Study specific approval for *Einson et al. Genetic control of mRNA splicing as a potential mechanism for incomplete penetrance of rare coding variants*

The following email was sent on December 11th, 2022 to request study specific approval for inclusion of genetic data, which was used in the final manuscript:

From: Tuuli Lappalainen <tlappalainen@nygenome.org>
Sent: Sunday, December 11, 2022 5:06 PM
To: p&p@whi.org; clk@fredhutch.org; Walsh, Ann (NIH/NHLBI) [E] <walshac@nhlbi.nih.gov>; kmutalik@bu.edu; BarbaraK@BloodworksNW.org; ruth.loos@mssm.edu; eimear.kenny@mssm.edu; ecterry@uw.edu; genpp@uw.edu; Myriam.Fornage@uth.tmc.edu; lsellers@uabmc.edu; moore.b.shoemaker@vumc.org; dan.roden@vumc.org; darbar@uic.edu; Robert.kaplan@einstein.yu.edu; ellinor@mgh.harvard.edu; heckbert@uw.edu; m.rienstra@umcg.nl; rcosenti@som.umaryland.edu
Subject: [EXTERNAL] Study-specific review of TOPMed manuscript submission

Dear colleagues,

We are happy to share our manuscript, which uses TOPMed data from your study, for your review and (hopefully) your study-specific approval.

The manuscript has already been approved by the TopMed population genetics working group, and it is based on paper proposal #14988. We plan to submit it to Genetics.

Please let us know if you have any revisions to suggest.

Best regards,
Tuuli

Tuuli Lappalainen, PhD
Professor, KTH Royal Institute of Technology
Director, National Genomics Infrastructure & Genomics Platform, SciLifeLab
Associate Faculty Member, New York Genome Center

The following cohorts were contacted. We received a reply and approval from the groups highlighted in green. There were no study-specific review requirements for the studies highlighted in blue. Groups who did not respond within 14 days are highlighted in Grey.

Cohort #	Cohort	Contact Person	Status
1	WHI	WHI P&P and Charles Kooperberg	Approved
2	COPD		No specific instructions
3	ARIC		Submitted Form, No response
4	FHS	Ann Walsh	Approved
5	MLOF	Barbara Konkle	No Response
6	BioMe	Ruth Loos & Eimear Kenny	No Response
7	CHS	Ellen Terry	Approved
8	MESA	Jane Fulcher	Approved
9	CARDIA	Myriam Fornage	No Response
10	VTE		Submitted Form, No response
11	LTRC		No specific instructions
12	BioVU_AF		No specific instructions
13	VU_AF		No specific instructions
14	HCHS_SOL	Robert Kaplan	No Response
15	SARP		No specific instructions
16	MGH_AF		No specific instructions
17	HVH		No specific instructions
18	GGAF	Michael Rienstra	Approved
19	Amish	Rhea Cosentino	Approved

Documentation of approval is attached subsequently.

WHI Clinical Coordinating Center

M E M O R A N D U M

Date: January 13, 2023

To: Tuuli Lappalainen

From: Lindsey Bull
P&P Committee Coordinator

Subject: Manuscript 4779 – Genetic control of mRNA splicing as a potential mechanism for incomplete penetrance of rare coding variants

Congratulations! The Publications and Presentations (P&P) Committee has approved this paper. Please see the reviews at the end of this memo for details.

You may now submit your manuscript for publication. It is important to keep WHI updated of your manuscript's status on an ongoing basis. Please notify P&P when your manuscript is submitted to a journal and accepted for publication by e-mailing (p&p@whi.org). As they become available, please send (1) a copy of the manuscript as accepted by the journal, (2) the published manuscript in PDF form, and (3) the NIH Manuscript Submission number/PubMed Central number. Authors are required to submit their published manuscript to PubMed Central; see http://publicaccess.nih.gov if you are unfamiliar with the NIH Public Access Policy.

Please be aware that lead authors are responsible for identifying and reporting any conflicts of interest among co-authors and noting these in the final manuscript, per journal requirements. Please ensure that all authors complete and report their conflicts on this paper. In addition, please be sure to keep all co-authors informed of your manuscript's progress. If a journal requires revisions, please solicit and incorporate co-author input and inform the P&P Chairs of any major disagreements among the writing group.

