**Rare protein-altering telomere-related gene variants in patients with chronic hypersensitivity pneumonitis**

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ONLINE DATA SUPPLEMENT

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## SUPPLEMENTAL METHODS

**Clinical Data Collection:**
Clinical data collection included demographics, pulmonary function tests, and radiologic, and histopathologic studies. Race and ethnicity were self-reported on enrollment questionnaires. Family history of interstitial lung disease was self-reported on enrollment questionnaires and verified by review of ILD clinical notes. The date of death was recorded clinically and confirmed using the United States Social Security Death Index. Lung transplants and date of lung transplants were recorded clinically. HRCTs were scored by expert chest radiologists (B.M.E. or T.S.H.) using a structured data collection form that included assessment of 2011 ATS/ERS/JRS/ALAT criteria for UIP patterns, semi-quantitative extent of fibrosis, and individual morphologic features (Figure E1). Surgical lung biopsies were scored prospectively in the UCSF cases only, at the time of multidisciplinary team discussion, by an expert lung pathologist (K.J.D.) using a structured pathology data collection form (Figure E2).

**DNA Sequencing:**
Sequencing was performed on DNA isolated from peripheral blood in both cohorts. Whole genome sequencing data was generated in the discovery cohort to a read depth of 30X using the Illumina HiSeq X Ten sequencer (Human Longevity Inc, San Diego, CA, USA) and KAPA Hyper Library Kit (Roche Sequencing, Pleasanton, CA, USA). Whole exome sequencing data was generated in the replication cohort to a read depth of 50X using the Illumina Novaseq 6000 S4 Flowcell sequencer (Novogene, Sacramento, CA, USA) and the SureSelect Human All Exome V6 capture kit (Agilent, Santa Clara, CA, USA).

**Variant discovery**
*Discovery cohort:* Detailed variant discovery methods for this cohort are as described in [E1].
*Replication cohort:* Raw Illumina paired-end 150bp reads were first subjected to quality control. Adapters were removed from the sequencing reads using scythe (https://github.com/vsbuffalo/scythe, version 0.994 beta). Base quality was controlled using a window-based method, sickle (https://github.com/najoshi/sickle, version 1.33), with the cutoff set at 30. Reads that are less than 30bp in length were discarded. Next, reads that have passed the quality control were mapped to GRCh38 reference genome using BWA-MEM[E2] with parameter -M for downstream analysis compatibility. PCR duplicates were removed using Picard-tools (http://broadinstitute.github.io/picard/, version 2.18.4). Variants were identified using HaplotypeCaller function in GATK[E3] (version 4.0.5.2), followed by variant recalibration using the recommendations from GATK developers.

Variants were annotated for genomic effect using snpEff (v4.3q) and identifiers using dbSNP build 150 (release July 10, 2017).

Samples in both cohorts were excluded for call rates less than 90% (no samples were excluded), identity by descent analysis (patient relatedness), $\hat{\pi}$ 0.125 or greater (i.e. third-degree relatives), or sex mismatch. Variant sites were excluded for call rates less than 95%.

**Principle Component Analysis**
Principal component analysis (PCA) was performed in Plink version 1.9 (see Figures E3-E6). A European subgroup was selected using the first two principal components corresponding to the cluster of self-reported non-Hispanic white patients (discovery cohort: PC1 range -0.05 to -0.022, PC2 range -0.025 to 0.025; replication cohort: PC1 and range 0.0-0.05). PCA was then repeated in this subgroup and outliers greater than 3 standard deviations of the mean of PC1 or in the restricted PCA were further excluded.

**Case-Control Analysis**
*Discovery Cohort*: Discovery cohort cases were age- and sex-matched to age-related macular degeneration (AMD) and asthma samples that were sequenced on the same platform during the same calendar years as described in reference [E1]. Cases and controls of European ancestry (EUR admixture >=0.8) were included in the analysis:

| Variable | CHP cases | Controls |
|---|---|---|
| N | 117 | 351 |

| | | |
|---|---|---|
| Age in years, mean (sd) | 63.5 (11.2) | 63.6 (10.8) |
| Female, N (%) | 68 (58.1) | 180 (51.3) |
| N AMD | NA | 124 |
| N Asthma | NA | 227 |

The frequency of qualifying variants in cases and controls (per individual) were compared using the odds ratio and Fischer's exact p-values.

*Replication Cohort:* Qualifying variants were identified in the entire Exome Aggregation Consortium (v0.3.1) (ExAC) dataset (n=60,706) and the ExAC non-Finnish European (NFE) sub-population (n=33,370) using the same criteria as CHP cases. The frequency of qualifying variants in cases and controls (per individual) were compared using the odds ratio and Fischer's exact p-values. This was done for all CHP cases compared to the entire ExAC cohort and again restricted to the CHP cases of non-Hispanic white race/ethnicity compared to the ExAC NFE sub-population.

**References**

[E1] Dressen A, Abbas AR, Cabanski C, et al. Analysis of protein-altering variants in telomerase genes and their association with MUC5B common variant status in patients with idiopathic pulmonary fibrosis: a candidate gene sequencing study. The Lancet Respiratory medicine (2018).
[E2] L. H., Aligning sequence reads, clone sequences and assembly contigs with BWA-MEM, arXiv:1303.3997 (2013).
[E3] R. Poplin, V. Ruano-Rubio, M.A. DePristo, T.J. Fennell, M.O. Carneiro, G.A. Van der Auwera, D.E. Kling, L.D. Gauthier, A. Levy-Moonshine, D. Roazen, K. Shakir, J. Thibault, S. Chandran, C. Whelan, M. Lek, S. Gabriel, M.J. Daly, B. Neale, D.G. MacArthur, E. Banks, Scaling accurate genetic variant discovery to tens of thousands of samples, bioRxiv (2018).

