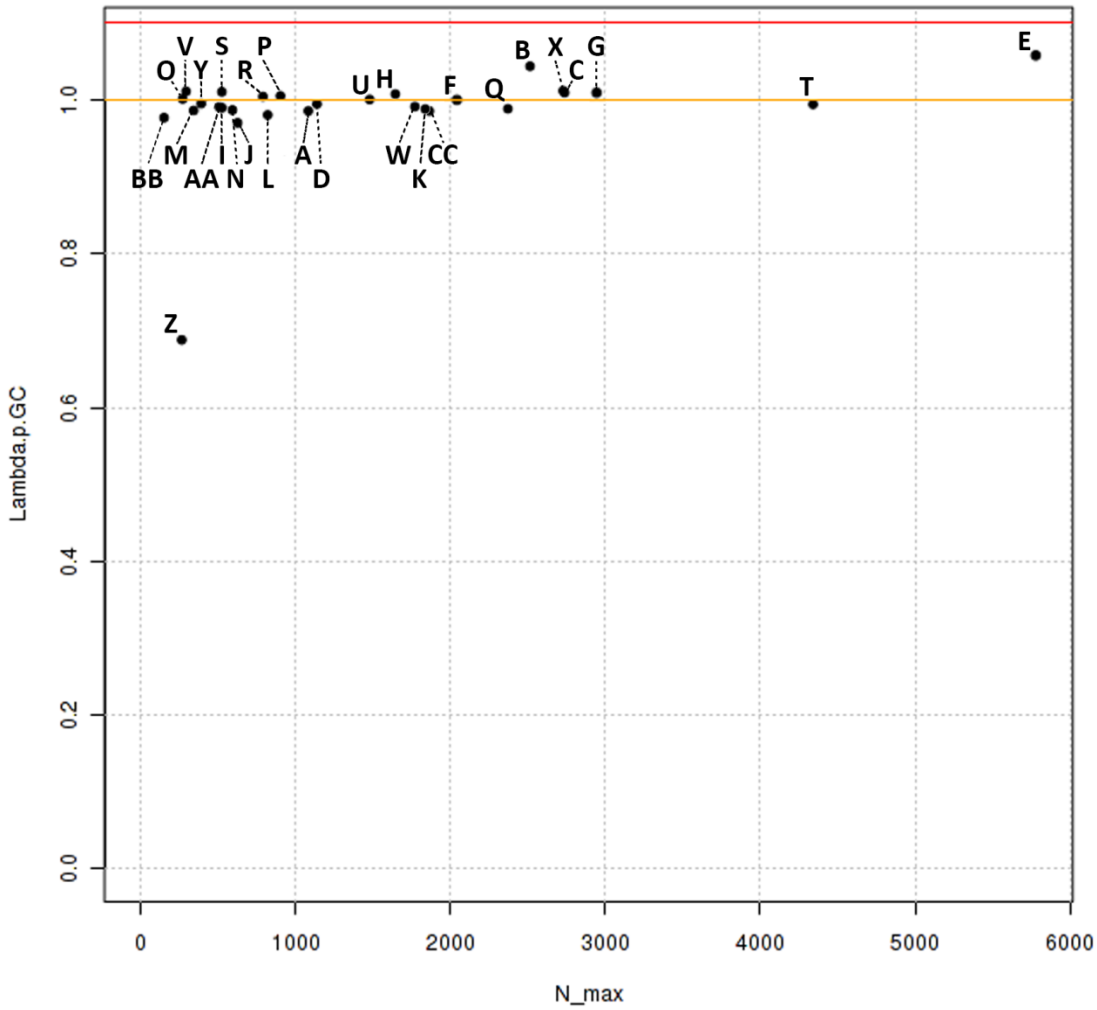
Supplementary Figure 2.2.1: QQ-plots per cohort in CREAM-EUR generated from EasyQC
A=EPIC (n=1084), B=ERF (n=2610), C=GHS1 (n=2738), D=GHS2 (n=1140), E=RSI (n=5787), F=RSII (n=2038), G=RSIII (n=2950), H=1958BBC (n=1658), I=ALIENOR (n=509), J=ANZRAG (n=648), K=ALSPAC (1865), L=CROATIA-KORCULA (n=822), M=CROATIA-SPLIT (n = 344), N=CROATIA-VIS (n=527), O=WESDR (n=295), P=EGCUT (n=904), Q=KORAF (n=2372), R=DCCT (n=791), S=OGP (n=509), T=TWINSUK (n=4342), U=YFS (n=1480), V=FITSA (n=329), W=AREDS (n=1842), X=FRAM (n=2729), Y=FECD (n=393), Z=TEST (n=267), AA=ORCADES (n=1165), BB=BATS (n=158), CC=BMES (n=1896).



Supplementary Figure 2.2.2: PZ-plots per cohort in CREAM-EUR generated from EasyQC
A=EPIC (n=1084), B=ERF (n=2610), C=GHS1 (n=2738), D=GHS2 (n=1140), E=RSI (n=5787), F=RSII (n=2038), G=RSIII (n=2950), H=1958BBC (n=1658), I=ALIENOR (n=509), J=ANZRAG (n=648), K=ALSPAC (1865), L=CROATIA-KORCULA (n=822), M=CROATIA-SPLIT (n = 344), N=CROATIA-VIS (n=527), O=WESDR (n=295), P=EGCUT (n=904), Q=KORAF (n=2372), R=DCCT (n=791), S=OGP (n=509), T=TWINSUK (n=4342), U=YFS (n=1480), V=FITSA (n=329), W=AREDS (n=1842), X=FRAM (n=2729), Y=FECD (n=393), Z=TEST (n=267), AA=ORCADES (n=1165), BB=BATS (n=158), CC=BMES (n=1896).

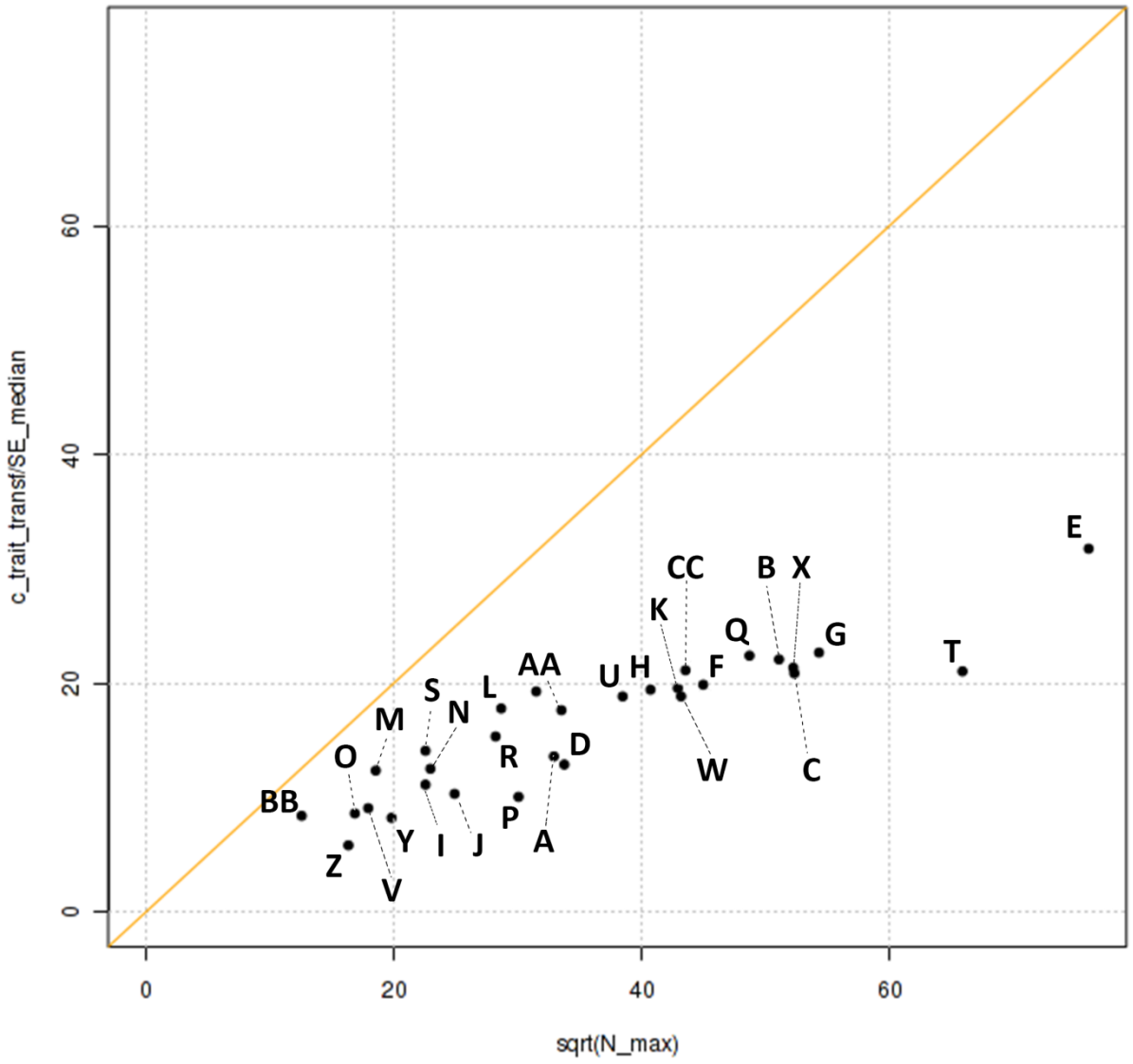


Supplementary Figure 2.2.3: AF-plots per cohort in CREAM-EUR generated from EasyQC
A=EPIC (n=1084), B=ERF (n=2610), C=GHS1 (n=2738), D=GHS2 (n=1140), E=RSI (n=5787), F=RSII (n=2038), G=RSIII (n=2950), H=1958BBC (n=1658), I=ALIENOR (n=509), J=ANZRAG (n=648), K=ALSPAC (1865), L=CROATIA-KORCULA (n=822), M=CROATIA-SPLIT (n = 344), N=CROATIA-VIS (n=527), O=WESDR (n=295), P=EGCUT (n=904), Q=KORAF (n=2372), R=DCCT (n=791), S=OGP (n=509), T=TWINSUK (n=4342), U=YFS (n=1480), V=FITSA (n=329), W=AREDS (n=1842), X=FRAM (n=2729), Y=FECD (n=393), Z=TEST (n=267), AA=ORCADES (n=1165), BB=BATS (n=158), CC=BMES (n=1896).



Supplementary Figure 2.2.4: Lambda-N plot of cohorts in CREAM-EUR generated from EasyQC

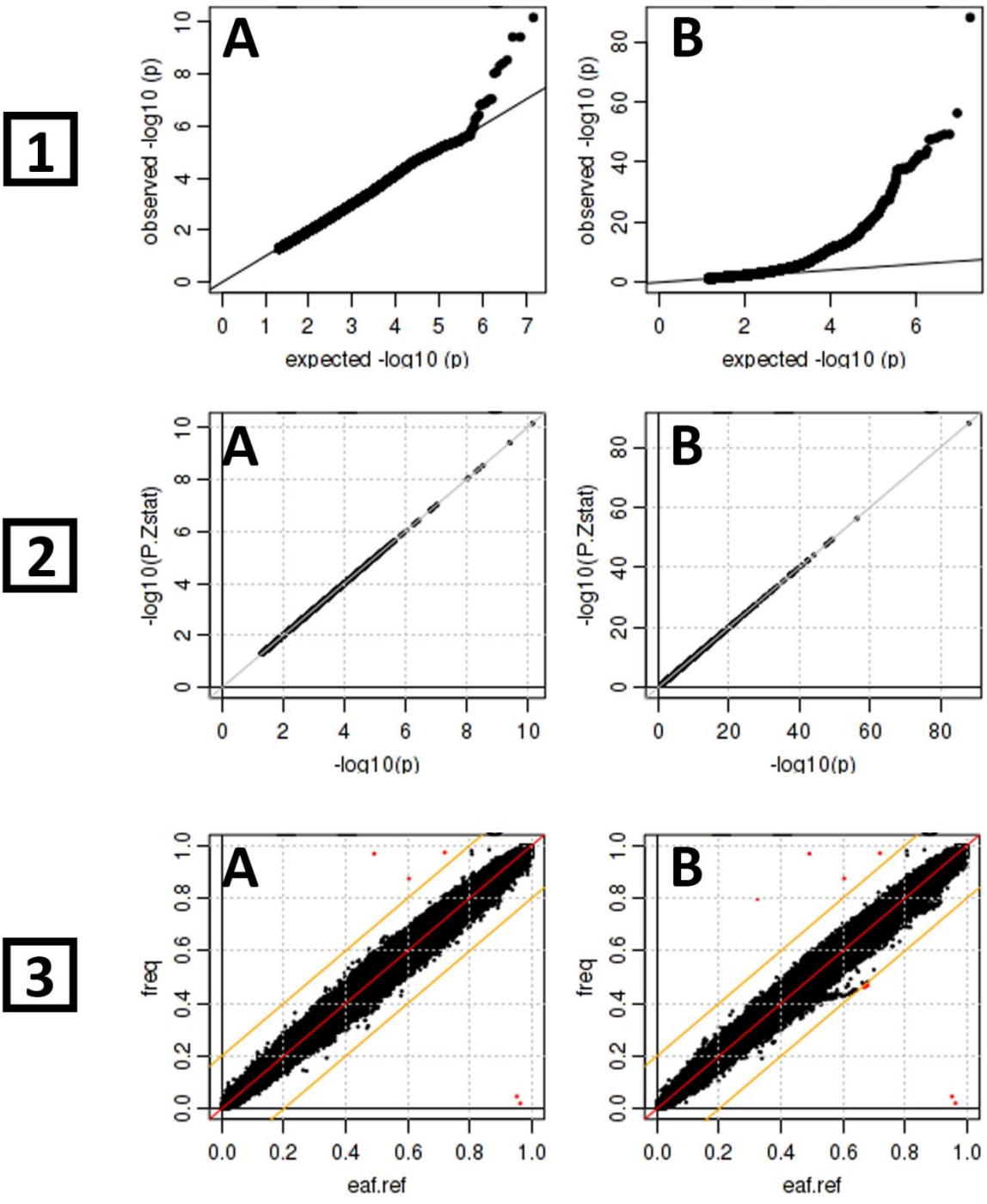
A=EPIC (n=1084), B=ERF (n=2610), C=GHS1 (n=2738), D=GHS2 (n=1140), E=RSI (n=5787), F=RSII (n=2038), G=RSIII (n=2950), H=1958BBC (n=1658), I=ALIENOR (n=509), J=ANZRAG (n=648), K=ALSPAC (1865), L=CROATIA-KORCULA (n=822), M=CROATIA-SPLIT (n = 344), N=CROATIA-VIS (n=527), O=WESDR (n=295), P=EGCUT (n=904), Q=KORAF (n=2372), R=DCCT (n=791), S=OGP (n=509), T=TWINSUK (n=4342), U=YFS (n=1480), V=FITSA (n=329), W=AREDS (n=1842), X=FRAM (n=2729), Y=FECD (n=393), Z=TEST (n=267), AA=ORCADES (n=1165), BB=BATS (n=158), CC=BMES (n=1896).



