A shared chromosome 12 rare-variant locus links sudden sensorineural hearing loss, vestibular neuritis, and serum potassium homeostasis

Argyro Bizaki-Vallaskangas[1,2], Elmo Saarentaus[3,4,5], Minjin Jeong[6], Eeva Sliz[7], Joel Rämö[3], Ilkka Kivekäs[1,2], Tytti Willberg[4,8], Vesa P. Hytönen[1,9], Aarno Palotie[3,10,11], Konstantina M. Stankovic[6,12,13], Antti Mäkitie[3,4,5]

[1] University of Tampere, Department of Medicine and Health Technology, Tampere, Finland
[2]Department of Otorhinolaryngology, Tampere University Hospital, Tampere, Finland
[3] Institute for Molecular Medicine Finland (FIMM), HiLIFE University of Helsinki ,Finland
[4]Department of Otorhinolaryngology – Head and Neck Surgery Helsinki University Hospital and University of Helsinki ,Finland
[5] Research Program in Systems Oncology, Faculty of Medicine University of Helsinki, Helsinki, Finland
[6]Department of Otolaryngology-Head and Neck Surgery, Stanford University School of Medicine, Stanford, California, USA
[7] University of Oulu, Biocenter Oulu and Center for Life Course Health Research, Finland
[8]University Hospital of Turku, Department of Otolaryngology, Turku, Finland
[9] Fimlab Laboratories, Tampere, Finland
[10]The Stanley Center for Psychiatric Research and Program in Medical and Population Genetics, The Broad Institute of MIT and Harvard, Cambridge, MA, USA.
[11] Analytic and Translational Genetics Unit, Department of Medicine, Department of Neurology and Department of Psychiatry Massachusetts General Hospital, Boston, MA, USA.
[12]Department of Neurosurgery, Stanford University School of Medicine, Stanford, California,
[13]Wu Tsai Neurosciences Institute, Stanford University, Stanford, California, USA

Corresponding author: Argyro Bizaki-Vallaskangas
arbizaki@gmail.com

SUPPLEMENTARY METHODS

S1. FinnGen R13 study description

The FinnGen study (https://www.finngen.fi/en) is a public-private research project established in 2017 that combines longitudinal genomic and digital health-care data from approximately 500,000 Finnish biobank participants. FinnGen Data Freeze 13 (R13), released in 2025, was used in the present study and contained 500,186 samples (293,218 female, 226,754 male). Disease diagnoses and clinical procedures were obtained from the Care Register for Health Care maintained by the Finnish Institute for Health and Welfare (THL) and from the Causes of Death Register maintained by Statistics Finland.

S2. Sample source and biobank governance

FinnGen samples comprise two categories. Prospective ("new") samples are collected upon voluntary biobank consent and donation, typically during diagnostic sampling in hospital laboratories or wards (Hospital Biobanks, Terveystalo Biobank), during blood donation (Finnish Red Cross Blood Service Biobank), or during research-sample collection (THL Biobank). Legacy samples are older cohorts collected for specific research projects before the Finnish Biobank Act came into force (September 2013) and later transferred to a biobank under Article 13 of the Act. All Finnish biobanks are members of the BBMRI.fi infrastructure (https://www.bbmri-eric.eu/national-nodes/finland/). FINBB (https://finbb.fi/) coordinates BBMRI-ERIC operations in Finland, and biobank data access is managed through the Fingenious service (https://site.fingenious.fi/en/).

S3. Ethical approvals and biobank access decisions

Study subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected prior the Finnish Biobank Act came into effect (in September 2013) and start of FinnGen (August 2017), were collected based on study-specific consents and later transferred to the Finnish biobanks after approval by Fimea (Finnish Medicines Agency), the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) statement number for the FinnGen study is Nr HUS/990/2017.The FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019 and THL/1524/5.05.00/2020), Digital and population data service agency (permit numbers: VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 134/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020), Findata permit numbers THL/2364/14.02/2020, THL/4055/14.06.00/2020, THL/3433/14.06.00/2020, THL/4432/14.06/2020, THL/5189/14.06/2020, THL/5894/14.06.00/2020, THL/6619/14.06.00/2020, THL/209/14.06.00/2021, THL/688/14.06.00/2021, THL/1284/14.06.00/2021, THL/1965/14.06.00/2021, THL/5546/14.02.00/2020, THL/2658/14.06.00/2021,

