Additional File1: Genetic Disruption of Serine Biosynthesis is a Key Driver of Macular Telangiectasia Type 2 Etiology and Progression

Additional Images:

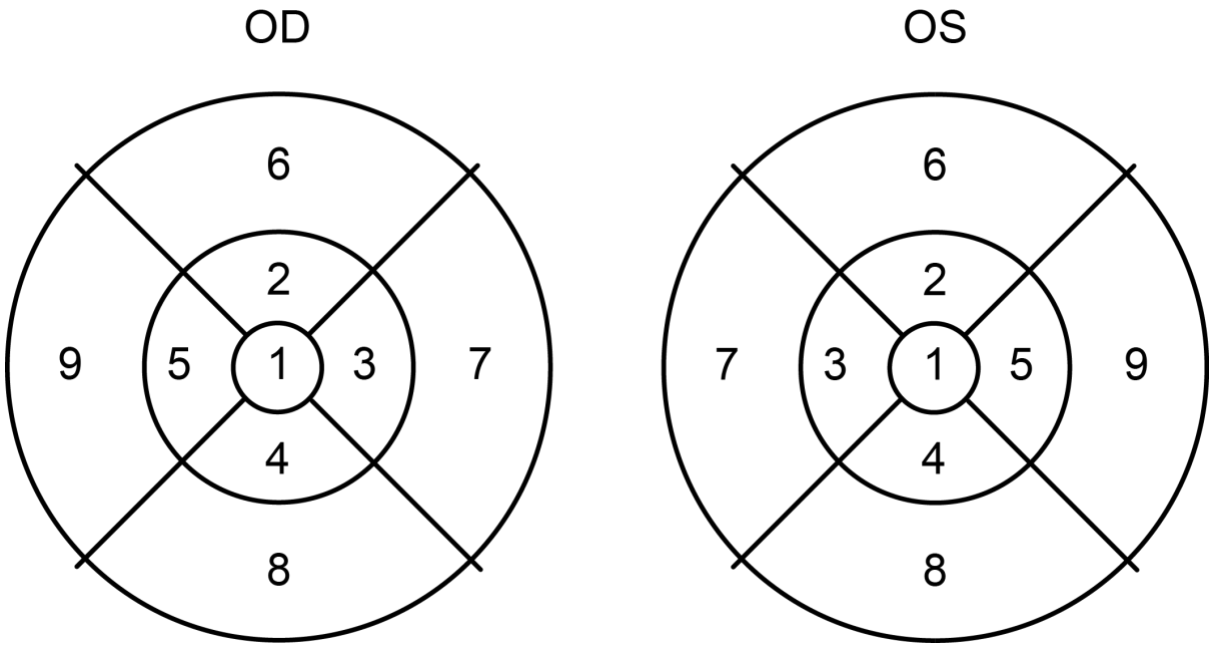

Fig S1: Right (OD) and left (OS) eyes macula, were divided into 9 areas according to the ETDRS grid [1]. 1: foveal area, 2: superior inner area (progression area), 3: nasal inner area (progression area), 4: inferior inner area (progression area), 5: temporal inner area (MacTel area), 6: superior outer area, 7: nasal outer area, 8: inferior outer area, and 9: temporal outer area.