Supplementary Figure 2.2.5: SE-N plot of cohorts in CREAM-EUR generated from EasyQC

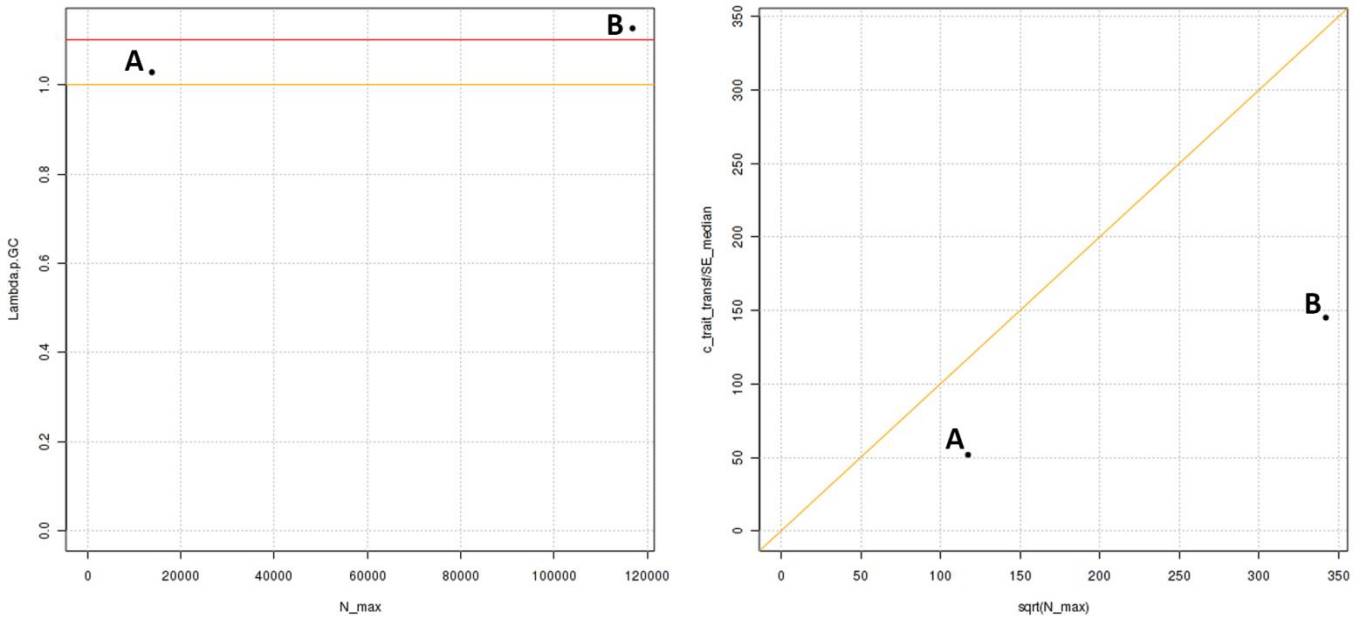
A=EPIC (n=1084), B=ERF (n=2610), C=GHS1 (n=2738), D=GHS2 (n=1140), E=RSI (n=5787), F=RSII (n=2038), G=RSIII (n=2950), H=1958BBC (n=1658), I=ALIENOR (n=509), J=ANZRAG (n=648), K=ALSPAC (1865), L=CROATIA-KORCULA (n=822), M=CROATIA-SPLIT (n = 344), N=CROATIA-VIS (n=527), O=WESDR (n=295), P=EGCUT (n=904), Q=KORAF (n=2372), R=DCCT (n=791), S=OGP (n=509), T=TWINSUK (n=4342), U=YFS (n=1480), V=FITSA (n=329), W=AREDS (n=1842), X=FRAM (n=2729), Y=FECD (n=393), Z=TEST (n=267), AA=ORCADES (n=1165), BB=BATS (n=158), CC=BMES (n=1896).

Supplementary Figure 2.3: EasyQC plots per cohort – 23andMe



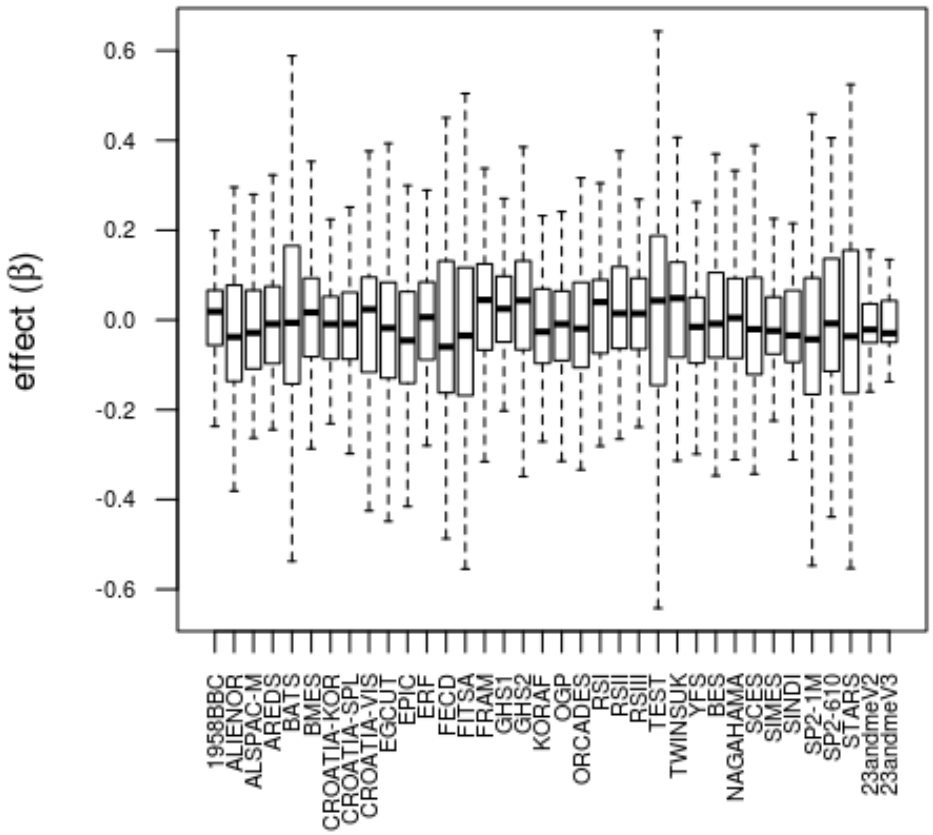
Supplementary Figure 2.3.1: Quality control – QQ, P-Z, AF-plots per cohort in 23andMe generated from EasyQC

Panel 1: QQ-plots per cohort in 23andMe; Panel 2: P-Z plots per cohort in 23andMe; Panel 3: AF plots per cohort in 23andMe; A=23andMe_V2 (n=12128), B=23andMe_V3 (n=92165).



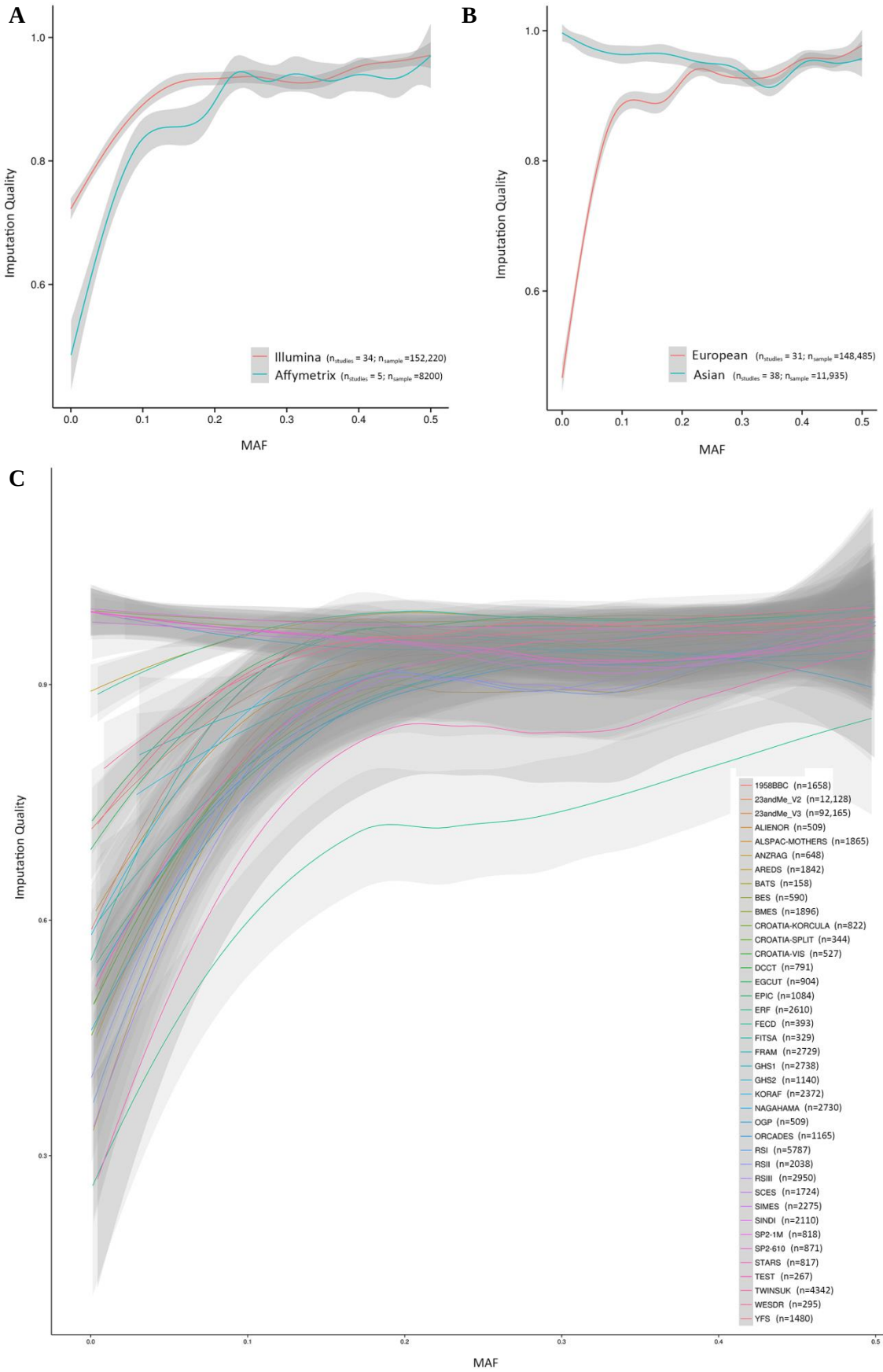
Supplementary Figure 2.3.2: Lambda-N and SE-N plots per cohort in 23andMe generated from EasyQC
A=23andMe_V2 (n=12128), B=23andMe_V3 (n=92165).

Supplementary Figure 3: Boxplots of effect sizes per cohort

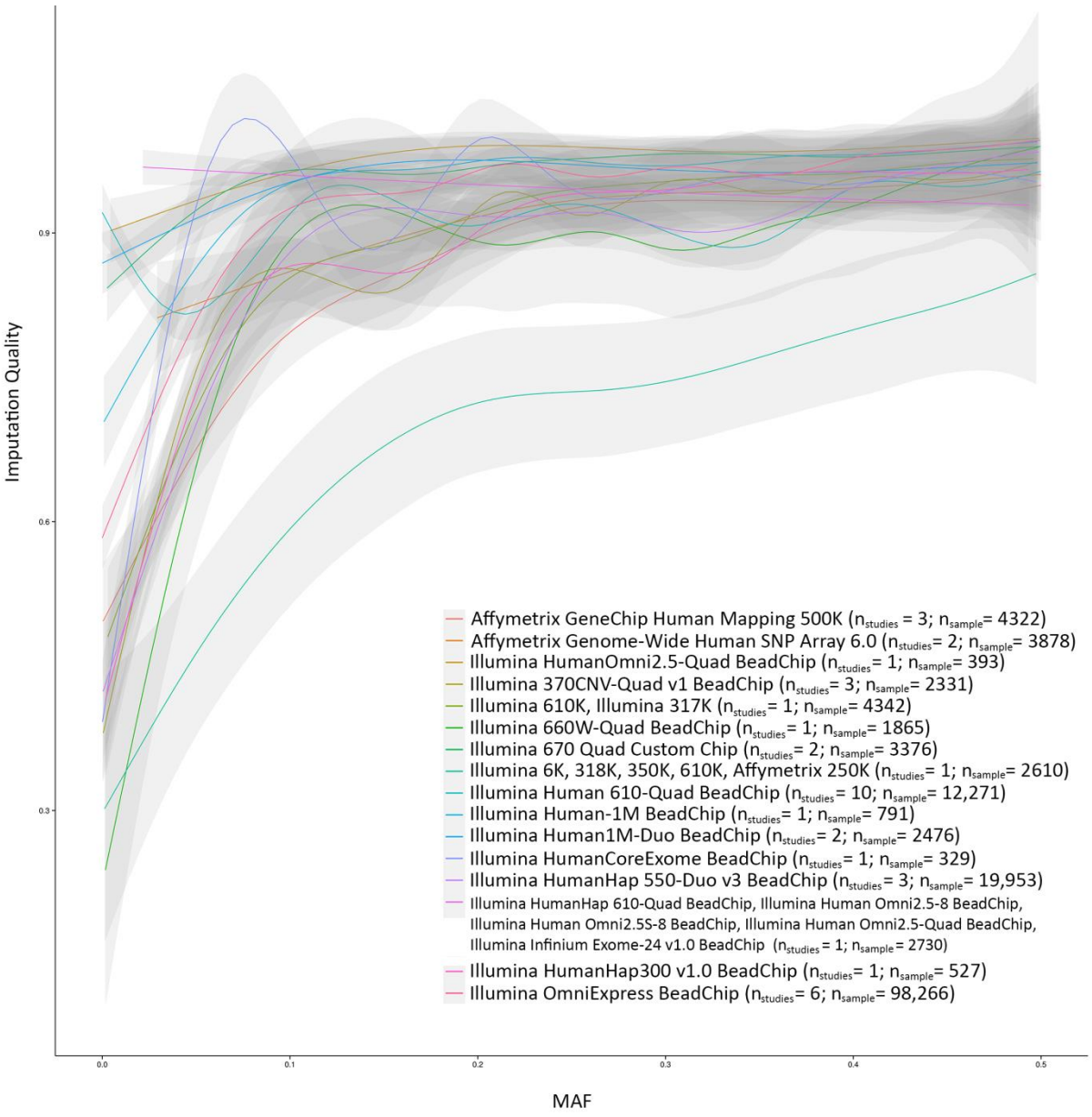


Tukey style box plots of the effect sizes of the 167 independent genetic variants associated with refractive error and myopia derived from the meta-analysis of stage 3 (n=160,420). The bottom and top of the box depict the first and third quartiles, the band is the median and the whiskers extend to the lowest and highest data points. Outliers were not plotted.