THL/4235/14.06.00/2021, THL/4990/14.02.00/2023 Statistics Finland (permit numbers: TK-53-1041-17 and TK/143/07.03.00/2020 (earlier TK-53-90-20) TK/1735/07.03.00/2021, TK/3112/07.03.00/2021) and Finnish Registry for Kidney Diseases permission/extract from the meeting minutes on 4th July 2019.The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 13 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, BB2021_65, BB22-0025-A01, BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, THLBB2024_30. Finnish Red Cross Blood Service Biobank 7.12.2017, 13.11.2023, 001-2023, Helsinki Biobank HUS/359/2017, HUS/248/2020, HUS/430/2021 §28, §29, HUS/150/2022 §12, §13, §14, §15, §16, §17, §18, §23, §58, §59, HUS/128/2023 §18, BB22-0025-A01, BB22-0025-A02, BB22-0025-A05, BB22-0025-A07, BB22-0025-A09, BB22-0025-A10, BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, Amendment_BB22-0025-A05, Decision allowing to continue data processing until 31st Aug 2027: BB_2021-0140, HUS/150/2022 §12, BB_2021-0139, HUS/150/2022 §13, BB_2021-0161,HUS/150/2022 §14, BB_2021-0164, HUS/150/2022 §15, BB_2021-0169, HUS/150/2022 §16, BB_2021-0170, HUS/150/2022 §17, BB_2021-0179, HUS/150/2022 §18, BB_2022-0262, HUS/150/2022 §58, BB22-0067, HUS/150/2022 §59, Auria Biobank AB17-5154 and amendment #1 (August 17 2020) and amendments BB_2021-0140, BB_2021-0156 (August 26 2021, Feb 2 2022), BB_2021-0169, BB_2021-0179, BB_2021-0161, AB20-5926 and amendment #1 (April 23 2020) and it´s modifications (Sep 22 2021), BB_2022-0262, BB_2022-0256, BB22-0025-A01, BB22-0025-A02, BB22-0025-A03, BB23-0222_A01, BB22-0025-A02, BB22-0025-A05, BB22-0025-A07, BB22-0025-A09, BB22-0025-A10, BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, Decision allowing to continue data processing until 31st Aug 2027: AB20-5926, BB_2021- 0140, BB_2021-0156, BB_2021-0161, BB_2021- 0161, BB_2021-0164, BB_2021-0169, BB_2021-0179, BB_2022-0262, Biobank Borealis of Northern Finland_2017_1013, 2021_5010, 2021_5010 Amendment, 2021_5018, 2021_5018 Amendment, 2021_5015, 2021_5015 Amendment, 2021_5015 Amendment_2, 2021_5023, 2021_5023 Amendment, 2021_5023 Amendment_2, 2021_5017, 2021_5017 Amendment, 2022_6001, 2022_6001 Amendment, 2022_6006 Amendment, 2022_6006 Amendment_2, BB22-0067, 2022_0262, 2022_0262 Amendment, BB22-0025-A01, BB22-0025-A02, BB22-0025-A05, BB22-0025-A07, BB22-0025-A09, BB22-0025-A10, BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, Decision allowing to continue data processing until 31st Aug 2027: BB/2021/5015, BB/2021/5017, BB/2021/5018, BB/2021/5023, BB/2022/6006, BB/2022/6001, BB/2022-0262, BB/2021/5010, Biobank of Eastern Finland 1186/2018 and amendment 22§/2020, 53§/2021, 13§/2022, 14§/2022, 15§/2022, 27§/2022, 28§/2022, 29§/2022, 33§/2022, 35§/2022, 36§/2022, 37§/2022, 39§/2022, 7§/2023, 32§/2023, 33§/2023, 34§/2023, 35§/2023, 36§/2023, 37§/2023, 38§/2023, 39§/2023, 40§/2023, 41§/2023, BB22-0025-A01, BB22-0025-A02, BB22-0025-A05, BB22-0025-A07, BB22-0025-A09, BB22-0025-A10, BB22-0025-A03,

BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, Decision allowing to continue data processing until 31st Aug 2027: MO-BB_2021-0179-A0, MO-BB_2021-0156_PRE-A01, BB_2021-0140, MO-BB_2021-0170_PRE-A0, MO-BB_2021-0169-A01, MO-BB_2022-0256-A01, MO-BB_2021-0161-A01, MO-BB_2021-0161-A02, BB22-0067-A01, MO-BB_2022-0262-A0, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 & 06.10.2020), BB2021-0140 8§/2021, 9§/2021, §9/2022, §10/2022, §12/2022, 13§/2022, §20/2022, §21/2022, §22/2022, §23/2022, 28§/2022, 29§/2022, 30§/2022, 31§/2022, 32§/2022, 38§/2022, 40§/2022, 42§/2022, 1§/2023, BB2021-0140, BB22-0025-A01, BB_2021-0161, BB22-0025-A02, BB22-0025-A05, BB22-0025-A07, BB22-0025-A09, BB22-0025-A10, BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, Decision allowing to continue data processing until 31st Aug 2027: BB_2021- 0140, BB_ 2021- 0161, BB_ 2021- 0179, BB_ 2021- 0156, BB_ 2021- 0169, BB_ 2021- 0170, BB22- 0067- A01, Central Finland Biobank 1-2017, BB_2021-0169, BB_2021-0179, BB_2022-0256, BB_2022-0262, Decision allowing to continue data processing until 31st Aug 2027 for projects: BB_2021-0179, BB22-0067,BB_2022-0262, BB_2021-0170, BB_2021-0164, BB_2021-0161, and BB_2021-0169, BB22-0025-A01, BB22-0025-A02, BB22-0025-A05, BB22-0025-A07, BB22-0025-A09, BB22-0025-A10, BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08, Terveystalo Biobank STB 2018001 and amendment 25th Aug 2020, Finnish Hematological Registry and Clinical Biobank decision 18th June 2021, Amendment 2nd January 2024 and Arctic biobank P0844: ARC_2021_1001, ARC_2023_3003 (BB22-0025-A01), BB22-0025-A03, BB23-0222-A01, BB22-0025-A04, BB22-0025-A06, BB22-0025-A08.

S4 Animal and human-tissue ethics

Mouse procedures were approved by the University of Tampere (permit ESAVI/23659/2018) and conducted in accordance with the AVMA Guidelines for the Euthanasia of Animals: 2020 Edition.[34] Human vestibular tissue procedures were reviewed by the Mass General Brigham Institutional Review Board (protocol 2020P003329, 2 December 2020) and determined exempt; all procedures were conducted in accordance with the Declaration of Helsinki.

S5. Genotyping and imputation

FinnGen samples were genotyped on Illumina (Illumina Inc., San Diego, CA, USA) and Affymetrix (ThermoFisher Scientific, Santa Clara, CA, USA) GWAS arrays. Legacy samples used various generations of Illumina and Affymetrix arrays; genotype calls were made with GenCall and zCall (Illumina) and AxiomGT1

Figure S1 : Locus zoom for 12:49564549:G:A (rs746992172) variant (included +/- 1 Mb window around the primary leading variant)