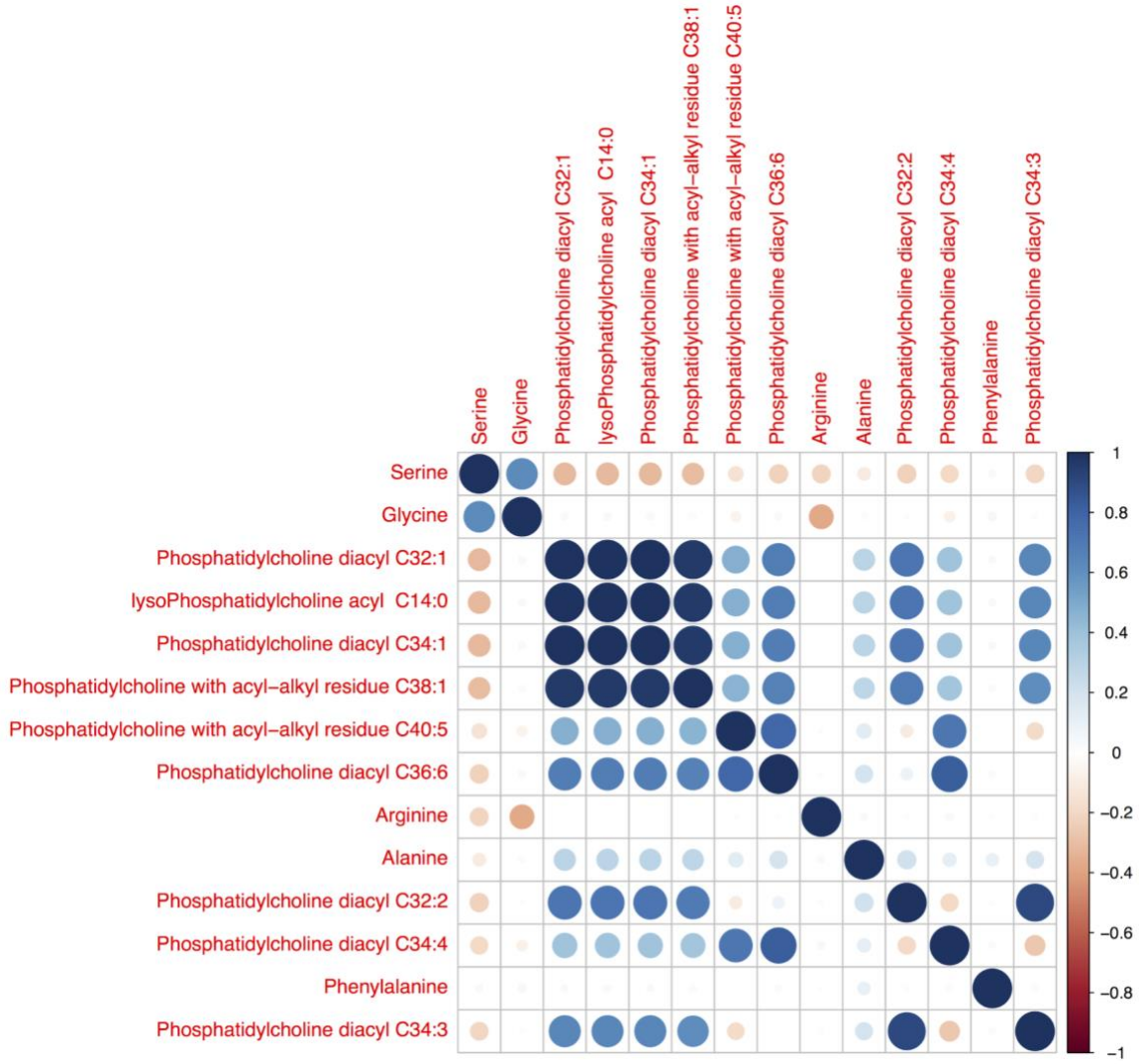

Fig S2: Correlation between mPRS that achieved multiple testing corrected significance ($p < 0.05$). Bigger dots and saturated colour indicate stronger correlations. Blue indicates a positive correlation while red indicates a negative one.