Supplementary Figure 4: Imputation Quality of genetic variants of Stage 3



D

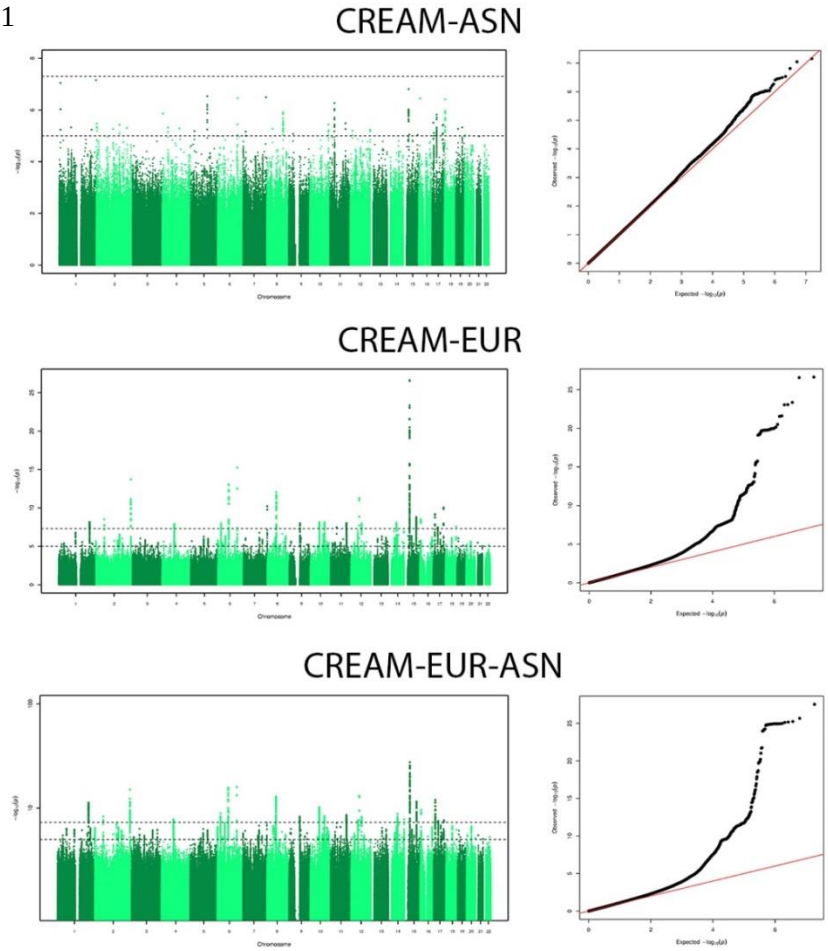


Imputation quality per MAF computed in R (ggplot2)

A) Overall imputation quality (r^2) of the 167 genetic variants before filtering (i.e. $r^2 > 0.3$ and MAF < 0.01 CREAM or < 0.001 23andMe) of the stage 3 meta-analysis of all cohorts using an Illumina or Affymetrix platform, plotted against the minor allele frequency (MAF). **B)** r^2 of the 167 genetic variants before filtering of the stage 3 meta-analysis comparing all European cohorts and Asian, plotted against the minor allele frequency (MAF). **C)** r^2 of the 167 genetic variants before filtering of the stage 3 meta-analysis of all participating cohorts. **D)** r^2 of the 167 genetic variants before filtering of the stage 3 meta-analysis based on type of array used. Bands indicate the 95% confidence intervals; $n_{studies}$: number of cohorts; n_{sample}: number of participants tested.

Supplementary Figure 5: Manhattan plots and QQ plots per Stage (1-3)

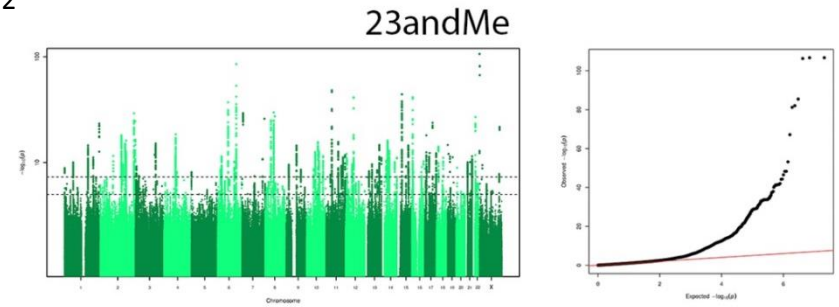
Stage 1



Shown are the Manhattan plots and QQ plots depicting P values for association of the meta-analysis of Stage 1.

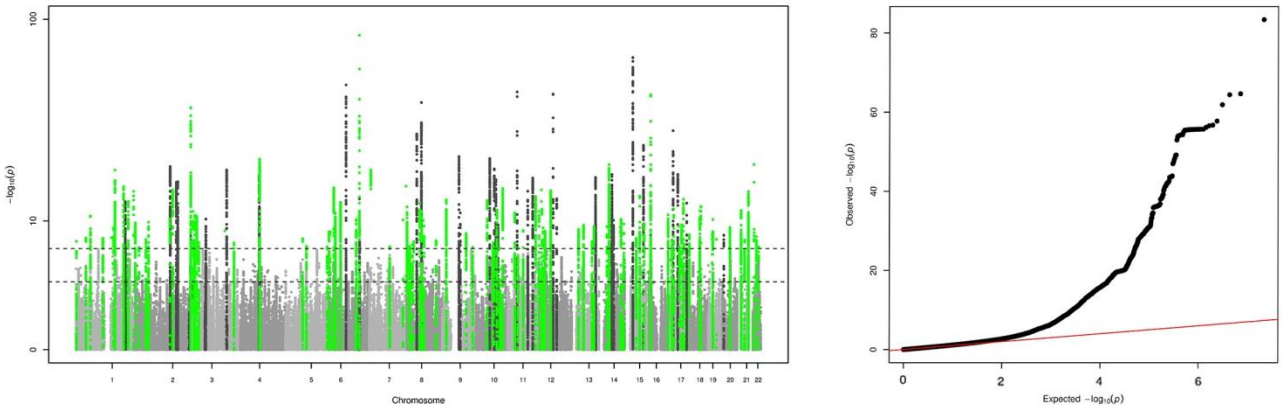
CREAM-EUR (n_{sample}= 44,192 participants; $n_{genetic\ variants}$ =9.6M); $\lambda_{genomic\ inflation}$ = 1.119. CREAM-ASN (n_{sample} = 11,935 participants; $n_{genetic\ variants}$ = 7.8M); $\lambda_{genomic\ inflation}$ = 1.022. CREAM-EUR-ASN (n_{sample} = 56,127 participants; $n_{genetic\ variants}$ = 9.3M); $\lambda_{genomic\ inflation}$ = 1.124. The red lines in the QQ plots indicate x=y.

Stage 2



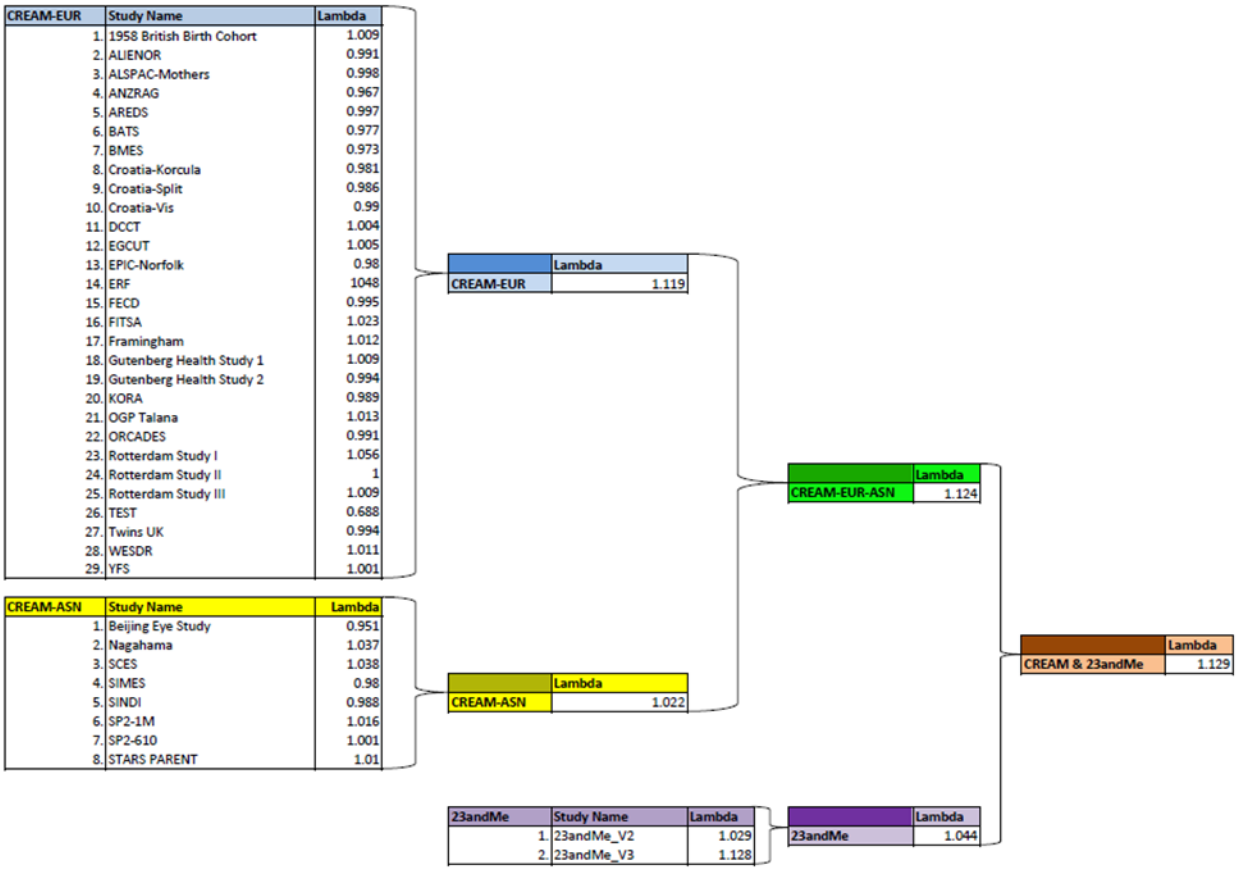
23andMe (n_{sample}= 104,293 participants; $n_{genetic\ variants}$ = 10.6M); $\lambda_{genomic\ inflation}$ = 1.119. The red line in the QQ plot indicates x=y.

Stage 3

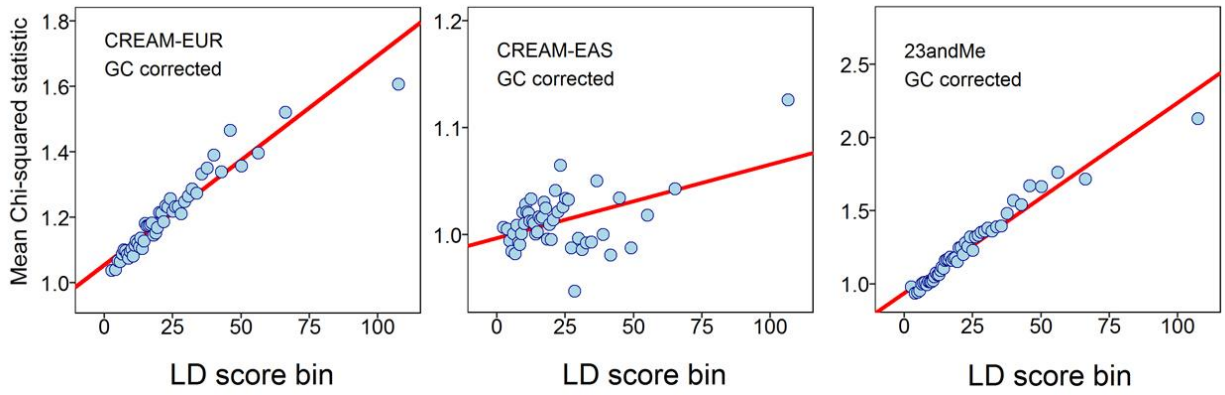


Shown is the Manhattan plot depicting P values for association of the meta-analysis of CREAM-EUR&ASN and 23andMe (n_{sample}=160,420 participants; $n_{genetic\ variants}$ = 11M), highlighting new ($P < 5 \times 10{-}8$ for the first time; green) and known (dark grey) refractive error loci previously; $\lambda_{genomic\ inflation}$ = 1.129. The red line indicates x=y.