Please be reminded that, in accordance with the data use agreement you signed to obtain WHI data for this paper, the data may only be used for this approved analysis and may not be shared with anyone without authorization from WHI.

WHI Policy requires papers to be published with an appendix acknowledging WHI Investigators; please use the "short" list of WHI investigators that is available online at https://www-whi-org.s3.us-west-2.amazonaws.com/wp-content/uploads/WHI-Investigator-Short-List.pdf. All WHI publications must also include an acknowledgement that approximates the following: "The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through 75N92021D00001, 75N92021D00002, 75N92021D00003, 75N92021D00004, 75N92021D00005." We also request that you consult www.whi.org for exact wording if you include a description of the WHI trials in your manuscript.

1100 Fairview Ave. N., PO Box 19024, M3-A410, Seattle, Washington 98109-1024
206-667-2923 Fax: 206-667-4142

Cohort 3: ARIC (Email sent, with no response)

Jonah Einson <jeinson@nygenome.org>

Study-specific review of TOPMed manuscript submission

Jonah Einson <jeinson@nygenome.org> Tue, Dec 13, 2022 at 2:39 PM
To: "aricjhu@jhu.edu" <aricjhu@jhu.edu>
Cc: Tuuli Lappalainen <tlappalainen@nygenome.org>

Dear colleagues,

We are happy to share our manuscript, which uses TOPMed data from the ARIC and Mayo VTE cohorts, for your review and (hopefully) your study-specific approval. We request an expedited review of the manuscript.

The manuscript has already been approved by the TOPMed population genetics working group, and it is based on paper proposal #14988. We plan to submit it to Genetics.

Please let us know if you have any revisions to suggest.

Best regards,

Jonah Einson and Tuuli Lappalainen

--

Jonah Einson | Postdoctoral Research Associate
New York Genome Center
101 Avenue of the Americas, New York, NY 10013
jeinson@nygenome.org

2 attachments

Splicing Modifiers of Penetrance -10_24_22 FINAL.pdf
2324K

PopGenApproval_2022_14988_Einson.docx
253K

Cohort 4: FHS

Jonah Einson <jeinson@nygenome.org>

FW: Study-specific review of TOPMed manuscript submission Genetic control of mRNA splicing as a potential mechanism for incomplete penetrance of rare coding variants

2 messages

Tuuli Lappalainen <tlappalainen@nygenome.org> Tue, Jan 3, 2023 at 3:45 AM
To: Jonah Einson <jeinson@nygenome.org>

From: Walsh, Ann (NIH/NHLBI) [E] <walshac@nhlbi.nih.gov>
Date: Thursday, December 22, 2022 at 4:17 PM
To: Tuuli Lappalainen <tlappalainen@nygenome.org>
Cc: Nancy Heard-Costa <nheard@bu.edu>
Subject: RE: Study-specific review of TOPMed manuscript submission Genetic control of mRNA splicing as a potential mechanism for incomplete penetrance of rare coding variants

Dear Tuuli,

Per Nancy Heard Costa; FHS approves with a suggestion to include acknowledgment for each cohort at the end or in Supplemental Materials.

Thank you for your consideration,

Ann Walsh on behalf of Nancy Heard Costa

From: Tuuli Lappalainen <tlappalainen@nygenome.org>
Sent: Sunday, December 11, 2022 5:06 PM
To: p&p@whi.org; clk@fredhutch.org; Walsh, Ann (NIH/NHLBI) [E] <walshac@nhlbi.nih.gov>; kmutalik@bu.edu; BarbaraK@BloodworksNW.org; ruth.loos@mssm.edu; eimear.kenny@mssm.edu; ecterry@uw.edu; genpp@uw.edu; Myriam.Fornage@uth.tmc.edu; lsellers@uabmc.edu; moore.b.shoemaker@vumc.org; dan.roden@vumc.org; darbar@uic.edu; Robert.kaplan@einstein.yu.edu; ellinor@mgh.harvard.edu; heckbert@uw.edu; m.rienstra@umcg.nl; rcosenti@som.umaryland.edu
Subject: [EXTERNAL] Study-specific review of TOPMed manuscript submission

Dear colleagues,

Jonah Einson <jeinson@nygenome.org>

Record update from chs-nhlbi.org

2 messages

chsnhlbi@u.washington.edu <chsnhlbi@u.washington.edu> Tue, Jan 3, 2023 at 4:43 PM
Reply-To: chsnhlbi@u.washington.edu
To: jeinson@nygenome.org

Hello, authors.