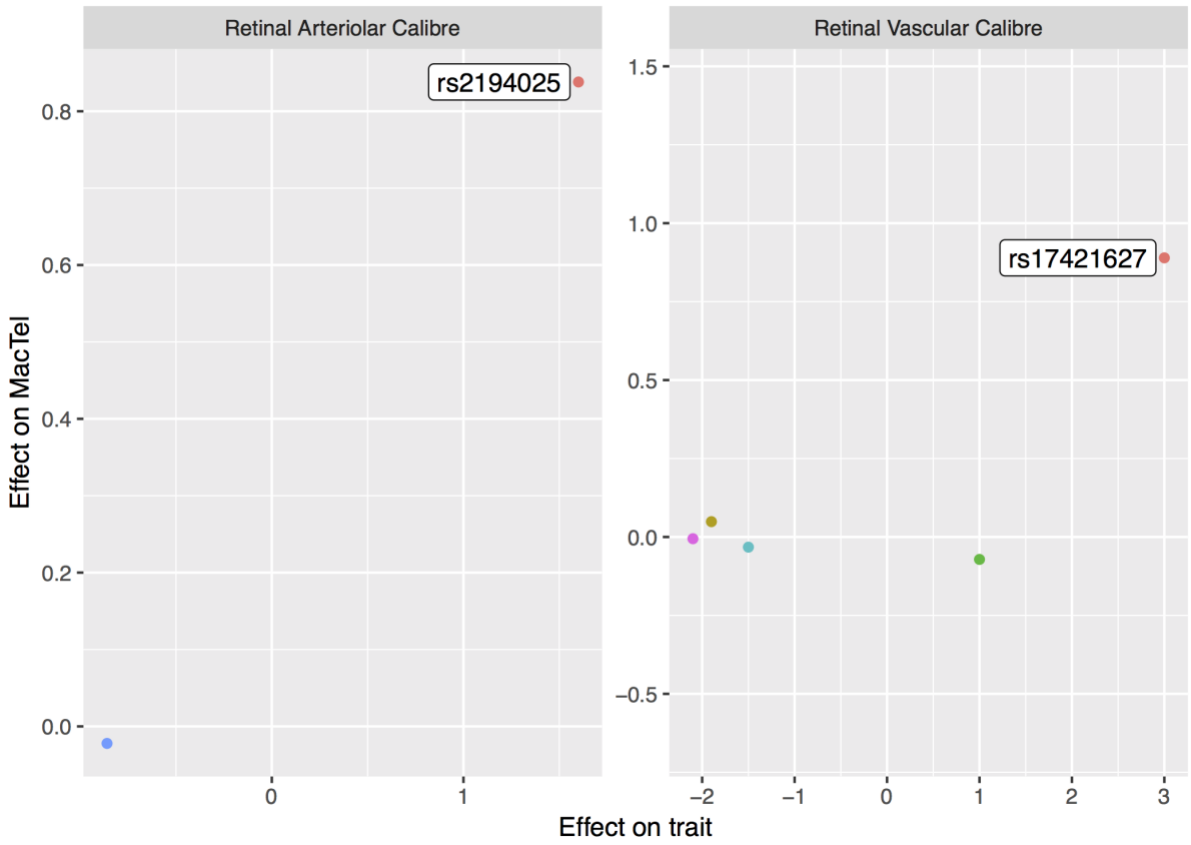

Fig S3: Comparison between SNPs effect on vasculature traits and MacTel. Each dot is a SNP which was found to be significantly associated with a vasculature trait. The x-axis represents the effect that the SNP has on the particular trait while the y-axis displays the effect that the SNP has on MacTel. Most SNPs have no effect on MacTel. The only two SNPs that have an effect are the SNPs rs2194025 and rs17421627 which are very close to each other and in strong LD with SNP rs73171800 (r^2=0.94 and r^2=0.67).