Supplementary Figure 6: Lambdas of all cohorts and fixed effects meta-analyses

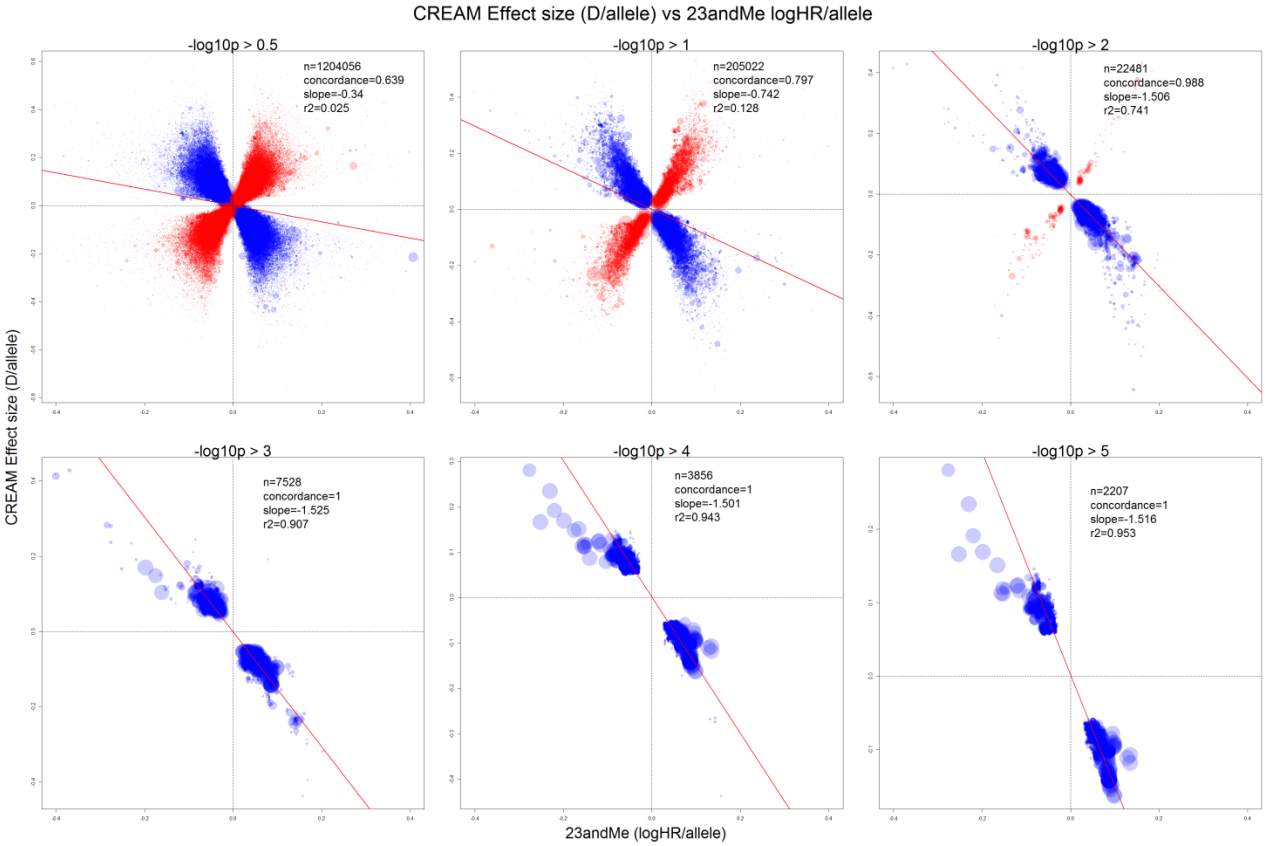


Supplementary Figure 7: LD-score regressions per ancestry of CREAM and 23andMe



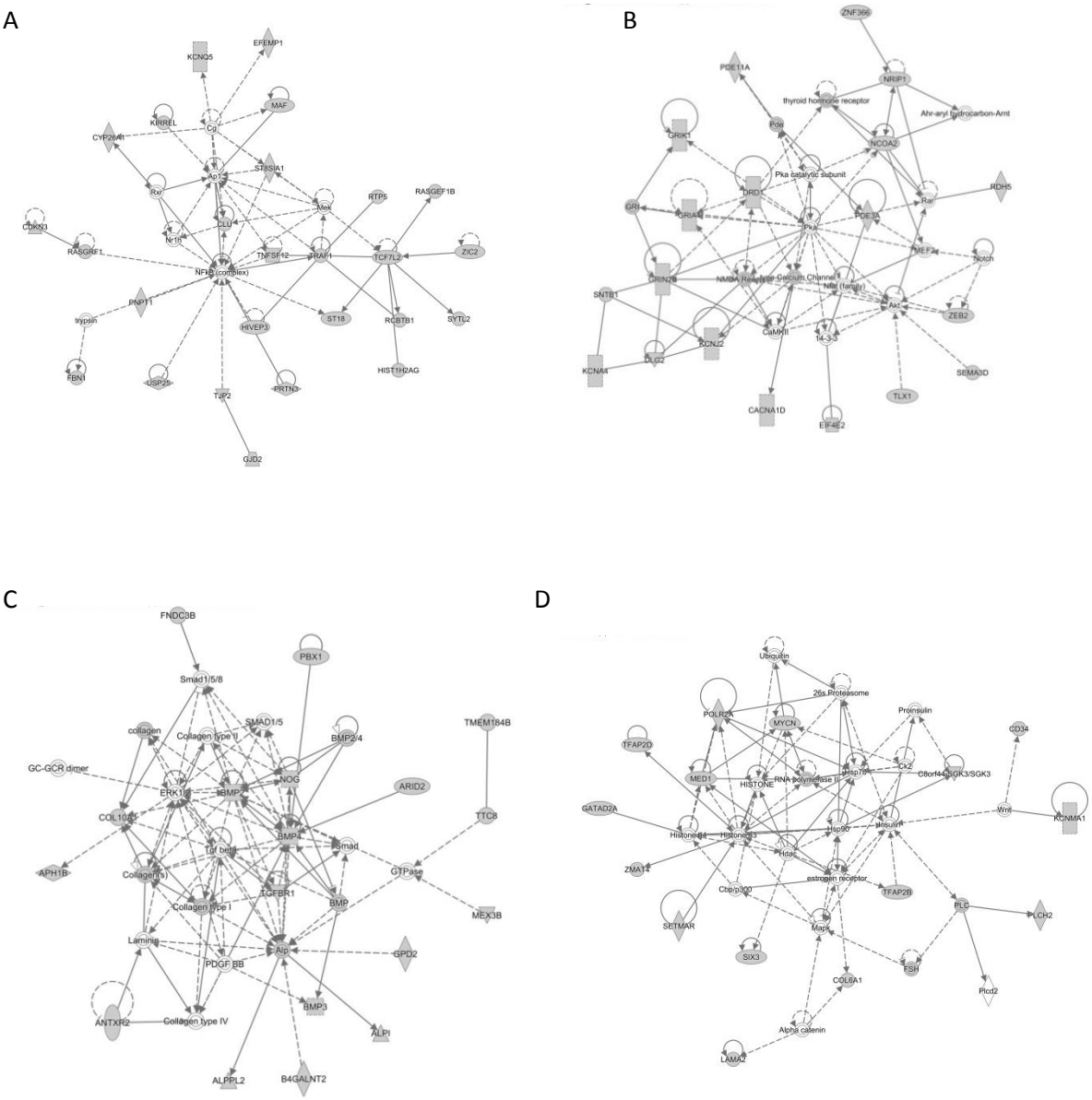
We used Popcorn[57] to investigate ancestry-related differences in the genetic architecture of refractive error and myopia. Pairwise analyses were carried out using the GWAS summary statistics from the 23andMe (n=104,292), CREAM-EUR (n=44,192) and CREAM-EAS (n=9,826) meta-analyses. Only SNPs with MAF ≥ 5% were included, resulting in a final set of 3,625,602 SNPs for analyses involving 23andMe and 3,642,928 SNPs for the CREAM-EUR vs. CREAM-EAS analysis.

Supplementary Figure 8: Effects comparison SphE and AODM using different p-value thresholds



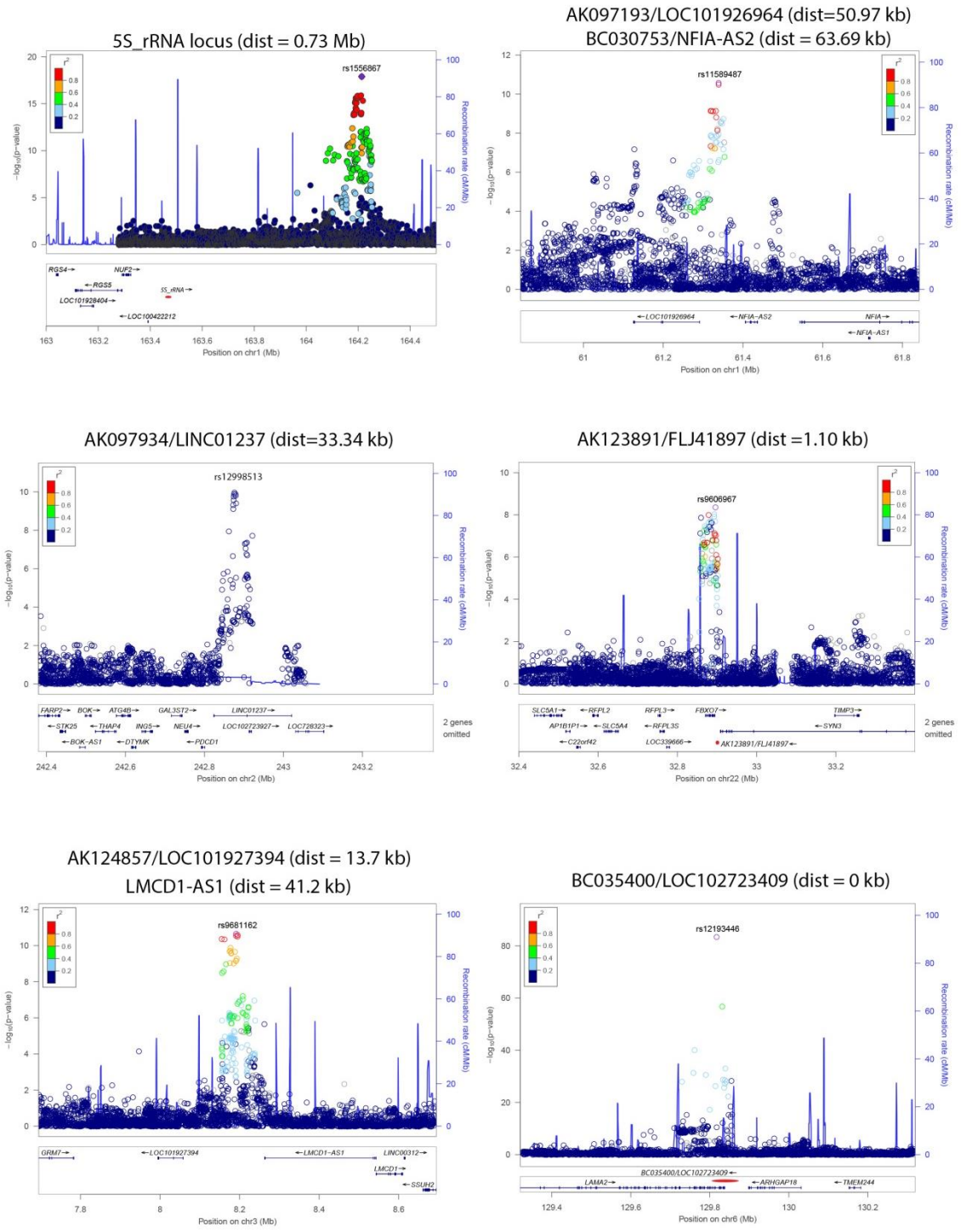
Shown are the graphs for the comparison of the effects, SphE and AODM, using different p-value thresholds. These p-values are derived from the meta-analysis of stage 1 and 2, i.e. CREAM and 23andMe. Red line = regression line; n = number of genetic variants tested at different *P* value thresholds (-log10p > 0.5 – -log10p >5); concordance = concordance of correlation coefficient; slope = slope of regression line; r^2= Pearson correlation coefficient.

Supplementary Figure 9: Top canonical pathways of Ingenuity Pathway Analysis



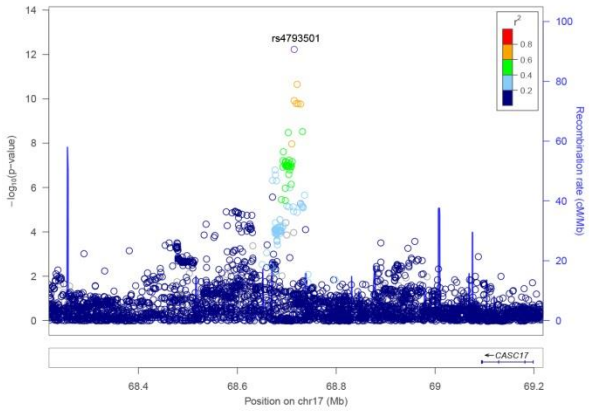
The 197 of the 208 genes annotated to the top hits identified at Stage 3 were present in the IPA database and mapped to networks and pathways. The networks were identified by right-tailed Fisher's exact tests. Genes within the network indicated in grey are genes associated with refractive error. A) Glutamate receptor signaling, *P* value = $1.56E^{-4}$; B) Factors Promoting Cardiogenesis in Vertebrates, *P* value = $1.78E^{-4}$; C) CREB Signaling in Neurons; *P* value = $1.37E^{-3}$; D) Human Embryonic Stem Cell Pluripotency, *P* value = $1.83E^{-3}$

Supplementary Figure 10: Locus Zoom plots of RNA gene regions

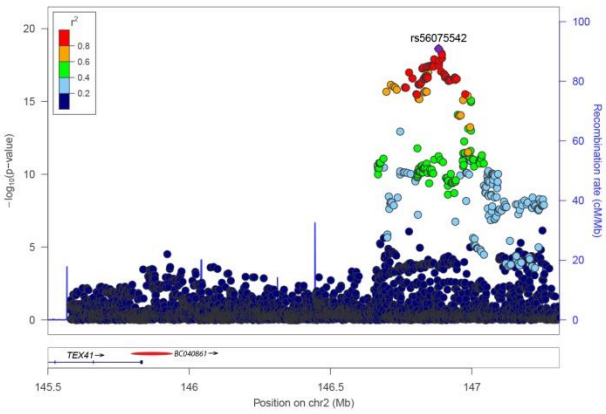


Regional plots of the RNA genes depicting the p-values derived from the meta-analysis of stage 3 (n=160,420), linkage disequilibrium and recombination ratio. Some of the RNA genes were not depicted by the Locus Zoom software, in which case they were added as the red regions between the genes annotated by Locus Zoom; dist, distance; $r^2 = r^2$ of linkage disequilibrium.

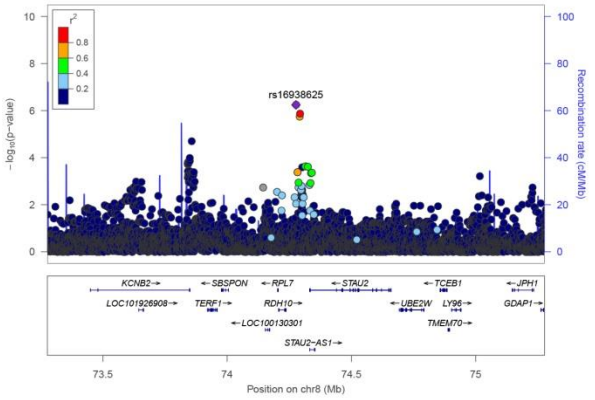
BC039327/CASC17 (dist = 0.38 Mb)



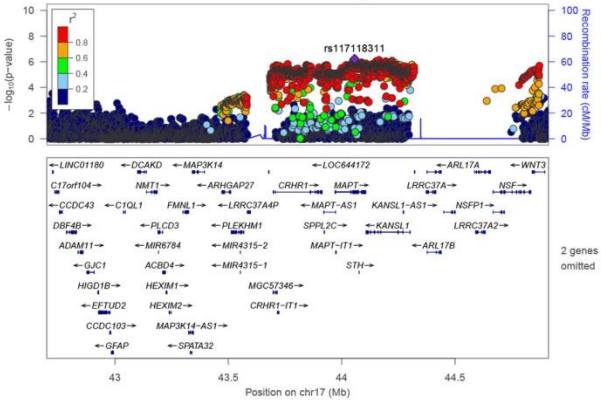
BC040861 (dist = 0.97 Mb)



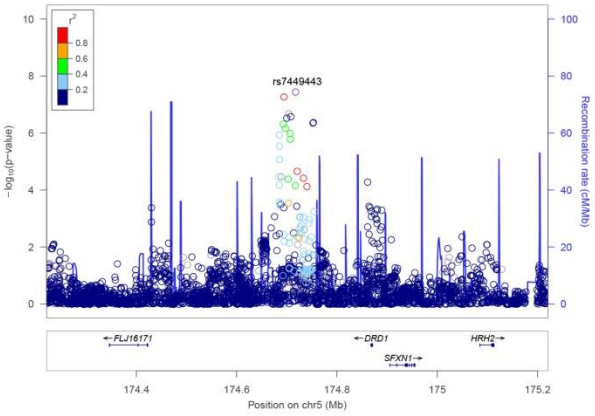
BC127738/LOC100130301 (Gene based finding; dist = 105.1 kb)



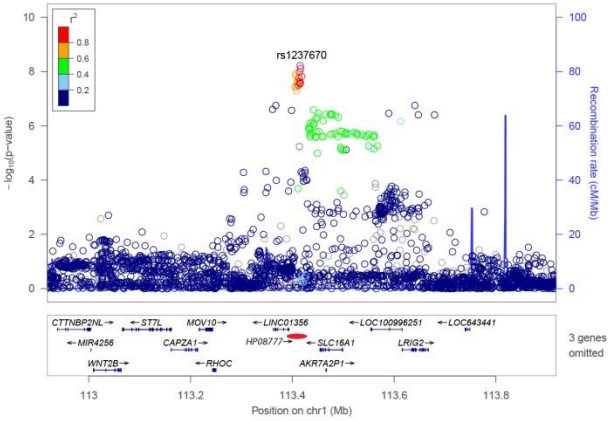
CRHR1-IT1 (Gene based finding; dist = 2.26 Mb)



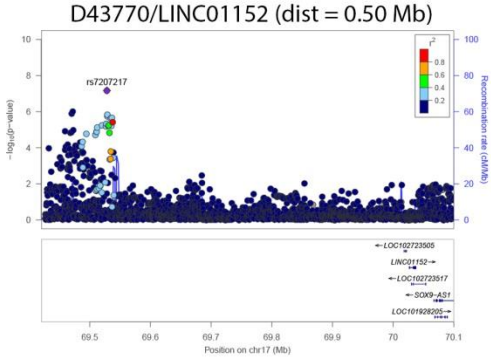
FLJ16171/LINC01951 (dist = 0.30 Mb)



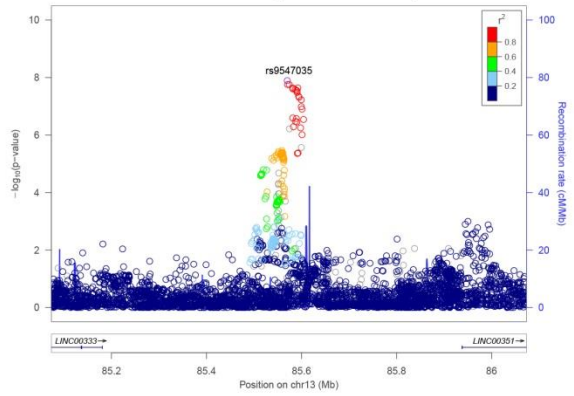
HP08777 (dist = 0 kb)



