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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All samples were sequenced at IGM with the IDT's Exome Research Panel Version 1 (differing capture kits) or off-site using mostly AgilentV5 and V7 kits. All exome data were processed using the IGM alignment and annotation pipeline for standardized analysis outcome.
Data analysis	DRAGEN Bio-IT Platform v. 2.5.1 (Illumina) was used to align reads to the Genome Reference Consortium Human Build 37, calling variants in accordance with the Genome Analysis Tool Kit (GATK, v. 4.0.2.1) Best Practices Workflow, using ATAV (7.0.16), an IGM variant-calling pipeline. Kinship pruning was evaluated using KING (1.4.2). Population substructures were corrected using the EIGENSTRAT (6.1.4) pruning algorithm with a list of 13,000 common variants. For all collapsing models, we used the two-tailed Fisher's exact test (FET) (SciPy module, Python 2.7.7). To account for bias due to small numbers of qualifying variants in logistic regression models, we applied a Firth correction with profile likelihood confidence intervals. For all models, with 18,852 genes being tested, we used the Bonferroni multiple-test correction to set a study-wide significance threshold of p = 1.33×10-6. Quantification of protein abundance was performed with Image J (version 1.50b).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The datasets generated during and/or analyzed during the current study, if not presented in the manuscript, are available at GitHub (https://github.com/igm-team/MacTel), and/or from the corresponding author on reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Genetic analyses included, after pruning, WES data from 793 cases and 17,610 controls; i.e., the case cohort included all samples available to our consortium. Therefore, we did not calculate the sample size, but judging from the results, it was adequate to achieve highly statistically significant result under given analysis conditions and parameters. For cellular assays no statistical methods were used to determine sample size. Sample sizes were chosen based on the maximum cell lines we could obtain.
Data exclusions	No exclusions
Replication	An independent replication cohort was not used due to the rarity of the disease. Practically all MacTel cases of non-Finnish European origin around the world were recruited under our consortium. Enzymatic assays and metabolite measurements of secreted metabolites were repeated in three separate experiments. All replication attempts were successful. Lipid measurements and isotope tracing experiments were performed once with multiple different cell lines. These experiments were not repeated because of the size and diversity of genetic replicates were adequate. No other experiments in the study required replication.
Randomization	Randomization was not part of the employed methods.
Blinding	Clinical diagnosis of MacTel was confirmed by masked readers at the Moorfields Eye Hospital MacTel Reading Centre in London. Technicians were blinded to the identity of samples for enzymatic assay and mass spec measurements. No other experiments required blinding.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	anti-PHGDH antibody, Sigma-Aldrich HPA021241; anti-rabbit secondary, LI-COR 926-32213; anti-b-actin, Cell Signaling Technology 3700; HRP secondary antibody, Sigma-Aldrich AP160P.
Validation	Anti-PHGDH antibody is produced in rabbit, a Prestige Antibody, is developed and validated by the Human Protein Atlas (HPA) project. Validation available at: (www.proteinatlas.org).

The anti-rabbit secondary antibody was isolated by affinity chromatography using antigens coupled to agarose beads. Based on ELISA, this antibody reacts with the heavy and light chains of rabbit IgG and with the light chains common to most rabbit immunoglobulins. This antibody has been tested by ELISA and/or solid-phase adsorbed to ensure minimal cross-reaction with bovine, chicken, goat, guinea pig, hamster, horse, human, mouse, rat, and sheep serum proteins, but the antibody may cross-react with immunoglobulins from other species. The conjugate has been specifically tested and qualified for Western blot and In-Cell Western Assay applications. Validation available at: https://www.licor.com/documents/ri8oae8r69uvqndq72g3l9a4d0do4u44.
Validation for anti-b-actin antibody is available at: https://www.cellsignal.com/products/primary-antibodies/b-actin-8h10d10-mouse-mab/3700.
The HRP secondary antibody is isolated from antisera by immunoaffinity chromatography using antigen coupled to agarose beads. Validation available at: https://www.sigmaaldrich.com/catalog/product/mm/ap160p?lang=en&region=US.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	iPSCs were derived in the laboratory. HEK293 cells were purchased from ATCC.
Authentication	Validated by normal karyotyping and expression of stem cell markers.
Mycoplasma contamination	All samples tested negative for Mycoplasma.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study.

Human research participants

Policy information about studies involving human research participants

Population characteristics	Patient cohort includes subjects who were diagnosed with MacTel by experienced retina specialists at 24 study centers from 7 countries around the world and were subsequently confirmed by masked readers at the Moorfields Eye Hospital MacTel Reading Centre in London. Controls were selected from studies at the Institute for Genomic Medicine (IGM) known to have no co-morbid phenotypes such as ophthalmic disease, metabolic disease, etc., and were matched by age and ethnicity. The male:female ratio in patients was 326:467 , in controls 8,721:8,889, and the average age 62.3 years (SD +/- 8.9).
Recruitment	Patients were recruited after being diagnosed with MacTel by experienced retina specialists at 24 study centers from around the world and were subsequently confirmed by masked readers at the MacTel Reading Centre. Confirmed diagnosis of MacTel was the only condition for recruitment; there was no recruitment bias based on any other criteria.
Ethics oversight	All enrolled patients read and signed informed consent forms approved by local Institutional Review Boards, and all clinical research complied with the Declaration of Helsinki and HIPAA privacy regulations. Patient recruitment and sharing of anonymized specimens for research was approved by site-specific Institutional Review Boards and ethics committees. 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; QIMR Berghofer Institute of Medical Research, Queensland, Australia; 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 de-identified subjects.

Note that full information on the approval of the study protocol must also be provided in the manuscript.