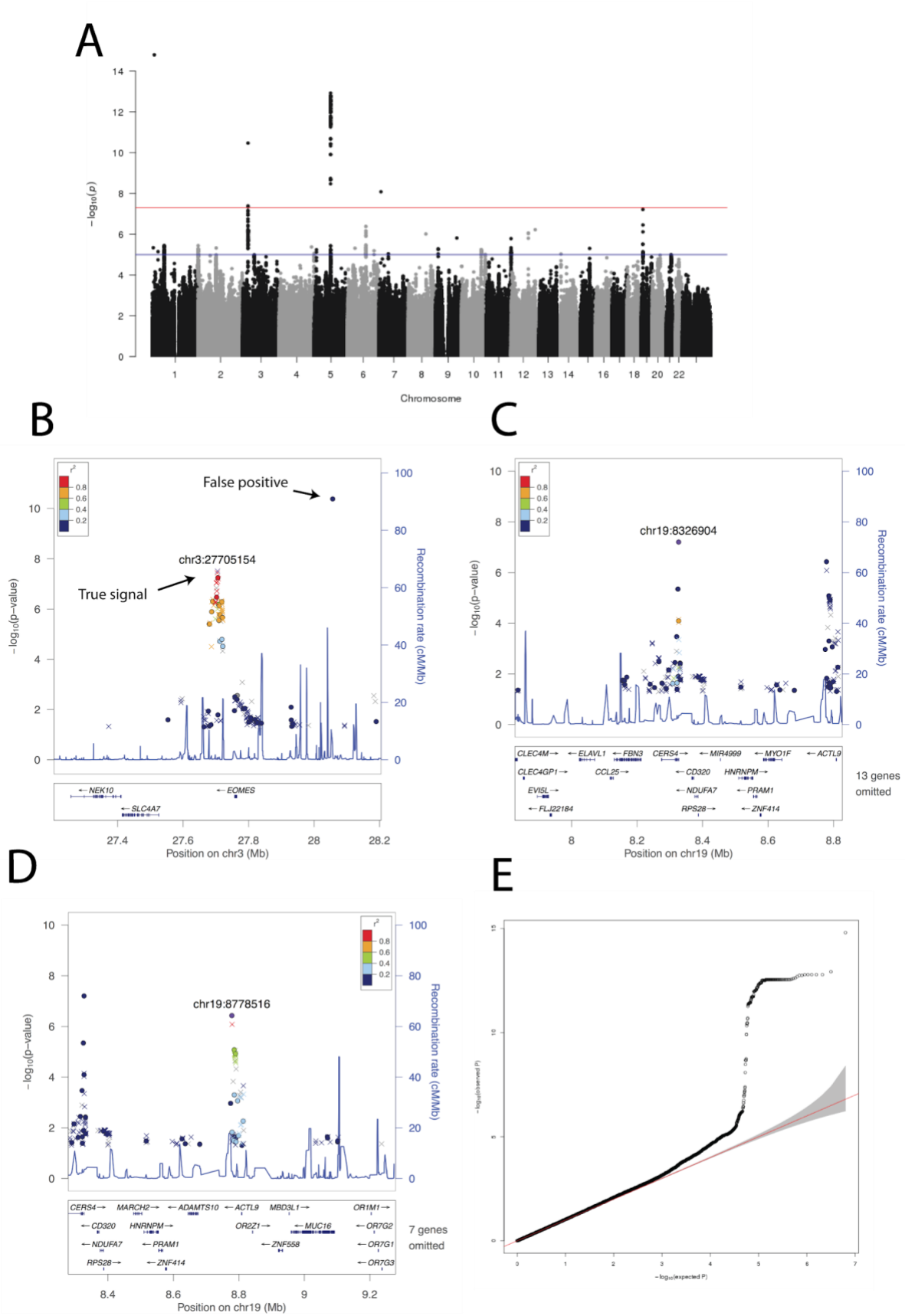

Fig S4: MacTel GWAS results conditioned by serine PRS and glycine PRS. A) Manhattan plot. B) Locus zoom plot of the significant signal on locus 3p24.1. C) Locus zoom plot of the

significant signal by SNP rs36259 on locus 19p13.2. D) Locus zoom plot of the significant signal by SNP rs4804075 on locus 19p13.2. E) QQ-plot of association p-values.