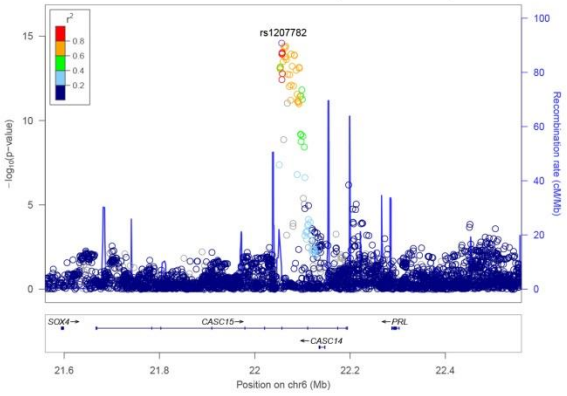
D43770/LINC01152 (dist = 0.50 Mb)



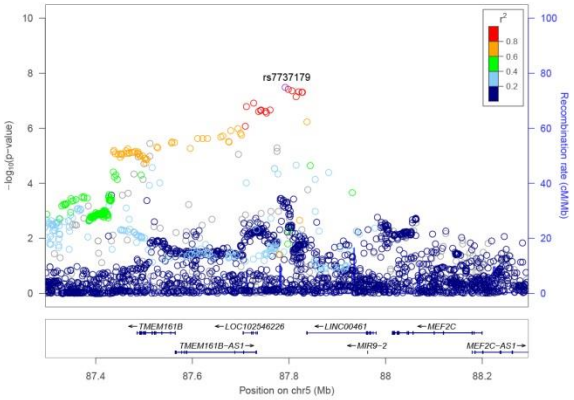
LINC00333 (dist = 393 kb)
LINC00351 (dist = 364 kb)



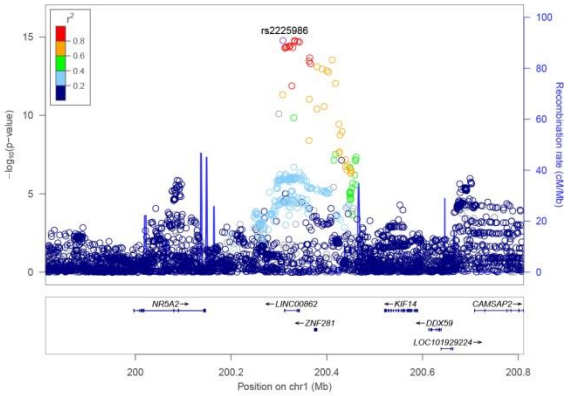
LINC00340/CASC15 (dist = 0 kb)



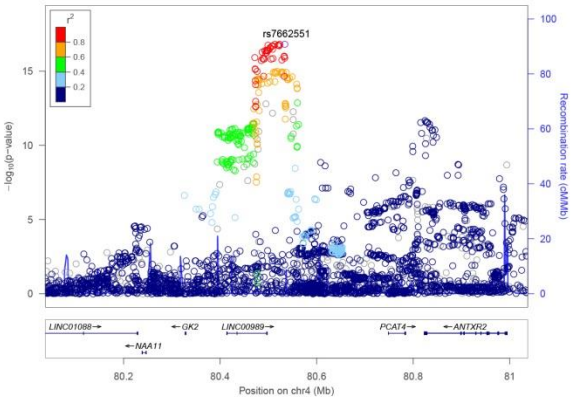
LINC00461 (dist = 41 kb)
TMEM161B-AS1 (dist = 63 kb)



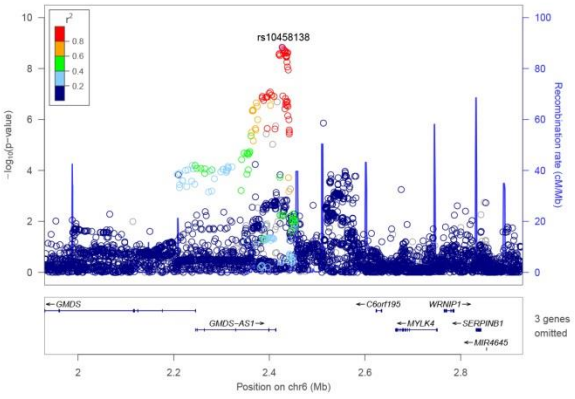
LINC00862 (dist = 0 kb)



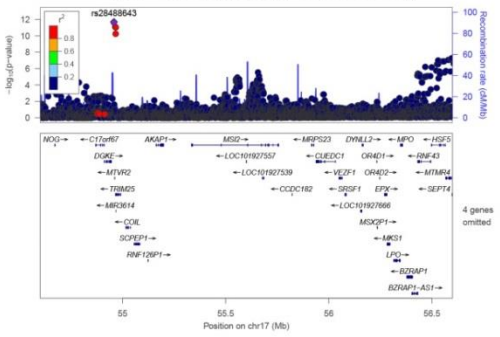
LOC100506035/LINC00989 (dist = 40 kb)



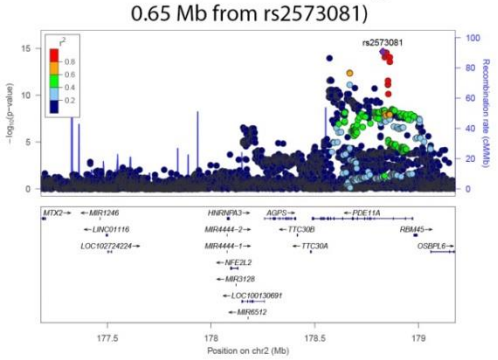
LOC100508120/GMDS-AS1 (dist = 0 kb)



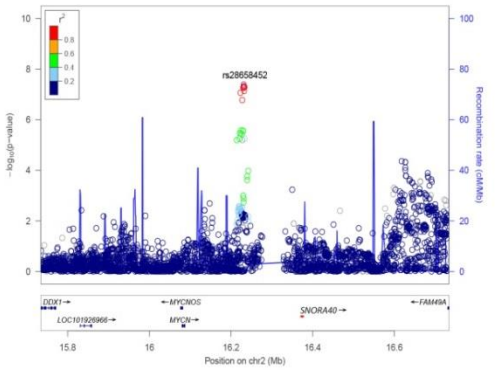
LOC101927557 (Gene based finding; dist = 0.64 Mb from rs28488643)



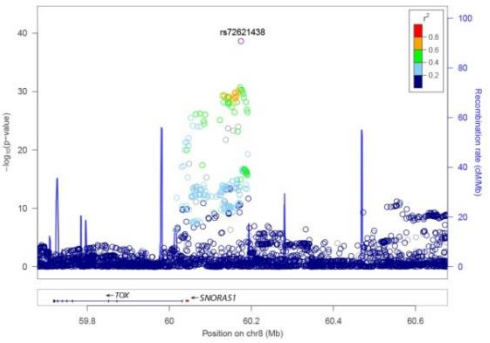
MIR6512 (Gene based finding; 0.65 Mb from rs2573081)



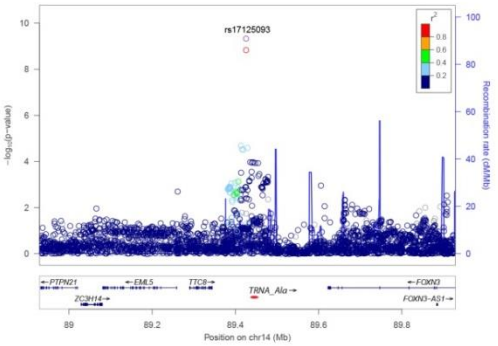
SNORA40 (dist = 146 kb)



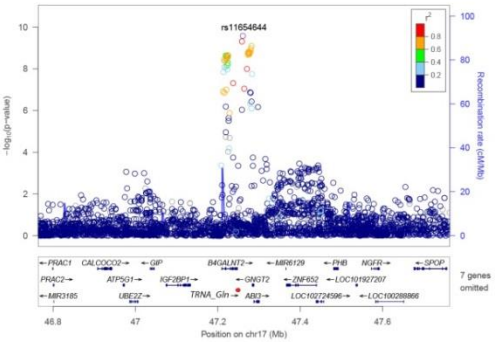
SNORA51 (dist = 129 kb)



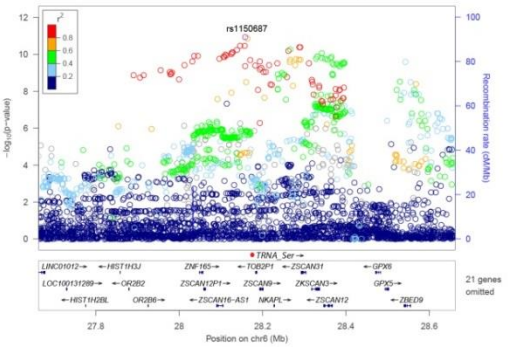
TRNA_Ala (dist = 16.5 kb)



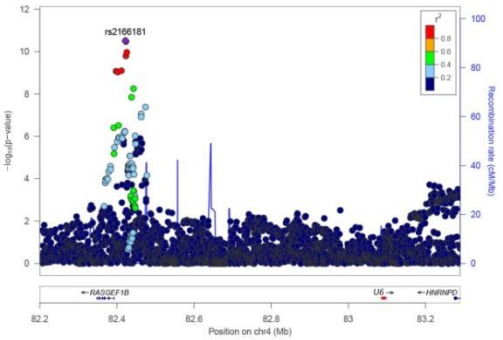
TRNA_Gln (dist = 6.4 kb)



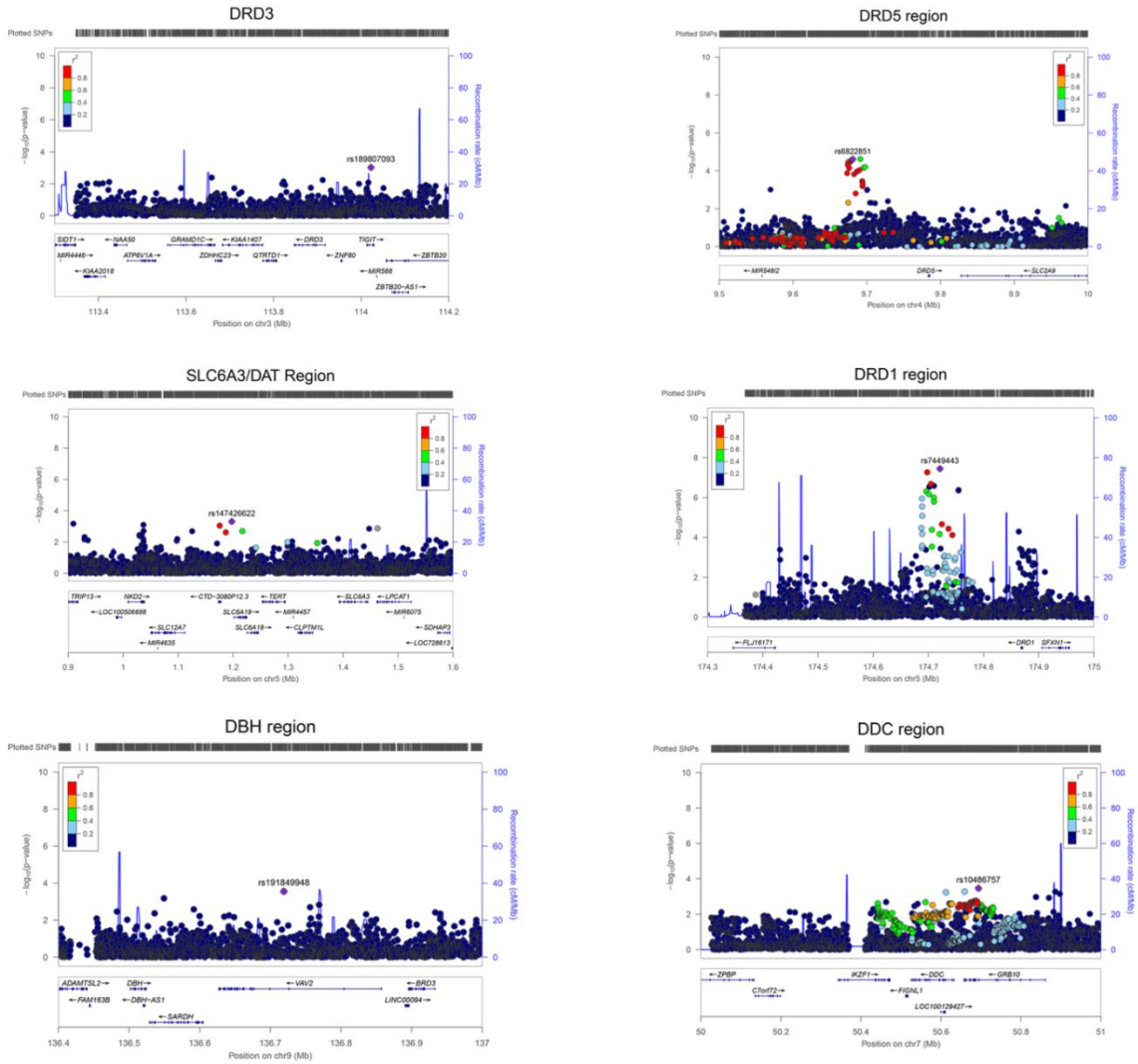
TRNA_Ser (dist = 18.4 kb)



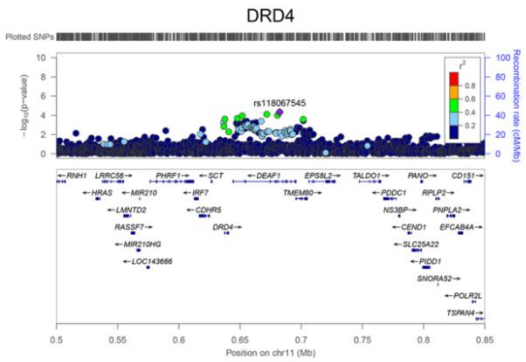
U6 (dist = 0.67 Mb)

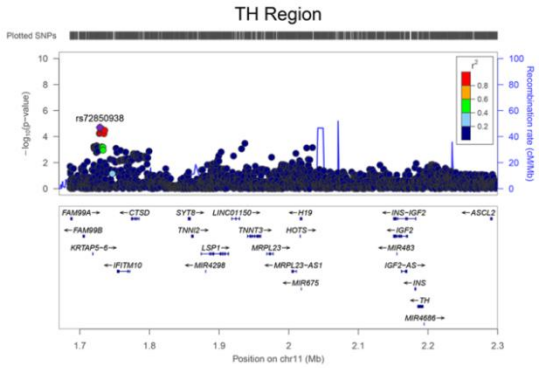


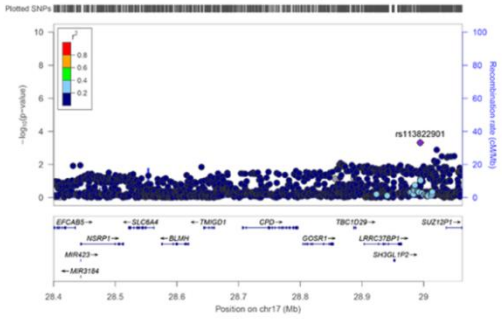
Supplementary Figure 11: Locus Zoom plots of dopamine pathway regions

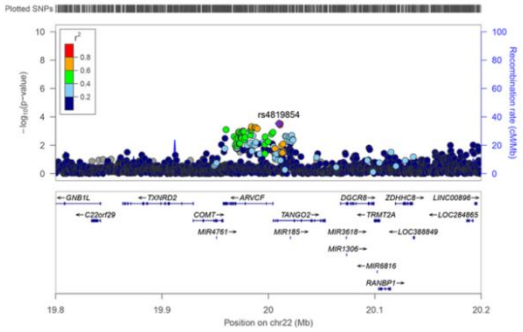


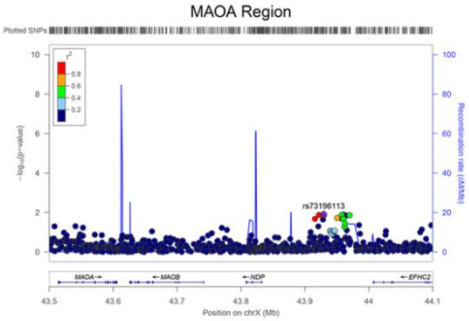
Regional plots of the key genes in the dopamine pathway depicting the p-values derived from the meta-analysis of stage 3 (n=160,420), linkage disequilibrium and recombination ratio; r^2 = r^2 of linkage disequilibrium.