Congratulations! Your penultimate draft, Genetic control of mRNA splicing as a potential mechanism for incomplete penetrance of rare coding variants, was approved by the Steering Committee pending the inclusion of the CHS funding statements (see below). Please see the updated status and details regarding your next steps at the following link: https://chs-nhlbi.org/node/9214.

Please include the current CHS acknowledgements, which you can view here: https://chs-nhlbi.org/pubs/PubAcknowGuidelines

"This research was supported by contracts HHSN268201200036C, HHSN268200800007C, HHSN268201800001C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, 75N92021D00006, and grants U01HL080295 and U01HL130114 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org."

Please also include the following disclaimer:
"The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health."

Please let me know if you have any questions.

Best,
Ellen

Ellen Terry
Publications Coordinator
CHS-NHLBI.org
ecterry@uw.edu

NOTES: Please make sure you are logged on to the CHS website before clicking the above link. This message was sent to the first author and all CHS co-authors.

chsnhlbi@u.washington.edu <chsnhlbi@u.washington.edu> Tue, Jan 3, 2023 at 4:43 PM
Reply-To: chsnhlbi@u.washington.edu
To: jeinson@nygenome.org

[Quoted text hidden]

Cohort 10: VTE (No response was received)

Jonah Einson <jeinson@nygenome.org>

Study-specific review of TOPMed manuscript submission

1 message

Jonah Einson <jeinson@nygenome.org> Tue, Dec 13, 2022 at 2:39 PM
To: "aricjhu@jhu.edu" <aricjhu@jhu.edu>
Cc: Tuuli Lappalainen <tlappalainen@nygenome.org>

Dear colleagues,

We are happy to share our manuscript, which uses TOPMed data from the ARIC and Mayo VTE cohorts, for your review and (hopefully) your study-specific approval. We request an expedited review of the manuscript.

The manuscript has already been approved by the TOPMed population genetics working group, and it is based on paper proposal #14988. We plan to submit it to Genetics.

Please let us know if you have any revisions to suggest.

Best regards,

Jonah Einson and Tuuli Lappalainen

--

Jonah Einson | Postdoctoral Research Associate
New York Genome Center
101 Avenue of the Americas, New York, NY 10013
jeinson@nygenome.org

2 attachments

Splicing Modifiers of Penetrance -10_24_22 FINAL.pdf
2324K

PopGenApproval_2022_14988_Einson.docx
253K

MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

MEMORANDUM

Date: January 13, 2023

To: Dr. Jonah Einson and Dr. Jerry Rotter

From: MESA Genetics P&P Committee

Re: MESA Genetics Manuscript G 953 (Genetic control of mRNA splicing as a potential mechanism for incomplete penetrance of rare coding variants)

The MESA Genetics P&P Committee has reviewed and approved the penultimate draft of your manuscript referenced above. **With this approval memo, you can now submit your manuscript to a journal.**

Publication information requested by P&P Committee:
Please inform the MESA Genetics P&P Coordinator when the manuscript is accepted at a journal (date of acceptance and journal name). Please be sure to include the MESA Genetics ID (G 953) in your communication. Please also notify the Coordinator when the manuscript has been published (complete citation and a PDF of the manuscript).

Publication information requested by the NHLBI:
The NHLBI no longer reviews MESA manuscripts (except those that include NHLBI staff members as authors), but to stay informed of findings from large studies and to prepare for press queries, the NHLBI Project Office would like authors to send them a courtesy copy of manuscript at or before the time of journal acceptance, particularly for "high-profile" papers. These generally include the following**:**

- Main results papers or key secondary results papers from clinical trials
- Papers with direct clinical implications, particularly if they impact NHLBI policies
- Papers on potentially sensitive topics
- Papers published in prestige high impact journals such as *Nature*, *Nature Genetics*, *Science*, *PLoS*, *NEJM*, *JAMA,* and *Lancet*.