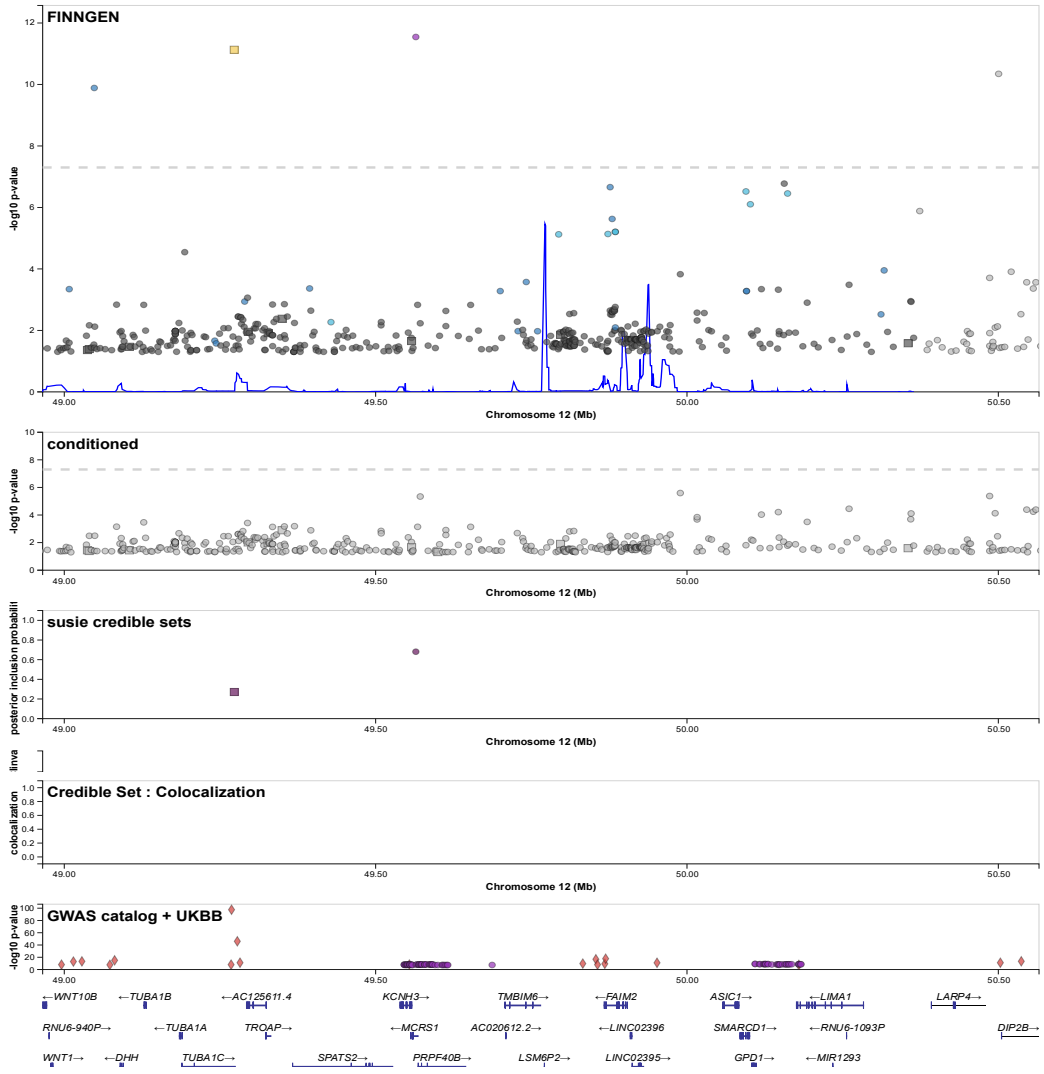

Figure S2 : PheWAS for variant 12:47077334:A:G (rs1328292306)

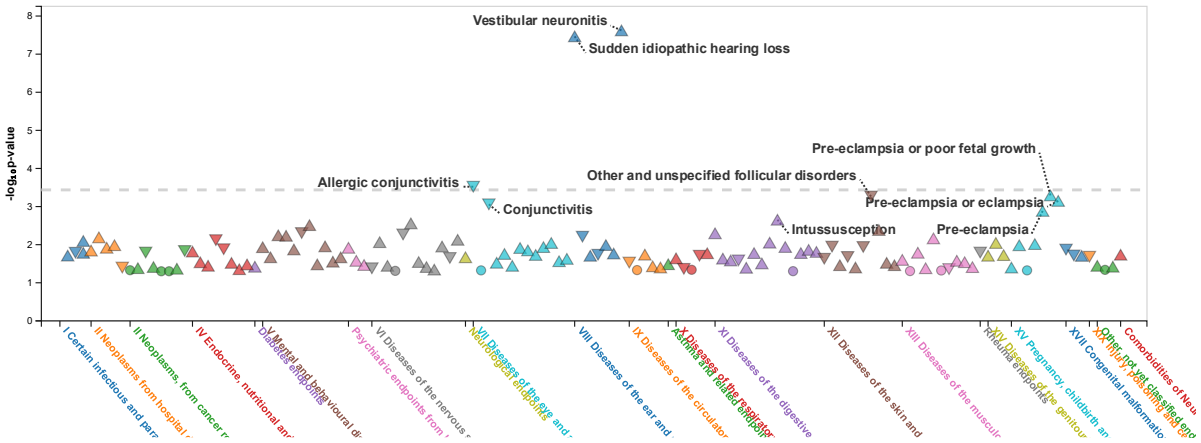

Figure S3. Locus zoom for the missense variant 12:49272869:C:T (rs200317762)