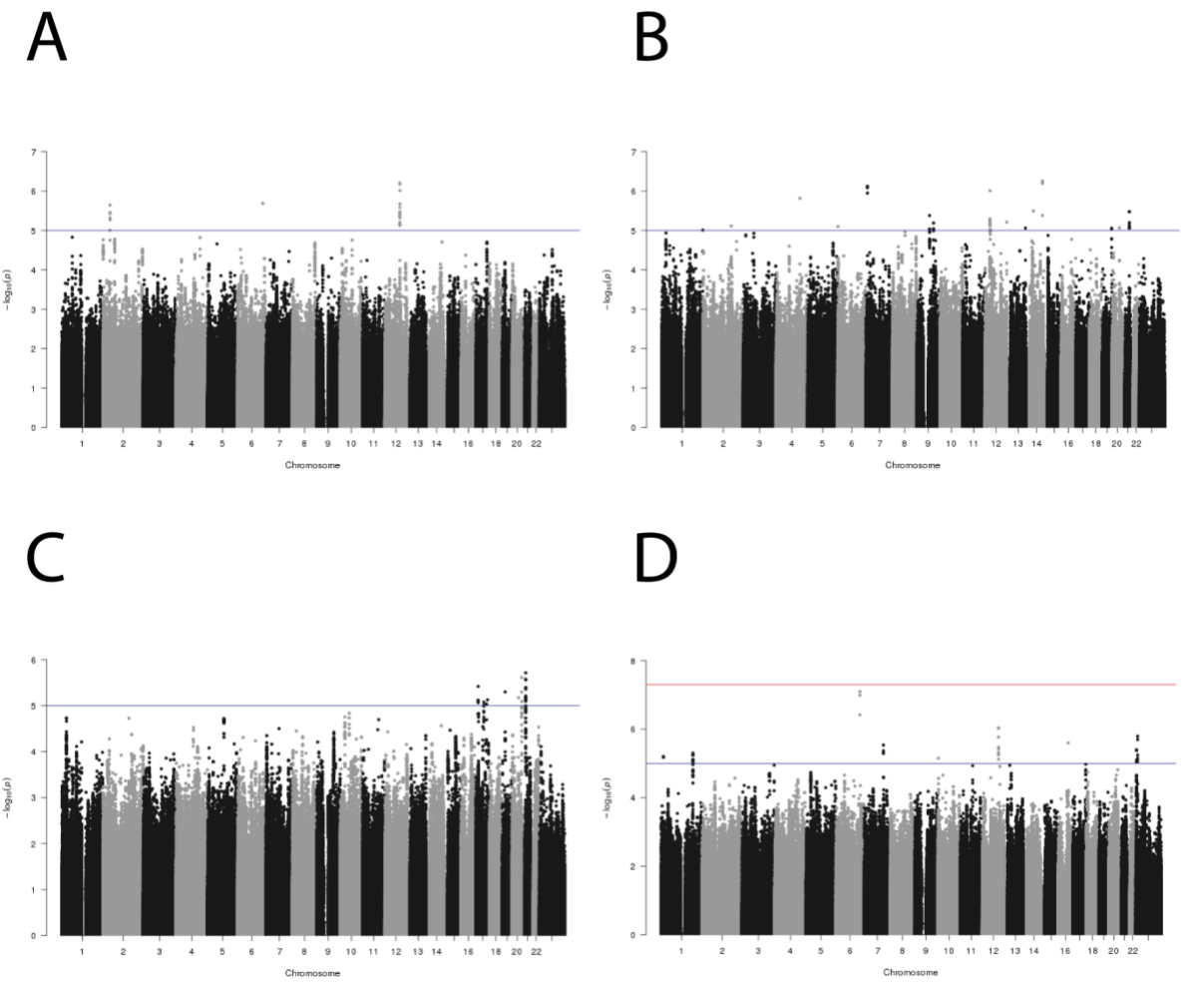

Fig S5: MacTel interaction GWAS results. A) Manhattan plot showing SNP interactions with serine PRS, B) Manhattan plot showing SNP interactions with glycine PRS, C) Manhattan plot showing SNPs interaction with SNP rs73171800 in locus 5q14.3, D) Manhattan plot showing SNP interactions with T2D PRS.