Most importantly, please inform Cashell Jaquish (jaquishc@nhlbi.nih.gov), NHLBI Program Director, as soon as you are notified that your manuscript has been accepted for publication at one of the high-profile journals mentioned above.

PubMed
Please note that as of April 7, 2008, all peer-reviewed manuscripts arising from NIH funds are subject to the NIH Public Access Policy and must be submitted to PubMed Central (PMC) upon acceptance. When you submit your paper for consideration for publication, you must inform the journal of the need to comply with this policy. For details about what you need to do with submission, please go to http://publicaccess.nih.gov/.

If you have any questions, please contact the MESA Genetics P&P Coordinator (genpp@uw.edu).

Collaborative Health Studies Coordinating Center
UNIVERSITY OF WASHINGTON
Building 29, Suite 210 ✪ 6200 NE 74th St. ✪ Seattle, WA 98115 ✪ Tel: 206-685-7123 ✪ Fax: 206-616-4075

Jonah Einson <jeinson@nygenome.org>

FW: Study-specific review of TOPMed manuscript submission

Tuuli Lappalainen <tlappalainen@nygenome.org> Sun, Dec 11, 2022 at 7:55 PM
To: Jonah Einson <jeinson@nygenome.org>

From: Susan R Heckbert <heckbert@uw.edu>
Date: Sunday, December 11, 2022 at 6:51 PM
To: Tuuli Lappalainen <tlappalainen@nygenome.org>
Subject: Re: Study-specific review of TOPMed manuscript submission

Hello Tuuli,

Very nice manuscript. I'm responding on behalf of the HVH study, which contributed a small number of observations to this analysis. I approve.

A suggestion for the abstract: it seems there may be a verb missing from this phrase: "and that natural selection alleles haplotype configurations that reduce the transcript inclusion of putatively pathogenic variants".

Susan

Susan R. Heckbert, MD, PhD
Professor, Department of Epidemiology

University of Washington
Cardiovascular Health Research Unit
UW Tower Box 359458, 4333 Brooklyn Ave NE
Seattle, WA 98195-9458

206.221.7775 | heckbert@uw.edu

From: Tuuli Lappalainen <tlappalainen@nygenome.org>
Date: Sunday, December 11, 2022 at 2:12 PM
To: "p&p@whi.org" <p&p@whi.org>, "clk@fredhutch.org" <clk@fredhutch.org>, "walshac@nhlbi.nih.gov" <walshac@nhlbi.nih.gov>, "kmutalik@bu.edu" <kmutalik@bu.edu>, "BarbaraK@BloodworksNW.org" <BarbaraK@BloodworksNW.org>, "ruth.loos@mssm.edu" <ruth.loos@mssm.edu>, "eimear.kenny@mssm.edu" <eimear.kenny@mssm.edu>, Ellen Terry <ecterry@uw.edu>, MESA Genetics PP <genpp@uw.edu>, "Myriam.Fornage@uth.tmc.edu" <Myriam.Fornage@uth.tmc.edu>, "lsellers@uabmc.edu" <lsellers@uabmc.edu>, "moore.b.shoemaker@vumc.org" <moore.b.shoemaker@vumc.org>, "dan.roden@vumc.org" <dan.roden@vumc.org>, "darbar@uic.edu" <darbar@uic.edu>, "Robert.kaplan@einstein.yu.edu" <Robert.kaplan@einstein.yu.edu>, "ellinor@mgh.harvard.edu" <ellinor@mgh.harvard.edu>,

Cohort 18: GGAF

Jonah Einson <jeinson@nygenome.org>

TOPMed manuscript for co-author review

Tuuli Lappalainen <tlappalainen@nygenome.org> Tue, Dec 13, 2022 at 7:36 AM
To: Jonah Einson <jeinson@nygenome.org>

From: Rienstra, M (thorax) <m.rienstra@umcg.nl>
Date: Tuesday, December 13, 2022 at 2:58 AM
To: Tuuli Lappalainen <tlappalainen@nygenome.org>
Subject: RE: TOPMed manuscript for co-author review

Hi Tuuli,

Some minor edits on name and affiliation added in the attached version.

Also can you add to Suppl Tablbe 2 at GGAF cohort the apprax sample size (column 6) = 2207.