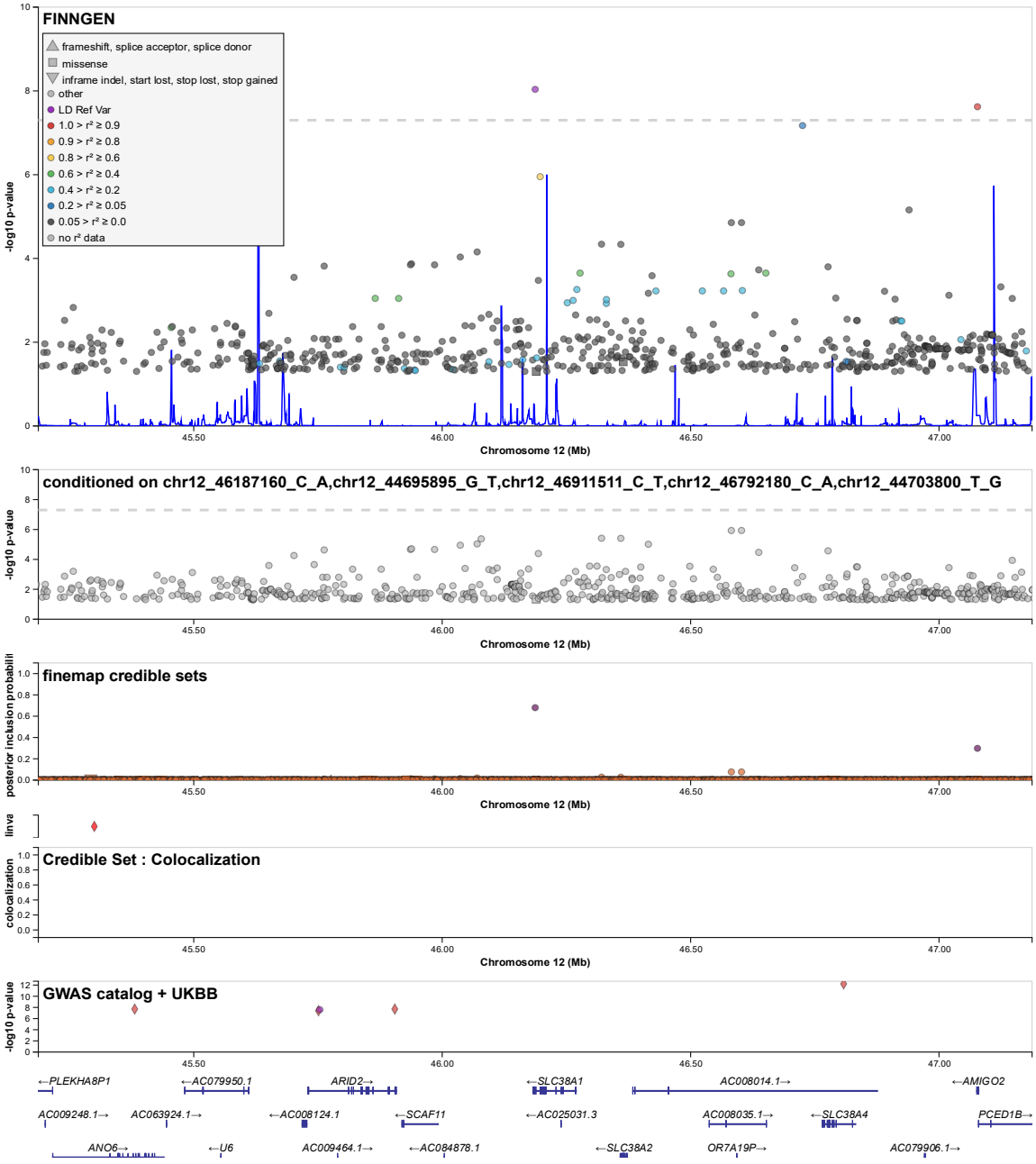

Figure S4 Locus zoom for leading variant 12:46187160:C:A (rs899415377)