DRD4
Plotted SNPs
rs11067545
Position on chr11 (Mb)

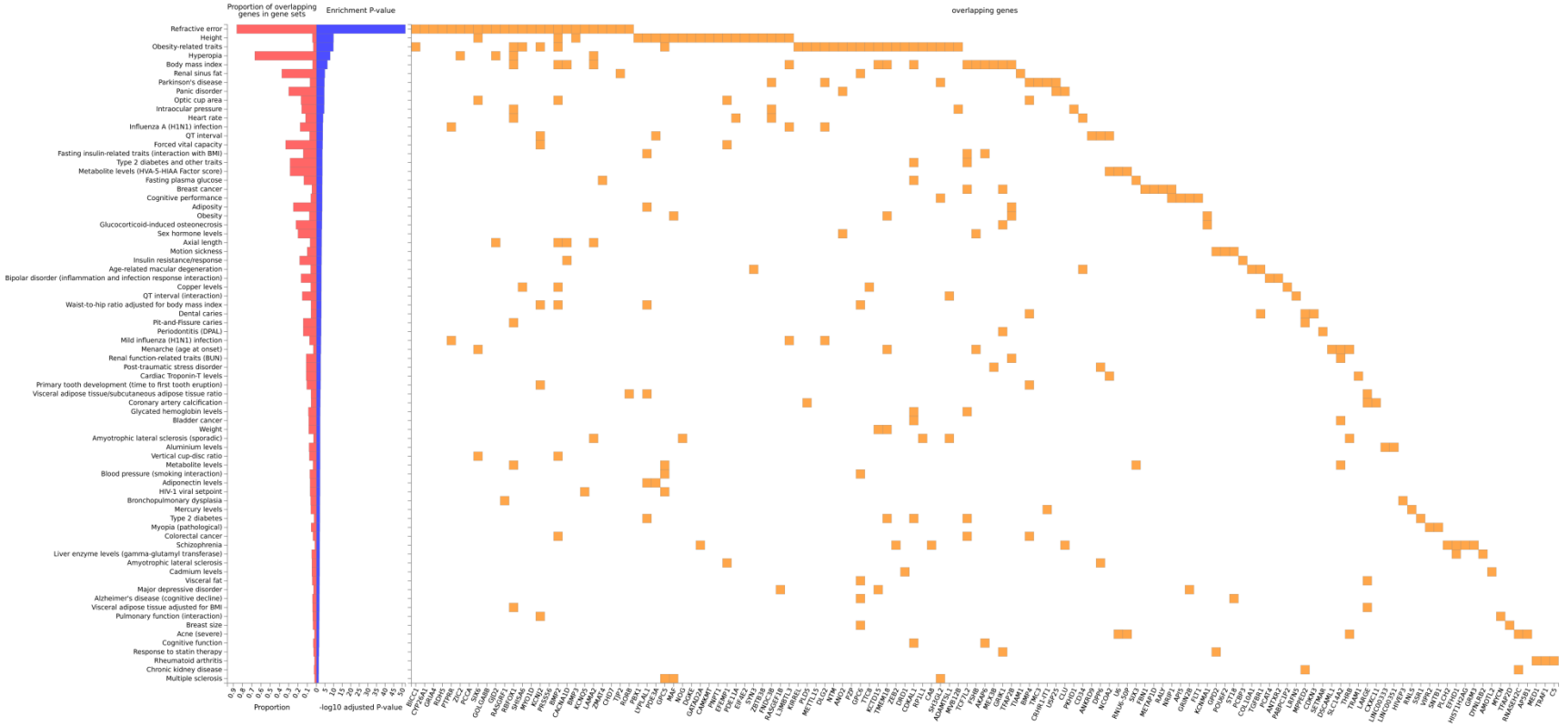

TH Region
Plotted SNPs
rs72850938
Position on chr11 (Mb)


SLC6A4/SERT Region
Plotted SNPs
rs113822901
Position on chr17 (Mb)


COMT region
Plotted SNPs
rs4819854
Position on chr22 (Mb)


MAOA Region
Plotted SNPs
rs73196113
Position on chrX (Mb)

Supplementary Figure 12: GWAS catalog comparison of refractive error genes with other diseases



Supplementary Table 1a: Descriptives per cohort

CREAM-EUR

Study Name	Origin	Study design	n	age (sd)	% female	mean SE
1958 British Birth Cohort	United Kingdom	population based study	1658	42.00 (0.00)	46.0	-0.96 (2.003)
ALIENOR	France	population based study	509	79.15 (4.06)	56.8	0.98 (1.97)
ALSPAC-Mothers	United Kingdom	population based study	1865	45.02 (4.53)	100.0	-0.76 (2.16)
ANZRAG	Australia	POAG cases	648	79.02 (12.08)	49.3	-0.21 (2.41)
AREDS	United States	population based study	1842	68.08 (4.71)	59.0	0.54 (2.16)
BATS	Australia	population based twin study	158	26.52 (2.41	56.3	-0.51 (1.15)
BMES	Australia	population based study	1896	67.09 (9.16)	57.3	0.62 (2.12)
Croatia-Korcula	Croatia	population based study	822	56.33 (13.34)	64.8	-0.15 (1.60)
Croatia-Split	Croatia	population based study	344	51.95 (13.02)	61.1	-1.27 (1.57)
Croatia-Vis	Croatia	population based study	527	56.29 (13.30)	60.0	-0.13 (1.74)
DCCT	United States	clinical trial	791	31.43 (4.13)	43.2	-1.47 (0.80)
EGCUT	Estonia	population based study	904	56.00 (17.00)	61.2	0.33 (3.36)
EPIC-Norfolk	United Kingdom	population based study	1084	68.81 (7.55)	56.3	0.34 (2.27)
ERF	The Netherlands	family based study	2610	48.72 (14.17)	55.0	0.13 (2.03)
FECD	United States	case-control (controls only)	393	71.50 (9.18)	60.2	-0.14 (2.49)
FITSA	Finland	population based twin study	329	68.56 (3.35)	100.0	1.22 (1.71)
Framingham	United States	population based study	2729	55.60 (8.90)	42.5	0.03 (2.410)
Gutenberg Health Study 1	Germany	population based study	2738	55.52 (10.81)	48.6	-0.38 (2.45)
Gutenberg Health Study 2	Germany	population based study	1140	54.81 (10.81)	50.4	-0.41 (2.57)
KORA	Germany	population based study	2372	55.14 (11.79)	67.0	-0.25 (2.22)
OGP Talana	Italy	population based study	509	51.43 (19.51)	59.2	-0.10 (1.67)
ORCADES	United Kingdom	population based study	1165	55.83 (13.76)	61.0	0.09 (2.07)
Rotterdam Study I	The Netherlands	population based study	5787	68.84 (8.84)	59.4	0.83 (2.55)
Rotterdam Study II	The Netherlands	population based study	2038	64.24 (7.75)	54.4	0.49 (2.49)
Rotterdam Study III	The Netherlands	population based study	2950	56.91 (6.54)	55.9	-0.28 (2.60)
TEST	Australia	population based twin study	267	46.10 (12.25)	50.3	-0.54 (1.99)
Twins UK	United Kingdom	population based twin study	4342	53.83 (11.12)	92.2	-0.34 (2.72)
WESDR	United States	case-control from population based study	295	34.63 (8.05)	51.2	-1.53 (2.02)
YFS	Finland	population based study	1480	41.94 (5.02)	55.4	-1.02 (1.99)
			44192			

CREAM-ASN

Study Name	Origin	Study design	n	age (sd)	% female	mean SE
Beijing Eye Study	China	population based study	590	62.13 (8.51)	66.1	-0.06 (1.87)
Nagahama	Japan	population based study	2730	51.29 (14.03)	66.6	-1.69 (2.78)
SCES	Singapore (Chinese)	population based study	1724	57.54 (8.99)	48.6	-0.77 (2.65)
SIMES	Singapore (Malay)	population based study	2275	58 (10.81)	50.9	-0.05 (1.86)
SINDI	Singapore (Indian)	population based twin study	2110	55.82 (8.82)	48.6	0.01 (2.14)
SP2-1M	Singapore	population based study	818	46.81 (10.16)	37.7	-1.81 (2.85)
SP2-610	Singapore	population based study	871	48.54 (11.32)	80.4	-1.51 (3.00)
STARS PARENT	Singapore	population based study	817	38.61 (5.345)	49.0	-2.75 (2.85)
			11935			

23andMe

Study Name	Origin	Study design	n	mean age of onset of myopia (sd)	% female
23andMe_V2	United States	population based study	12128	13.6 (5.8)	45.9
23andMe_V3	United States	population based study	92165	<10	45.3
			104293		

Supplementary Table 1b: Phenotyping and imputation methods per cohort

CREAM-EUR	Study Name	Phenotyping method	Genotyping chip	Pre-imputation QC metrics (exclusion criteria)	*N* excluded individuals Post-QC	Prephasing	Imputation method	GWAS software
				For MAF 0-0.05: SNP call rate of < 99%; for MAF >=0.05 SNP: call rate < 95%; p_HWE < 1x10-6; Sex	0	ShapeIt	IMPUTE2	SNPtest
1	1958 British Birth Cohort	Autorefractor Nikon Retinomax 2	Illumina Human1M-Duo Beadchip	disconcordance with reported, disconcordance with know controls/ repeats				
				SNPs: MAF <= 0.01, p_HWE <= 1e-6, SNP Call rate <= 0.98.				
	ALIENOR	Autorefractor Luneau SPEEDY K	Illumina Human 610-Quad BeadChip	Individuals: exclusion based on missingness + exclusion of duplicated/related individuals, individuals	20	SHAPEIT2	IMPUTE2	SNPtest
2				with discordance between clinical and genetic sex, or individuals with evidence of non-European				
3	ALSPAC-Mothers	Autorefractor Canon R50	Illumina 660W-Quad BeadChip	MAF <0.01, p_HWE <1x10-7, SNP call rate <95%	8196	SHAPEIT2	Minimac	mach2qtl
				MAF <0.01, p_HWE <5x10-10, SNP call rate <97%, individual call rate<97%. Identity by descent was				
				computed in PLINK based on autosomal markers, with one of each pair of individuals with relatedness				
				of > 0.2 removed. Participants with PC1 or PC2 values > 6 standard deviations from the known northern				
4	ANZRAG	Refractive details were obtained from clinical notes	Illumina Omni 1M/Illumina Omni Express	European ancestry group were excluded.	24	IMPUTE2	IMPUTE2	SNPtest
				MAF <0.02, p_HWE <1x10-4, SNP call rate <98%, individual call rate < 98%, used Illumina annotation to				
5	AREDS	Subjective Refraction	Illumina HumanOmni2.5-4v1_H array	identify and flip all the SNPs where the TOP allele was not on the "+" strand	0	SHAPEIT2	IMPUTE2	Plink
7	BMES	Autorefractor Zeiss Humphrey-530	Illumina 670 Quad Custom Chip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 95%	227	MACH	Minimac	ProbABEL
6	BATS	Autorefractor Zeiss Humphrey-598	Illumina HumanHap 610-Quad array	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	0	MACH	Minimac	MERLIN
8	Croatia-Korcula	Auto Ref/Keratometry NIDEK ARK30	Illumina 370CNV-Quad v1 BeadChip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	92	SHAPEIT2	IMPUTE2	ProbABEL
9	Croatia-Split	Auto Ref/Keratometry NIDEK ARK30	Illumina 370CNV-Quad v3 BeadChip and OMNI	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	41	SHAPEIT2	IMPUTE2	ProbABEL
10	Croatia-Vis	Auto Ref/Keratometry NIDEK ARK30	Illumina HumanHap300 v1.0 BeadChip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	65	SHAPEIT2	IMPUTE2	ProbABEL
11	DCCT	Subjective Refraction	Illumina Human-1M BeadChip	Sample QC: gender mismatch with typed X-linked markers (n=3), call rate < 0.95 (n=0), genotype	113	SHAPEIT2	IMPUTE2	SNPtest
				discrepancy with an earlier study (n=58), autosomal heterozygosity > 0.32 (n=0), cryptic relatedness				
				(n=2), self-reported ethnicity other than white (n=50), outliers in PCA (n=24)				
12	EGCUT	Eye glass prescriptions	Illumina Omni Express	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	0	IMPUTE2	IMPUTE2	SNPtest
				SNP QC: callrate (95% minimum, male-specific on Y), cluster pattern (using Affymetrix SNPolisher),				
				plate effect on minor allele frequency, Hardy Weinberg p < 1e-8. Sample QC: CEL file not generated				
				(raw image quality to poor to process), DishQC < 0.82 (poor fluorescence signal contrast), Step 1 call				
				rate < 97% (calculated on a subset of SNPs, intended to ensure clustering uses only good quality data),				
13	EPIC-Norfolk	Autorefractor Zeiss Humphrey-500	Affymetrix GeneChip Human Mapping 500K Array Set	Sample identity unclear (lab team flagged, or unexpected duplicate or non-duplicate), Sex	N/A	SHAPEIT2	IMPUTE2	SNPtest
				discordance or other sex chromosome abnormality detected, Final sample callrate < 97%,				
				Heterozygosity outlier (calculated separately for SNPs with minor allele frequency >1% and <1%), Rare				
				allele count outlier (unusually high number of singleton, doubleton or tripleton counts), For				
				duplicate/triplicate samples, only the sample with the highest call rate was kept, After this cleaning,				
14	ERF	Topcon RM-A2000 autorefractor	Illumina 6K, 318K, 350K, 610K, Affymetrix 250K	MAF <0.005, p_HWE < 1x10-8, SNP call rate < 98%	1048	MACH	Minimac	ProbABEL
15	FECD	Subjective Refraction	HumanOmni2.5-Quad BeadChip	MAF < 0.02, p_HWE < 1x10-4 SNP call rate < 98%, individual call rate < 98%, > 1 Mendelian error	0	SHAPEIT2	IMPUTE2	Plink
16	FITSA	TOPCON AT	Illumina HumanCoreExome	MAF < 0.01, p_HWE < 1x10-6, SNP call rate < 95%	4	SHAPEIT2	IMPUTE2	SNPtest
17	Framingham	Subjective Refraction	Affymetrix Mapping500K (Nsp & Sty) + 50K HumanHap	Individual-level QC: Non-caucasian by history, individual missing genotypes > 0.10, mendelian	N/A	SHAPEIT2	IMPUTE2	MixABEL
			supplement	inconsistencies > 0.1,; Marker-level QC: MAF < 0.01, SNP call rate < 97%, p_HWE in unrelateds < 10e-05;				
				Note: Baseline QC was carried out on all genotyped Framingham Study Participants (N=9,270) in order				
				maximize the accuracy of marker-level and family-level statistics.				
18	Gutenberg Health Study 1	Zeiss Humphrey® Automated Refractor/Keratometer (HARK) 599™	Affymetrix Genome-Wide Human SNP Array 6.0	MAF ≤0.01, p_HWE≤0.0001, SNP call rate ≤ 98%	N/A	IMPUTE2	IMPUTE2	SNPtest
19	Gutenberg Health Study 2	Zeiss Humphrey® Automated Refractor/Keratometer (HARK) 599™	Affymetrix Genome-Wide Human SNP Array 6.0	MAF ≤0.01, p_HWE≤0.0001, SNP call rate ≤ 98%	N/A	IMPUTE2	IMPUTE2	SNPtest
20	KORA	Nikon Retinomax and Eye glass prescriptions	Illumina Omni 2.5/Illumina Omni Express	MAF < 0.01, p_HWE < 1x10-6, SNP call rate < 98%	N/A	SHAPEIT2	IMPUTE2	SNPtest
21	OGP Talana	Autorefractor Topcon RK-8100	Affymetrix GeneChip Human Mapping 500K	MAF <0.05, p_HWE < 1x10-4, SNP call rate < 95%	0	SHAPEIT2	IMPUTE2	ProbABEL
22	ORCADES	KOWA	Illumina HumanHap 300v2, 370CNV-Quad and OMNI	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	98	SHAPEIT2	IMPUTE2	ProbABEL
23	Rotterdam Study I	Topcon RM-A2000 autorefractor	Illumina HumanHap 550-Duo v3 BeadChip, Illumina HumanHap 610-Quad BeadChip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	504	MACH	Minimac	ProbABEL
24	Rotterdam Study II	Topcon RM-A2000 autorefractor	Illumina HumanHap 550-Duo v3 BeadChip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	119	MACH	Minimac	ProbABEL
25	Rotterdam Study III	Topcon RM-A2000 autorefractor	Illumina HumanHap 610-Quad BeadChip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	98	MACH	Minimac	ProbABEL
26	TEST	Autorefractor Zeiss Humphrey-598	Illumina HumanHap 610-Quad BeadChip	MAF <0.01, p_HWE < 1x10-6, SNP call rate < 98%	0	MACH	Minimac	MERLIN
27	Twins UK	ARM-10 Autorefractor (Takagi Ltd)	Illumina 610K, Illumina 317K	For MAF 0-0.05: SNP call rate of < 99%; for MAF >=0.05 SNP: call rate < 95%; p_HWE < 1x10-6;			IMPUTE2	SNPtest
				Heterozygosity within 3SD (individuals); Sex disconcordance with reported, disconcordance with know				
28	WESDR	Subjective Refraction	Illumina Omni1-Quad BeadChip	Sample QC: gender mismatch with typed X-linked markers (n=9), cryptic relatedness (n=24),	58	SHAPEIT2	IMPUTE2	SNPtest
				autosomal heterozygosity > 0.3 (n=5), call rate < 0.95 (n=29), self-reported ethnicity other than white				
				(n=3), outliers in MDS analysis (n=4); SNP QC: duplicate SNPs, high missing rate [maf>=0.05 &				
				MISS>0.05, 0.05>MAF>=0.01 & MISS>0.01, MAF<0.01 & MISS>0], p_HWE<1E-9				
29	YFS	NIDEK AR-310AR autorefractor	Illumina 670K Custom Array	MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%	963	SHAPEIT1	IMPUTE2	SNPtest