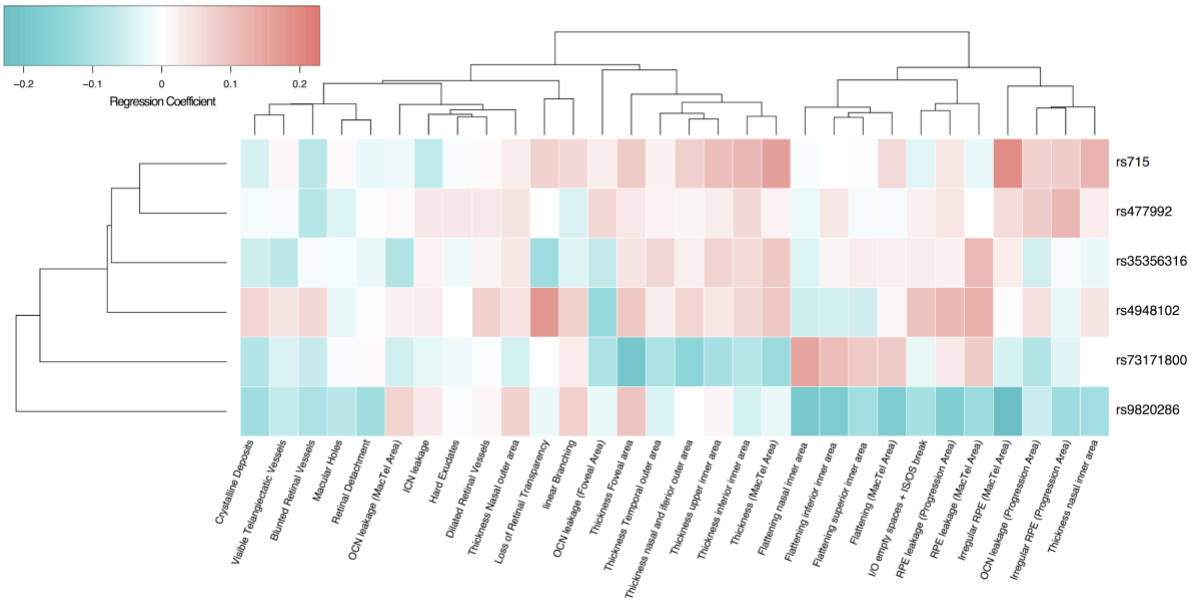

Fig S6: Loci clustering heatmap. This clustering heatmap visualises the regression coefficients of each SNP on the endophenotypes. Rows and columns of the heatmaps were ordered according to the hierarchical clustering to give a visual representation of the similarities. SNP rs73171800 (5q14.3) and SNP rs9820286 (3q21.3) have very different effects from the other four SNPs which show a more consistent, shared pattern.

Additional Methods:

Study Population

Our MacTel Project consortium (**Table S7**) recruited cases and controls at 23 participating clinical centers in seven countries (Australia, Germany, France, UK, Switzerland, Israel and United States). Informed written consent was obtained in accordance with ethics protocols for human subjects approved by the appropriate governing body at each site in accordance with the Declaration of Helsinki. Protocols and records of consent were centrally managed by the EMMES Corporation. The following ethics boards granted approval for human subject enrollment: Quinze-Vingts, Paris, France: Comité de Protection des Personnes Hôpital Saint-Antonie; Centre for Eye Research, Victoria, Australia: The Royal Victorian Eye and Ear Hospital; Clinique Ophtalmolgie de Creteil, Paris, France: Comité de Protection des Personnes Hôpital Saint-Antonie; Hospital Lariboisiere, Paris, France: Comité de Protection des Personnes Hôpital Saint-Antonie; Jules Stein Eye Institute, UCLA, California, USA: The UCLA Institutional Review Board; Lions Eye Institute, Nedlands, Australia: Sire Charles