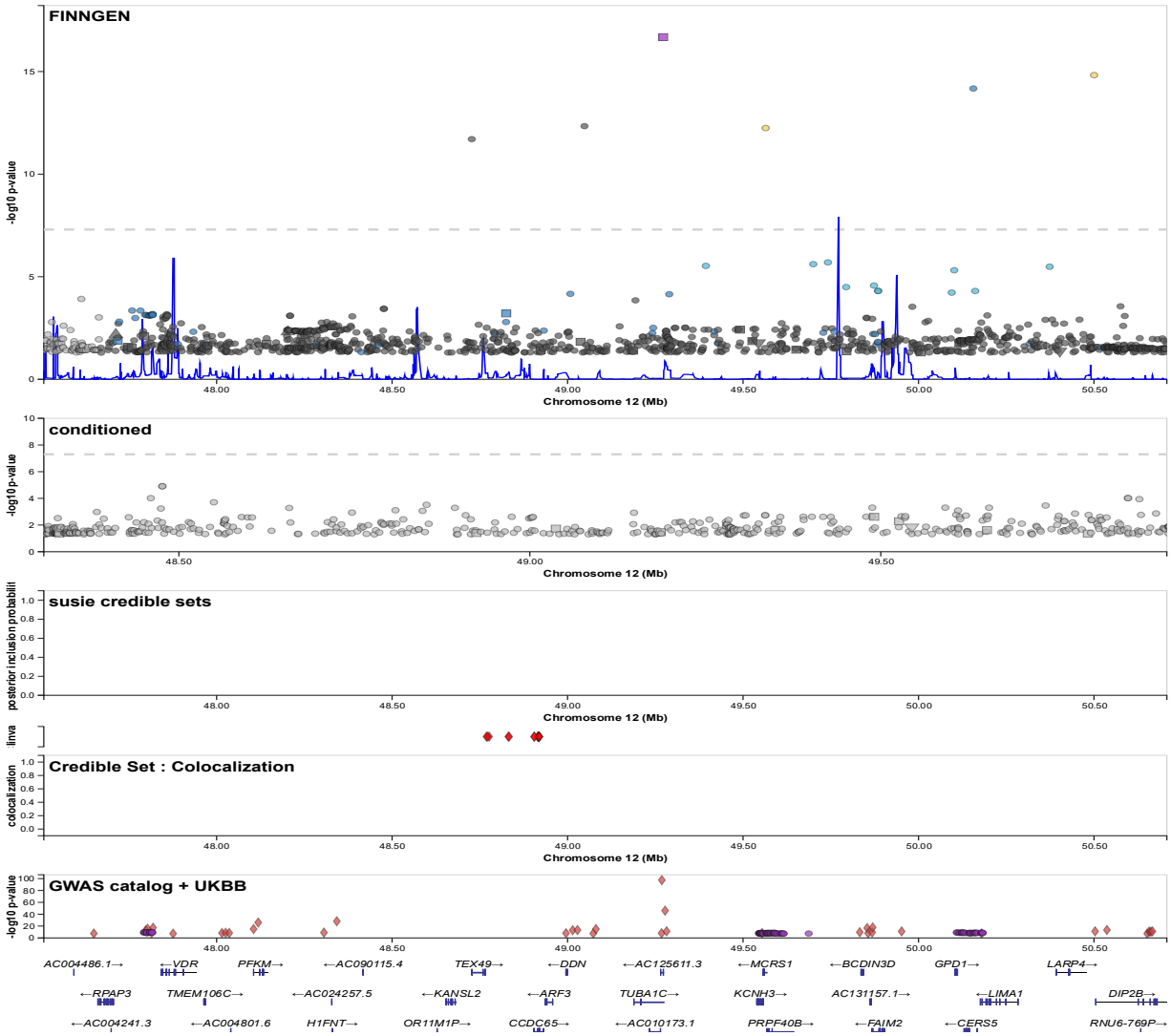

Figure S5. Immunohistochemistry for TUBA1C
Legend of Figure 2 : Strong TUBA1C immunoreactivity outlines SGN cell bodies. Strong non-specific immunoreactivity only in spiral ligament and stria vascularis.