And I could not find the cohort description of GGAF, added it here:

Groningen Genetics of Atrial Fibrillation (GGAF): The GGAF cohort (n=2207) is a genotype and phenotype repository of individuals with AF and age- and sex-matched controls from 5 different sources. All studies were approved by the ethical committee, and all individuals provided written informed consent. Individuals with AF (n=1108) were included in 3 registry cohorts at the University Medical Center, and Maastricht University Medical Center (AF-Risk n=6). The AF-Risk study (ClinicalTrials.gov Identifier: NCT01510210) is an observational hospital-based cohort (n=500; in GGAF 334) to seek for markers of severity of atrial remodeling and predict outcome of a rhythm control treatment strategy. Patients with a short history of AF were included. Detailed phenotypic information was collected, including non-invasive vascular function measurements, body surface mapping, and detailed information on presence or progression of AF during 5-years follow up is obtained by use of serial ECGs, 24-hour Holter monitoring and recordings from loop recorders. The Young-AF study is an observational hospital-based cohort (n=500; in GGAF 314) to describe the phenotypic profile of patients with AF onset at age <60 years and the occurrence of AF progression during 5 years follow up. The phenotypic data that was collected is similar to the AF risk profile study. The Biomarker AF study (ClinicalTrials.gov Identifier: NCT01510197) is an observational hospital-based cohort (n=500; in GGAF 460) to identify a risk profile to guide AF therapy in all-comers with AF. The project is similar in design as the AF risk profile study, with a few modifications. No extra phenotypic information on top of our standard clinical AF protocol was performed, except blood sampling. Age-and sex-matched individuals without AF (controls) were included from two cohorts at the University Medical Center Groningen. The GIPS study is a randomized-controlled trial (n=380; in GGAF 362) to evaluate the effect of metformin treatment on preservation of left ventricular function in patients without diabetes presenting with ST-segment elevation myocardial infarction (STEMI). Mean left ventricular ejection fraction after four months, assessed by magnetic resonance imaging was 53.1%, and the use of metformin compared with placebo did not improve left ventricular ejection fraction. The PREVEND cohort study (www.prevend.org) is a community-based cohort study including 8592 inhabitants of the city of Groningen, The Netherlands. PREVEND is one of the AFGen consortium participants, see further for more

details on cohort description. In the GGAF cohort we included 742 individuals without AF, not previously included in GWAS.

Thanks for having me, good luck with submission!

Michiel

[Quoted text hidden]

Cohort 19: Amish

Jonah Einson <jeinson@nygenome.org>

FW: Study-specific review of TOPMed manuscript submission

Tuuli Lappalainen <tlappalainen@nygenome.org> Mon, Dec 12, 2022 at 12:16 PM
To: Jonah Einson <jeinson@nygenome.org>

From: Cosentino, Ruth <rcosenti@som.umaryland.edu>
Date: Monday, December 12, 2022 at 11:13 AM
To: Mitchell, Braxton <bmitchel@som.umaryland.edu>
Cc: Tuuli Lappalainen <tlappalainen@nygenome.org>
Subject: RE: Study-specific review of TOPMed manuscript submission

Hi Brackie,

Is acknowledging the dbGAP reference number sufficient? Anyone using Amish data should acknowledge that "The Amish studies upon which these data are based were supported by NIH grants R01 AG18728, U01 HL072515, R01 HL088119, R01 HL121007, and P30 DK072488. See publication: PMID: 18440328"

Kind Regards,

Rhea

From: Cosentino, Ruth
Sent: Monday, December 12, 2022 10:00 AM
To: Tuuli Lappalainen <tlappalainen@nygenome.org>
Subject: RE: Study-specific review of TOPMed manuscript submission

Oh Gosh I missed it as I sped past to look up a reference! Thanks!

Rhea

From: Tuuli Lappalainen <tlappalainen@nygenome.org>
Sent: Monday, December 12, 2022 9:59 AM
To: Cosentino, Ruth <rcosenti@som.umaryland.edu>; Mitchell, Braxton <bmitchel@som.umaryland.edu>
Subject: Re: Study-specific review of TOPMed manuscript submission

Thanks, we will review! The acknowledgements are there, between methods and references.