Gairdner Group Human Research Ethics Committee; Manhattan Eye, Ear and Throat Hospital, New York, USA: Lenox Hill Hospital Institutional Review Board; Moorfields Eye Hospital, London, UK: National Research Ethics Service; Retina Associates of Cleveland, Inc., Cleveland, Ohio, USA: Sterling Institutional Review Board; Save Sight Institute, Sydney, Australia: South Eastern Sydney Illawarra Area Health Service Human Research Ethics Committee–Northern Hospital Network; Scripps Research Institute, La Jolla, California, USA: Scripps Institutional Review Board; St. Franziskus Hospital, Munster, Germany: Ethik-Kommission der Arztekammer Westfalen-Lippe und der Medizinishchen Fakultat der Westfallschen Wilhelms-Universitat; The Goldschleger Eye Institute, Tel Hashomer, Israel: Ethics Committee The Chaim Sheba Medical Center; The New York Eye and Ear Infirmary, New York, USA: The Institutional Review Board of the New York Eye and Ear Infirmary; The Retina Group of Washington, Olympia, Washington, USA: Western Institutional Review Board; University of Bonn, Bonn, Germany: Rheinische Friedrich-Wilhelms-Universität Ethik-Kommission; University of Chicago, Chicago, Illinois, USA: The University of Chicago Division of Biological Sciences–The Pritzker School Institutional Review Board; University of Michigan, Ann Arbor, Michigan, USA: Medical School Institutional Review Board (IRBMED); University of Wisconsin, Madison, Wisconsin, USA: Office of Clinical Trials University of Wisconsin School of Medicine and Public Health; The Wilmer Eye Institute of Johns Hopkins University, Baltimore, Maryland, USA: Johns Hopkins School of Medicine Office of Human Subjects Research; Scheie Eye Institute University of Pennsylvania, Philadelphia, Pennsylvania, USA: University of Pennsylvania Office of Regulatory Affairs; University of Bern, Bern, Switzerland: Kantonale Ethikkommission Bern; John Moran Eye University of Utah, Salt Lake City, Utah, USA: The University of Utah Institutional Review Board; Bascom Palmer Eye Institute University of Miami, Miami, Florida, USA: The University of Miami Human Subjects Research Office; Columbia University, New York, New York, USA: Columbia University Medical Center Institutional Review Board Category 4 waiver for research involving specimens obtained from deidentified subjects. Participants were given a standardized ophthalmic examination, including best corrected visual acuity, fundus photography, fluorescein angiography, optical coherence tomography and blue light reflectance. Images were adjudicated at the Reading Center at Moorfields Eye Hospital, London.

mPRS & tPRS calculation

We used the formula $PRS(M/T)_i = \sum_{j \in i} \quad m_j * SNP_j$, where $PRS(M/T)_i$ is the polygenic risk score of metabolite (*M*) or trait, Ti. SNP_j is the jth SNP that was significantly associated with the metabolite or trait i. m_j is the magnitude (weight) that the SNP_j has on the metabolite or trait. The weight m_j was obtained as $m_j = \beta_j$ where β_j is the linear coefficient of the regression of SNP_j on the metabolite or trait i. We used a total of 499 SNPs to predict the abundances of 142 metabolites in blood serum, 37 SNPs to construct a genetically predicted T2D risk, 5 for retinal venular calibre and 2 for the retinal arteriolar calibre. mPRSs and tPRSs were normalized to have a mean of zero and unit standard deviation.

Imputation of phenotypic data

The phenotyping dataset contained multiple missing data points. Most missingness was related to imperfections in the ophthalmological images. By assuming missingness at random we imputed the missing data using predictive mean matching through chained equations, available in the package MICE [2].

Generation of Endophenotypes with Factorial Analysis

The phenotypic data was summarised into endophenotypes. Endophenotypes have been defined as “measurable components unseen by the unaided eye along the pathway between disease and distal genotype”[3]. To identify and construct these underlying endophenotypes while ensuring that each only contained phenotypes strongly related to each other, we used an iterative factorial analysis algorithm. Given the very different nature of the phenotypes observed we performed two separate analyses for the creation of the endophenotypes one to capture macular thickness endophenotypes, and the other to capture macular abnormality phenotypes.

Starting with 43 phenotypic measurements for macular thickness and 76 for macular abnormality phenotypes we reduced these two data sets further, by only retaining correlated phenotypes within each dataset.
We discarded all those phenotypes/variables which:

- Had an absolute value of Spearman correlation with all other variables less than 0.3.
- Had an absolute value of Spearman correlation with the overall dataset score of less than 0.3.
- Would decrease the Cronbach's alpha of the dataset

This procedure retained 33 phenotypes for macular thickness and 52 phenotypes for macular abnormalities. Variables that were retained after this step underwent an iterative factorial analysis procedure:

1. Perform a *parallel analysis* on the dataset to discover the number of factors F needed to summarise the phenotypic data
2. Run a *factorial analysis* with F number of factors
3. Rotate the factors using the *oblimin* rotation to allow for correlation between endophenotypes and obtain a loading value for each phenotype in each factor.
4. Create a sequence of loading thresholds T from 0.2 to 0.5 by 0.01
5. For each loading threshold $t \in T$ and for each factor $f \in F$, create a dataset that contains all the phenotype that have a loading greater than t. This results in F datasets.
6. Calculate the Cronbach's alpha in each dataset assessing the reliability of each factor.
7. Calculate the average of all factor’s alphas
8. Select the loading threshold $t*$ that maximize the average alpha.