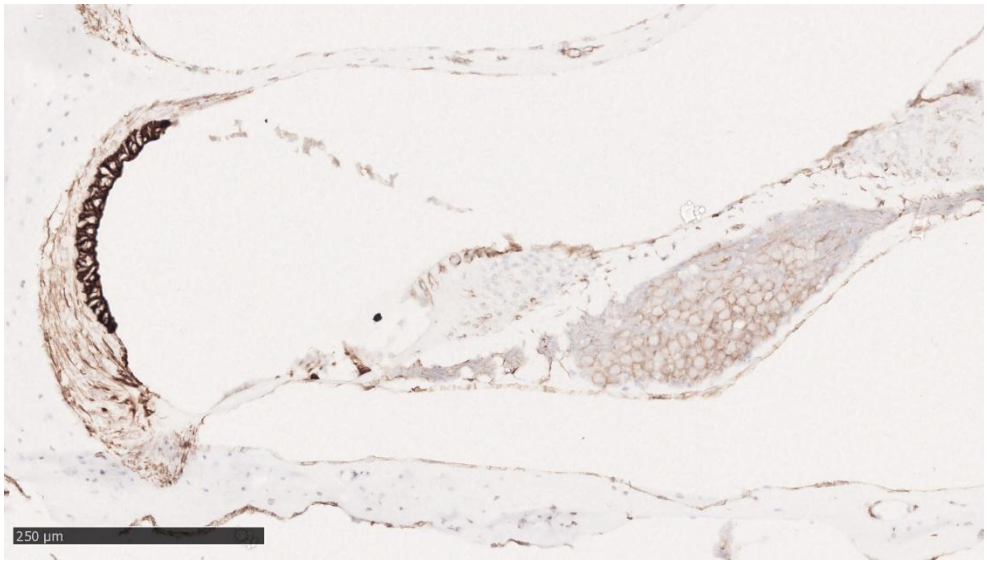

Table S1. PheWAS for missense variant 12:49272869:C:T

dataset	trait	trait_original	chr	pos	ref	alt	mlog10p	beta	se	pip	cs_id	cs_size	cs_min_r2	aaf	most_severe	gene_most_severe
FinnGen_R13_MVP_UKBB_labs	3023103	3023103	12	49272869	C	T	14.34	-1.77E-01	2.26E-02	0.6493	12_49272869_(	2	0.9235	0.00236346	missense_variant	TUBA1C
FinnGen_R13_UKBB	s_of_vestibular_function_	H8_VERTIGO	12	49272869	C	T	8.41	5.26E-01	8.93E-02	0.5847	12_49272869_(	3	0.778	0.00233409	missense_variant	TUBA1C
FinnGen_R13	H8_HL_IDIOP	H8_HL_IDIOP	12	49272869	C	T	12.1306	1.18E+00	1.64E-01	0.2727	l55773341-5106	3	0.6853	2.20E-03	missense_variant	TUBA1C
FinnGen_R13	H8_VERTIGO	H8_VERTIGO	12	49272869	C	T	8.4123	5.26E-01	8.93E-02	0.5819	l7772869-5077.	2	0.6873	2.20E-03	missense_variant	TUBA1C
FinnGen_R13	H8_VESTIBNEUR	I8_VESTIBNEUI	12	49272869	C	T	19.6091	1.46E+00	1.58E-01	0.9889	l7772869-5241	1	1	2.20E-03	missense_variant	TUBA1C
FinnGen_R13_UKBB	den_idiopathic_hearing_l	H8_HL_IDIOP	12	49272869	C	T	12.13	1.18E+00	1.64E-01	0.2661	12_49564549_(	3	0.778	0.00233009	missense_variant	TUBA1C
FinnGen_R13_UKBB	Vestibular_neuronitis	I8_VESTIBNEUI	12	49272869	C	T	19.61	1.46E+00	1.58E-01	0.99	12_49272869_(	1	1	0.00231955	missense_variant	TUBA1C

dataset	trait_original	chr	pos	ref	alt	mlog10p	beta	se	pip	cs_id	cs_size	cs_min_r2	aaf	most_severe	gene_most_severe
nGen_R13_MVP_UKBB_L	3023103	12	5E+07	G	A	14.06	-2.23E-01	2.88E-02	0.3407	chr12_49272869_C_T	2	0.9235	0.00185	synonymous_variant	MCRS1
FinnGen_R13_UKBB	H8_VERTIGO	12	5E+07	G	A	6.42	5.87E-01	1.16E-01	0.01	chr12_49272869_C_T	3	0.778	0.00183	synonymous_variant	MCRS1
FinnGen_R13	H8_HL_IDIOP	12	5E+07	G	A	12.534	1.51E+00	2.07E-01	0.6673	r12:45577334-51064549	3	0.6853	2.05E-03	synonymous_variant	MCRS1
FinnGen_R13_UKBB	H8_HL_IDIOP	12	5E+07	G	A	12.53	1.51E+00	2.07E-01	0.6683	chr12_49564549_G_A	3	0.778	0.00182	synonymous_variant	MCRS1

Table S2 . External meta-analysis for MCRS1 synonymous variant NC_000012.12:g.49564549G>A (rs746992172) in FinnGen + UK Biobank two-way meta-analysis and FinnGen × All of Us meta-analysis