CREAM-ASN	Study Name	phenotyping method	GWAS chip	QC parameters genotypes	Post-QC	Prephasing	Imputation method	GWAS software
1	Beijing Eye Study	Canon RK-5 Auto Ref-Keratometer	Illumina Human 610 Quad Beadchip	MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%, Samples with cryptic relatedness, populati	156	MACH	Minimac	SNPtest
2	Nagahama	Nidek-ARK530A	Illumina HumanHap 610-Quad BeadChip, Illumina Human Omni2.5-8 BeadChip, Illumina Human Omni2.5-Quad BeadChip, Illumina Human Omni2.5S-8 BeadChip, Illumina Infinium Exome-24 v1.0 BeadChip			SHAPEIT2	Minimac	Plink
				MAF<0.01, p_HWE<1x10-7, SNP call rate<90%, individual call rate<90%	0			
				MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%, Samples with cryptic relatedness,				
3	SCES	Canon RK-5 Auto Ref-Keratometer	Illumina Human 610 Quad Beadchip	population structure ascertainment and excessive heterogeneity	63	MACH	Minimac	SNPtest
4	SIMES	Canon RK-5 Auto Ref-Keratometer	Illumina Human 610 Quad Beadchip	MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%	530	MACH	Minimac	SNPtest
				MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%,Samples with cryptic relatedness,				
5	SINDI	Canon RK-5 Auto Ref-Keratometer	Illumina Human 610 Quad Beadchip	population structure ascertainment and excessive heterogeneity	415	MACH	Minimac	SNPtest
				MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%,Samples with cryptic relatedness,				
6	SP2-1M	Canon RK-5 Auto Ref-Keratometer	Illumina Human1M-Duo v3 BeadChip	population structure ascertainment and excessive heterogeneity	63	MACH	Minimac	SNPtest
				MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%,Samples with cryptic relatedness,				
7	SP2-610	Canon RK-5 Auto Ref-Keratometer	Illumina Human 610 Quad Beadchip	population structure ascertainment and excessive heterogeneity	321	MACH	Minimac	SNPtest
				MAF <0.01, p_HWE < 1x10-6, Sample and SNP call rate < 95%, samples with >1% SNPs showing				
8	STARS	Canon RK-F1 Autorefractor, Welch Allyn retinoscopy	Illumina Human 610 Quad Beadchip	Mendelian error,Samples with cryptic relatedness, population structure ascertainment and excessive	26	MACH	Minimac	SNPtest

23andMe	Study Name	phenotyping method	GWAS chip	QC parameters genotypes	Post-QC	Prephasing	Imputation method	GWAS software
1	23andMe_V2	Questionaire	Illumina!HumanHap550+ BeadChip	MAF < 0.001, individuals who have <97% European ancestry, p_HWE < 1x10-20, SNP call rate < 95%, or	N/A	Beagle	Minimac	Cox proportional hazards model using R and custom GWAS software
				with large allele frequency discrepancies compared to the 1000 Genomes reference data				
2	23andMe_V3	Questionaire	OmniExpress+ BeadChip	MAF < 0.001, individuals who have <97% European ancestry, p_HWE < 1x10-20, SNP call rate < 95%, or	N/A	Beagle	Minimac	Cox proportional hazards model using R and custom GWAS software
				with large allele frequency discrepancies compared to the 1000 Genomes reference data				

Supplementary Table 5: Index SNPs HapMap II from CREAM and 23andMe

SNP information				HAPMAPII CREAM and 23andMe topSNPs for Refractive Error and Age of Diagnosis Myopia								1000G meta-analysis results of CREAM and 23andMe topSNPs from HapMapII for Refractive Error and Age of Diagnosis Myopia									
Locus #	rsnumber	CHR	POSITION	A1/A2	Locus Name CREAM	CREAM Beta	CREAM SEM	CREAM P value	Locus Name 23andMe	23andMe HR (CI)	23andMe P value	A1	Freq1	Zscore	P-value	Direction	HetISq	HetChi	HetDf	HetPval	N
1	rs1652333	1	207470460	G/A	*CD55*	-0.1116533	0.0160072	3.05434E-12	-	-	-	G	0.6769	-7.242	4.42E-13	++	81.7	5.457	1	0.01949	160136
2	rs1656404	2	233379941	A/G	*PRSS56*	-0.1528567	0.0235048	7.86186E-11	-	-	-	A	0.1733	-11.253	2.25E-29	--	75	3.999	1	0.04554	156056
	rs1550094		233385396	A/G	-	-	-	-	*PRSS56*	1.087 (1.067 - 1.107)	5.8E-18	A	0.7005	12.738	3.64E-37	++	88.9	8.996	1	0.002705	159422
3	rs17400325	2	178565913	T/C	-	-	-	-	*PDE11A*	1.144 (1.099 - 1.190)	8.7E-11	T	0.9513	7.994	1.30E-15	++	92.1	12.616	1	0.0003824	150322
4	rs17412774	2	146773948	A/C	-	-	-	-	*PABPCP2*	0.933 (0.917 - 0.950)	1.5E-14	A	0.5506	-8.568	1.05E-17	--	88.9	9.033	1	0.002652	159506
5	rs17428076	2	172851936	C/G	-	-	-	-	*DLX1*	0.935 (0.916 - 0.955)	1.4E-10	C	0.768	-8.183	2.77E-16	--	88.8	8.899	1	0.002854	160151
6	rs1881492	2	233406998	T/G	*CHRNG*	-0.139	0.021	5.15E-11	-	-	-	T	0.2008	-10.252	1.16E-24	--	0	0.338	1	0.5611	159506
7	rs13091182	3	141133960	G/A	-	-	-	-	*ZBTB38*	0.940 (0.923 - 0.958)	3.6E-11	G	0.3352	-8.001	1.23E-15	--	83.8	6.166	1	0.01303	153193
8	rs14165	3	53847408	A/G	*CACNA1D*	0.096	0.017	2.14E-08	-	-	-	A	0.3014	6.25	4.10E-10	++	0	0.061	1	0.8045	149655
9	rs5022942	4	81959966	G/A	-	-	-	-	*BMP3*	1.076 (1.054 - 1.098)	4.2E-12	G	0.2416	9.258	2.08E-20	++	89.8	9.848	1	0.0017	160150
10	rs9307551	4	80530671	A/C	*LOC100506035*	-0.099	0.017	1.09E-08	-	-	-	A	0.2452	-7.972	1.56E-15	--	0	0.237	1	0.6265	160149
11	rs12205363	6	129834629	C/T	*LAMA2*	0.235	0.033	1.79E-12	-	-	-	C	0.9317	15.975	1.91E-57	++	96.6	29.438	1	5.78E-08	150327
	rs12193446		129820038	A/G	-	-	-	-	*LAMA2*	0.788 (0.763 - 0.813)	6.8E-53	A	0.9063	-19.431	4.21E-84	--	98.4	60.996	1	5.72E-15	150269
12	rs7744813	6	73643289	A/C	*KCNQ5*	-0.112	0.019	4.18E-09	-	-	-	A	0.5905	-14.555	5.43E-48	--	90.6	10.598	1	0.001132	160091
				A/C	-	-	-	-	*KCNQ5*	0.909 (0.893 - 0.926)	2.7E-25										
13	rs7837791	8	60179086	T/G	*TOX*	0.106	0.015	3.99E-12	-	-	-	T	0.4816	11.59	4.64E-31	++	53	2.127	1	0.1447	160152
	chr8:60178580		60178580	C/G	-	-	-	-	*TOX/CA8*	0.914 (0.897 - 0.931)	4E-22	C	0.6415	-13.137	2.03E-39	--	87	7.678	1	0.00559	160128
14	rs4237036	8	61701057	C/T	*CHD7*	0.089	0.016	1.82E-08	-	-	-	C	0.6669	5.205	1.94E-07	++	0	0.984	1	0.3212	160148
15	rs7829127	8	40726394	A/C	*ZMAT4*	-0.116	0.018	3.69E-10	-	-	-	A	0.7917	-10.911	1.02E-27	--	92.4	13.217	1	0.0002774	160132
	rs7829127			A/G	-	-	-	-	*SFRP1*	0.901 (0.880 - 0.923)	1.8E-18										
16	rs11145465	9	71766593	A/C	*TJP2*	-0.124	0.021	7.26E-09	-	-	-	A	0.2122	-9.546	1.35E-21	--	46.3	1.863	1	0.1722	153174
	rs11145746		71834380	G/A	-	-	-	-	*TJP2*	1.087 (1.063 - 1.112)	5.2E-13	G	0.2056	9.098	9.22E-20	++	68	3.127	1	0.07698	153113
17	rs7042950	9	77149837	G/A	*RORB*	-0.0964935	0.0175941	4.14842E-08	-	-		G	0.7323	-6.797	1.07E-11	--	0	0.012	1	0.9122	160153
18	rs10882165	10	94924324	T/A	*CYP26A1*	-0.107	0.016	1.03E-11	-	-	-	T	0.5869	-6.155	7.49E-10	--	69.1	3.237	1	0.07198	155329
19	rs6480859	10	79081948	C/T	-	-	-	-	*KCNMA1*	1.058 (1.039 - 1.077)	7.3E-10	C	0.363	8.202	2.36E-16	++	79	4.765	1	0.02904	160148
20	rs7084402	10	60265404	G/A	*BICC1*	-0.108	0.015	2.06E-13	-	-	-	G	0.5277	-8.828	1.07E-18	--	0	0.428	1	0.5129	160020
21	rs745480	10	85986554	C/G	-	-	-	-	*RGR*	1.063 (1.044 - 1.081)	8E-12	C	0.5109	8.314	9.26E-17	++	67.3	3.055	1	0.0805	159504
22	rs11601239	11	105556598	C/G	*GRIA4*	-0.0949272	0.0163137	5.92475E-09	-	-	-	C	0.485	-6.824	8.84E-12	--	0	0.008	1	0.9281	160118
23	rs1381566	11	40149607	T/G	-	-	-	-	*LRRC4C*	1.149 (1.122 - 1.176)	2.3E-30	T	0.81	13.593	4.43E-42	++	97.6	40.832	1	1.66E-10	157519
24	rs2155413	11	84634790	C/A	-	-	-	-	*DLG2*	1.061 (1.043 - 1.080)	1.7E-11	C	0.4823	7.755	8.85E-15	++	92.4	13.078	1	0.0002987	159504
25	rs12229663	12	71249996	G/A	*PTPRR*	0.099	0.017	5.47E-09	-	-	-	G	0.7527	7.362	1.81E-13	++	0	0.221	1	0.6386	160133
26	rs3138142	12	56115585	C/G	*RDH5*	0.119	0.017	4.44E-12	-	-	-	T	0.2115	13.766	4.06E-43	++	95.9	24.566	1	7.18E-07	157544
				C/G	-	-	-	-	*RDH5*	0.890 (0.870 - 0.911)	1.3E-23										
27	rs2184971	13	100818092	G/A	*PCCA*	0.085	0.015	2.11E-08	-	-	-	G	0.5441	5.232	1.68E-07	++	0	0.51	1	0.4751	160146
28	rs4291789	13	100672921	C/G	-	-	-	-	*ZIC2*	1.069 (1.046 - 1.092)	2.10E-08	C	0.6723	7.899	2.80E-15	++	86	7.146	1	0.007514	159988
29	chr14:54413001	14	54413001	G/C	-	-	-	-	*BMP4*	0.946 (0.929 - 0.963)	1.1E-09	G	0.4657	-7.118	1.09E-12	--	73.6	3.784	1	0.05174	160104
30	rs1254319	14	60903757	A/G	*SIX6*	-0.088	0.015	1.00E-08	-	-	-	A	0.3322	-5.602	2.12E-08	--	76.3	4.226	1	0.03981	160153
31	rs4778879	15	79372875	G/A	*RASGRF1*	-0.102	0.015	4.25E-11	-	-	-	G	0.5823	-9.898	4.24E-23	--	0	0.684	1	0.4081	160068
	rs28412916		79378167	A/C	-	-	-	-	*RASGRF1*	1.067 (1.048 - 1.086)	8.2E-13	A	0.5874	9.944	2.68E-23	++	0	0.161	1	0.6886	160152
32	rs524952	15	35005886	T/A	*GJD2*	0.1582561	0.019821	1.44329E-15	-	-	-	T	0.4748	17.075	2.28E-65	++	83	5.865	1	0.01544	160150
				T/A	-	-	-	-	*GOLGA8B/GJD2*	1.089 (1.070 - 1.108)	6.9E-22										
33	rs17648524	16	7459683	G/C	*A2BP1*	0.118	0.019	5.64E-10	-	-	-	G	0.3535	13.693	1.13E-42	++	96.3	26.829	1	2.22E-07	160122
			7459683	G/C	-	-	-	-	*RBFOX1*	1.102 (1.082 - 1.122)	4.1E-26										
34	rs17183295	17	31078272	T/C	*MYO1D*	-0.131	0.02	9.66E-11	-	-	-	T	0.1901	-8.177	2.91E-16	--	0	0.41	1	0.522	152597
35	rs2908972	17	11407259	T/A	*SHISA6*	0.101	0.015	7.29E-11	-	-	-	T	0.4146	11.125	9.46E-29	++	23	1.299	1	0.2544	160123
				T/A	-	-	-	-	*SHISA6*	1.074 (1.055 - 1.093)	5.2E-15										
36	rs4793501	17	68718734	C/T	*KCNJ2*	0.08040793	0.0144771	2.78971E-08	-	-	-	C	0.5748	7.212	5.53E-13	++	0	0.288	1	0.5917	160150
37	rs235770	20	6761765	T/C	*BMP2*	-0.089	0.016	1.57E-08	-	-	-	T	0.3717	-5.926	3.11E-09	--	0	0.362	1	0.5474	157521

Supplementary Table 6. LD score regression analysis and heritability explained by common SNPs

Sample	Ref. panel[1]	N[2]	λ_{GC}	LD score regression[3]		
				Intercept (se)	h^2 (se)	p
CREAM-EUR	EUR	44.192	1.165	1.023 (0.008)	0.214 (0.015)	2.4 x 10e-49
23andMe	EUR	104.292	1.108	0.892 (0.009)	0.172 (0.009)	1.6 x 10e-81
CREAM-EAS	EAS	9.826	1.017	1.001 (0.006)	0.053 (0.040)	0.190

[1]Reference panel used to calculate LD scores.