9. Eliminate from the dataset all the variables that do not have any loading greater than $t*$.
10. Eliminate all variables which create factors by themselves.
11. Repeat 1-10 the entire process until no variables are removed.

This procedure was followed by an additional step, where we took the phenotypes that were discarded from the previous step and re-introduced into the endophenotype creation process, by themselves. Those phenotypes that were discarded a second time, were manually collapsed into meaningful new endophenotypes from previous clinical knowledge. These endophenotypes were obtained by simply summing the phenotypes values together.

Each factor created by this process was considered an endophenotype in further analysis. All endophenotypes resulted in continuous variables for which higher values represented negative impacts on patient's eye health. Specifically, higher values of macular thickness endophenotypes represented a risk of macular thinning, higher values for foveal slopes endophenotypes represented increase risk of foveal flattening, and higher values for macular abnormalities endophenotypes represented an increased risk of observing that particular endophenotype. Most of the analyses to obtain the endophenotypes were performed using the R package Psych[4].

Following the method used by [5], we also created foveal slope measurements from each parafoveal area using the macular thickness endophenotypes. The formula used is was $Slope_j = tan^{-1}((Thick_j - Thick_1)/500)$. Where $Slope_j$ indicates the slope from the fovea to the parafoveal area $j$and$Thick_j$is the endophenotype of macular thickness in area j. Since the foveal slope is defined as the slope from the fovea to the parafoveal areas the only areas used were area 2, area 3, area 4, and area 5 of the ETDRS grid.

The factorial analysis results in 9 endophenotypes describing macular thickness and 19 describing macular abnormalities. We discarded one macular thickness endophenotype and one macular abnormalities endophenotype since they were believed to describe only a residual correlation between phenotypes and have no real clinical relevance. Additionally, we obtained 4 endophenotypes describing macular slope leading to a total of 30 endophenotypes to be used in the analysis.

Testing the identified disease key drivers and SNP loci against the endophenotypes

Endophenotypes were normalized to have zero average and unit standard deviation. Given the longitudinal nature of the data, we chose a linear mixed model approach to take into account the relationships within the subject and eye observation. Each model included all factors of interest as well as time defined as the number of days from the initial visit date, a quadratic function of visit year, gender, and age as covariates. Each model also contained a

random intercept and random time slope for each subject as well as a random intercept and random time slope for each eye within each subject. We included all these random effects since the log-likelihood of models that contained them and models which did not were significantly different (results not shown. Models that compared fixed effects were estimated using restricted maximum likelihood estimation. Given the large sample size, the p-values were obtained by assuming the asymptotic normality property of the t-values for each association. To take into account false discovery rate we used an adaptive Benjamini-Hochberg procedure [6]. We adopted this procedure rather than strict Bonferroni correction because of the very conservative nature of the linear mixed model and the small magnitude of SNP effect sizes.

Additional Results:

MR using Shin et al 2014 metabolomics study:

We also tried to perform MR testing on all metabolites available from one of the first studies on the genetic impact on metabolomics abundances by Shin et al 2014 [7,8] which contained many more metabolites than those initially available to us. Of the 248 mPRSs available we found few additional metabolites to be significant (Table S4), None of them was as strongly associated as glycine PRS and serine PRS and none retained significance after their inclusion as covariates.

Composition of the endophenotypes

A detailed list of phenotypes and respective loadings values used to estimate each of the endophenotypes is available in Supplementary Materials and **Table S6**. Interestingly, among the 30 retained endophenotypes, we noticed that some distinguished between abnormalities occurring in the initial MacTel region (area 5 in the ETDRS grid) and abnormalities expanding to the surrounding areas of the retina, which is usually denoted to indicate progression of the disease (areas 2, 3 and 4 on the ETDRS grid). For this reason, we defined these endophenotypes as "MacTel area" and "Progression" respectively.

Supplemental Table 7:

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