[2]The maximum sample size; not all markers were genotyped in all samples and therefore this number will vary from marker to marker.

[3]LD score regression intercept and heritability estimate (p-value relates to a test of the null hypothesis of $h^2=0$; intercepts above 1 give evidence of inflated association statistics due to residual population stratification or relatedness.

Supplementary Table 7: Exonic protein-altering variants

Marker name	Gene name	P-value meta-analysis Stage 3	chr:pos	Mutation	Amino acid change
rs5442	*GNB3*	5.48E-15	12:6954864	missense	Gly > Ser
rs807037	*KAZALD1*	4.59E-08	10:102824349	missense	Gly > Ala
rs1550094	*PRSS56*	3.64E-37	2:233385396	missense	Ala > Thr
rs1064583	*COL10A1*	6.90E-11	6:116446576	missense	Met > Thr
rs6420484	*TSPAN10*	2.80E-09	17:79612397	missense	Tyr > Cys
rs2303635	*AMOTL2*	1.14E-09	3:134086356	missense	Ala > Pro
rs35337422	*RD3L*	2.19E-10	14:104407243	missense	Ile > Arg
rs17400325	*PDE11A*	1.30E-15	2:178565913	missense	Tyr > Cys

P values derived from stage 3 meta-analysis (n=160,420)

***** This locus did not replicate in UKEV

Supplementary Table 8: Post-GWAS analyses additional genes

Gene	Chr	Start	End	N SNPs per region tested	P value stage 3 meta-analysis	Analysis	Remarks	Novel gene #
MIR6512	2	178178533	178178610	72	4.52E-07	fastBAT		1
RPP14	3	57062260	58625174	5003	4.46E-07	fgwas		2
IL4	5	132009678	132018368	1	1.70E-06	Eugene		3
HMGN4	6	26538633	26546482	7	1.00E-07	Eugene, fgwas		4
HIST1H2AG	6	27100816	27101314	58	1.38E-06	fastBAT		5
CDKAL1	6	19752146	21152237	5010	6.97E-08	fgwas	Genome wide significant in Discovery stage	
POU6F2	7	39017608	39504390	526	5.33E-07	fastBAT		6
CHD7	8	61591323	61780586	248	5.36E-07	fastBAT	Significant in Discovery stage after Bonferroni's correction and established in HapMap II analysis in 2013	7
C8orf84	8	73887862	75301149	5019	2.87E-07	fgwas	same locus 1	8
BC127738	8	73887862	75301149	5019	2.87E-07	fgwas	same locus 1	9
TRAF1	9	123664671	123691451	3	1.20E-06	Eugene		10
C5	9	123714613	123812554	109	1.10E-06	fastBAT		11
C10orf11	10	77542518	78317126	670	1.14E-06	fastBAT	Genome wide significant in Discovery stage	
TLX1	10	102891060	102897546	132	5.88E-07	fastBAT, fgwas		12
ACP2	11	47260853	47270457	4	1.10E-06	Eugene		13
SYTL2	11	85405267	85522184	4	1.60E-06	Eugene		14
CCDC89	11	85394892	85397320	74	5.50E-07	fastBAT		15
HNRNPKP3	11	43283053	43290919	115	4.72E-07	fastBAT	Genome wide significant in Discovery stage	
TP53AIP1	11	128804626	128813294	174	1.73E-07	fastBAT		16
ANKRD9	14	102973179	102976136	6	4.00E-07	Eugene		17
CRHR1-IT1	17	4369769	43725582	3	1.00E-07	Eugene		18
LOC101927557	17	55599608	55600958	190	1.12E-06	fastBAT		19
TNFSF12	17	7452374	7461207	117	1.82E-06	fastBAT	Genome wide significant in Discovery stage	
FAM83C	20	33873533	33880225	71	1.67E-06	fastBAT		20
TMEM184B	22	38615297	38669040	164	1.72E-06	fastBAT		21
LARGE	22	32001050	33156201	5019	4.13E-07	fgwas	same locus 2	22
ISX	22	32001050	33156201	5019	4.13E-07	fgwas	same locus 2	23
LOC388906	22	39756985	41941243	5019	2.00E-07	fgwas	same locus 3	24
BC038245	22	39756985	41941243	5019	2.00E-07	fgwas	same locus 3	25

P values derived from stage 3 meta-analysis (n=160,420)

Supplementary Table 9: Predictive power of the polygenic score in Rotterdam Studies (I, II, III)

Score	MEGA GWAS P-value threshold*	*n* variants in score	*R2*	P-value	% variance explained†
Reference**			0.052	NA	5.2
S1	5.00E-08	152	0.099	5.35E-122	4.7
S2	5.00E-07	214	0.101	1.17E-127	4.9
S3	5.00E-06	334	0.106	2.24E-139	5.4
S4	5.00E-05	661	0.112	2.33E-155	6.0
S5	5.00E-04	1815	0.122	1.91E-181	7.0
S6	0.005	7303	0.130	1.19E-203	7.8
S7	0.01	11763	0.129	2.20E-201	7.7
S8	0.05	37999	0.124	2.91E-188	7.2
S9	0.1	63106	0.119	8.93E-176	6.8
S10	0.5	183871	0.113	1.32E-159	6.2
S11	0.8	228198	0.113	3.25E-158	6.1
S12	1	243938	0.113	5.53E-158	6.1

* Meta-analysis results stage 3 (CREAM and 23andME) excluding RS-I-II-III (n=148,645)

**Reference model, mean Spherical Equivalent ~ age + sex + first 5PCs + cohort

† Variance explained by each score (S1-S12) was calculated by substraction of a full model (reference + score) from a reduced model (reference only)

Estimating the incremental *R2* from including the polygenic score (S1-S12) in a regression of mean spherical equivalent on age, sex, first 5 principal components and cohort

Supplementary Table 12: RNA genes – region look-ups

	Alias	Class of RNA	Chromosome:Position	Genetic variant (Stage 3 meta-	Description
5S_rRNA	5S ribosomal RNA	Ribosomal RNA	1:163479274-163479385	rs1556867	
AK097193/LOC101926964	AK097193: cDNA - transcript of LOC101926964: alias RP11-436K8.1	Uncharacterized non-protein coding RNA	1:61125303-61291256	rs11589487	
AK097934/LINC01237**	cDNA clone - transcript of LINC01237	Long intergenic non-protein coding RNA	2:242912834-242919427	rs12998513	LOC102723927 also in region
AK123891/FLJ41897	cDNA clone - transcript of FLJ41897	Uncharacterized non-protein coding RNA	22:32896532-32898414	rs9606967	
AK124857/LOC101927394	cDNA clone - transcript of LOC101927394	Uncharacterized non-protein coding RNA	3:7994492-8057994	rs9681162	
BC030753/NFIA-AS2	cDNA clone - transcript of NFIA-AS2 (alias: NFIA Antisense RNA 2)	Uncharacterized non-protein coding RNA	1:61405916-61436448	rs11589487	
BC035400/LOC102723409	cDNA clone - transcript of LOC102723409	Uncharacterized non-protein coding RNA	6:129800758-129873731	rs12193446	Overlap with LAMA2 region
BC039327/CASC17	cDNA clone - transcript of CASC17 (alias: cancer susceptibility 17)	Long intergenic non-protein coding RNA	17:69093915-69198318	rs4793501	Diseases associated with CASC17 include Prostate Cancer Susceptibility (genecards).
BC040861	cDNA clone	Uncharacterized non-protein coding RNA	2:145780382-145910072	rs56075542	
BC127738/LOC100130301	cDNA clone - transcript of LOC100130301	Uncharacterized non-protein coding RNA	8:74153659-74171737	Gene based (rs16938625 closest GWS tophit)	
CRHR1-IT1	Long Intergenic Non-Protein Coding RNA 2210; C17orf69	Long intergenic non-protein coding RNA	17:43716341-43723595	Gene based (rs117118311 closest GWS tophit)	
D43770/LINC01152	RNA of LINC01152	Long intergenic non-protein coding RNA	17:70026957-70035822	rs7207217	This RNA may play a significant role in differentiation or sex determination (NCBI)
FLJ16171/LINC01951	LINC01951	Long intergenic non-protein coding RNA	5:174346085-174422734	rs7449443	
HP08777	RP3-522D1.1	Uncharacterized non-protein coding RNA	1:113392522-113420491	rs1237670	Overlap with LINC01356 region
LINC00333	Long Intergenic Non-Protein Coding RNA 00333	Long intergenic non-protein coding RNA	13:84714737-85180903	rs9547035	
LINC00340/CASC15	CASC15, Cancer Susceptibility 15 (Non-Protein Coding); Lnc-SOX4-1; Long intergenic non-protein coding RNA 340	Long intergenic non-protein coding RNA	6:22146883-22194616	rs1207782	
LINC00351	Long Intergenic Non-Protein Coding RNA 00351	Long intergenic non-protein coding RNA	3:85937738-86118797	rs9547035	
LINC00461	long intergenic non-protein coding RNA 461; EyeLinc1; Visual Cortex Expressed; ECONEXIN	Long intergenic non-protein coding RNA	5:87836597-87980620	rs7737179	Highly conserved and expressed in the human macula (PMID: 23562822). ECONEXIN was the most highly conserved intergenic lncRNA containing 83.0% homology with the mouse ortholog (C130071C03Rik) for a region over 2500 bp in length within its exon 3. Expressions of ECONEXIN and C130071C03Rik were significantly upregulated in both human and mouse glioma tissues. PMID: 28368417
LINC00862	C1orf98; SMIM16;Small Integral Membrane Protein 16; Long Intergenic Non-Protein Coding RNA 862	Long intergenic non-protein coding RNA	1:200311672-200342920	rs2225986	
LMCD1-AS1	LMCD1 antisense RNA 1	Uncharacterized non-protein coding RNA	3:8235936-8543344	rs9681162	
LOC100506035/LINC00989	Long Intergenic Non-Protein Coding RNA 00989	Uncharacterized non-protein coding RNA	4:80413747-80497614	rs7662551	
LOC100508120/GMDS-AS1	GMDS antisense RNA 1	Uncharacterized non-protein coding RNA	6:2245987-2413825	rs10458138	
LOC101927557	Long Intergenic Non-Protein Coding RNA 101927557	Uncharacterized non-protein coding RNA	17:55599609-55600958	Gene based (rs28488643 closest GWS tophit)	
MIR6512	MicroRNA 6512	MicroRNA	2:178178534-178178610	Gene based (rs2573081 closest GWS tophit)	
SNORA40	Small nucleolar RNA 40, H/ACA box 40	Small nucleolar RNA	2:16380471-16380563	rs28658452	
SNORA51	Small nucleolar RNA 51, H/ACA Box 51; ACA51 SnoRNA; ACA51	Small nucleolar RNA	8:60049931-60050061	rs72621438	
TMEM161B-AS1	TMEM161B Antisense RNA 1 (Non-Protein Coding)	Uncharacterized non-protein coding RNA	5:87564699-87732491	rs7737179	
TRNA_Ala	Alanine tRNA	transfer RNA	14:89445442-89445514	rs17125093	
TRNA_Gln	Glutamine tRNA	transfer RNA	17:47269890-47269961	rs11654644	
TRNA_Ser	Serine tRNA	transfer RNA	6:28180815-28180896	rs1150687	
U6	RNA, U6 Small Nuclear	Small nucleolar RNA	4:83095700-83095806	rs2166181	Diseases associated with RNU6-1 include Poikiloderma With Neutropenia. Among its related pathways are mRNA Splicing - Major Pathway and RNA transport. (genecards)

** These loci were not included in the UKEV replication analysis

Supplementary Table 17: Genes in Dopamine pathway – region look-ups

Gene	Chromosome	Start	End	NCBI Reference Sequence
DRD1	5	174867675	174871163	NC_000005.9
DRD2	11	113280317	113346413	NC_000011.9
DRD3	3	113847499	113918254	NC_000003.11
DRD4	11	637305	640706	NC_000011.9
DRD5	4	9783258	9785633	NC_000004.11
COMT	22	19929263	19957498	NC_000022.10
DBH	9	136501485	136524466	NC_000009.11
DDC	7	50526134	50633154	NC_000007.13
MAOA	X	43514155	43606071	NC_000023.10
TH	11	2185159	2193107	NC_000011.9
SLC6A3/DAT	5	1392905	1445543	NC_000005.9
SLC6A4/SERT	17	28521337	28562986	NC_000017.10

Gene	Chr	Start	End	N_SNPs tested	Lowest P-value Stage 3 meta-analysis	TopVariant	Position Top Variant
COMT	22	19929263	19957498	3971	2.00E-04	rs4819854	19854659
DBH	9	136501485	136524466	5519	2.78E-04	rs191849948	136719162
DDC	7	50526134	50633154	4230	2.38E-04	rs2189432	51100959
DRD1	5	174867675	174871163	3733	3.58E-08	rs7449443	174720893
DRD2	11	113280317	113346413	3988	1.07E-04	rs188263557	113108780
DRD3	3	113847499	113918254	2915	9.41E-04	rs189807093	114022413
DRD4	11	637305	640706	4760	1.01E-04	rs80190876	680614
DRD5	4	9783258	9785633	5705	1.03E-04	rs57553236	9688140
MAOA	X	43514155	43606071	1591	5.76E-03	rs73196113	43972237
SLC6A3/DAT	5	1392905	1445543	5846	2.35E-04	rs147426622	1652855
SLC6A4/SERT	17	28521337	28562986	2426	4.77E-04	rs113822901	28994581
TH	11	2185159	2193107	4641	3.24E-04	rs112121578	1937116

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