# SUPPLEMENTAL TABLES AND FIGURES

**Figure E1**. Computed tomography of the chest data collection form

## Radiology Scoring and HRCT Classification Form

**Name** _____ **MRN** _____ **ILD #** _____ **Clinic Date** _____ **Biopsy Date** _____ **Review Date** _____ **Reviewer** _____

| **1. CT scan attributes** | |
|---|---|
| Date | No CT Available ☐ Yes |
| Min Section Thickness | |
| Skipped or full chest | ☐ Skipped ☐ Full chest |
| Supine images | ☐ No ☐ Yes |
| Prone images | ☐ No ☐ Yes |
| Expiratory Images | ☐ No ☐ Yes |
| Edge Enhanced | ☐ No ☐ Yes |
| Scanned-in films | ☐ No ☐ Yes |

| **2. Fibrosis** | ☒ No ☐ Yes |
|---|---|
| Irregular reticulation | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Traction bronchiectasis | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Honeycombing | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Craniocaudal distribution | ☐ Lower ☐ Middle ☐ Upper ☐ Diffuse |
| Axial distribution | ☐ Peripheral ☐ Central ☐ Diffuse |
| PMF-like opacities | ☐ No ☐ Yes |
| PPFE-like opacities | ☐ No ☐ Yes ☐ Analysis not performed |
| Assoc. pulm. ossification | ☐ No ☐ Yes ☐ Analysis not performed |

| **3. Ground glass opacity** | ☒ No ☐ Yes |
|---|---|
| Severity | ☐ Mild ☐ Moderate ☐ Severe |
| Craniocaudal distribution | ☐ Lower ☐ Middle ☐ Upper ☐ Diffuse |
| Axial distribution | ☐ Peripheral ☐ Central ☐ Diffuse |

| **4. Consolidation** | ☒ No ☐ Yes |
|---|---|
| Severity | ☐ Mild ☐ Moderate ☐ Severe |
| Craniocaudal distribution | ☐ Lower ☐ Middle ☐ Upper ☐ Diffuse |
| Axial distribution | ☐ Peripheral ☐ Central ☐ Diffuse |

| **5. Airways disease** | ☒ No ☐ Yes |
|---|---|
| MosaicPerfusion | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| AirTrapping | ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ N/A |
| Airways inflammation | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Non-traction bronchiectasis | ☐ None ☐ Mild ☐ Moderate ☐ Severe |

**DEFINITIONS**

**Ground glass opacity:** Confluent areas of opacity that do not obscure the underlying vessels. This is in the absence of significant associated irregular reticulation.
**Consolidation:** Confluent areas of opacity that do obscure the underlying vessels.
**Irregular reticulation:** Linear opacities that do not represent smooth or nodular interlobular septal thickening.
**Traction bronchiectasis:** Dilated and irregular bronchi due to adjacent fibrosis with a lack of inflammatory thickening or mucous impaction.
**Honeycombing:** Air density cysts with relatively thick walls that are first seen in the subpleural lung and then become stacked into multiple layers. At least 3 air density cysts lined up in the subpleural lung in a single row must be present. Also, at least one supportive sign of fibrosis must be present.
**Mosaic perfusion:** Geographic areas of decreased lung attenuation with sharp margins seen on inspiratory CT.
**Air trapping:** On expirtory images, the presence of areas of lung that do not significantly increase in attenuation when compared to the inspiratory images.
**Nodules:** Multiple rounded opacities.
**Emphysema:** Centrilobular emphysema are focal, air density lucencies without a wall typically predominating in the central portions of the upper lobes. Paraseptal emphysema are focal, air density lucencies with a thin wall located in the subpleural lung in a single layer. Panlobular emphysema is diffuse lung lucency with a lower lung predominance.
**Cysts:** Focal air attenuation lucencies with a thin, but perceptible wall that typically predominate in the central lung, however occasionally may be subpleural in location.

| **6. Nodules** | ☒ No ☐ Yes |
|---|---|
| Severity | ☐ Mild ☐ Moderate ☐ Severe |
| Definition | ☐ Ground glass ☐ Dense |
| Size | ☐ <5 mm ☐ 5-10 mm ☐ >10-30 mm ☐ >30 mm |
| Calcification | ☐ No ☐ Yes |
| Craniocaudal distribution | ☐ Lower ☐ Middle ☐ Upper ☐ Diffuse |
| Distribution | ☐ Perilymphatic ☐ Random ☐ Centrilobular |
| Tree-in-bud | ☐ No ☐ Yes |

| **7. Emphysema** | ☒ No ☐ Yes |
|---|---|
| Centrilobular | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Paraseptal | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Panlobular | ☐ None ☐ Mild ☐ Moderate ☐ Severe |

| **8. Misc. Lung Findings** | ☒ No ☐ Yes |
|---|---|
| Cysts | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Interlobular septal thick. | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Crazy Paving | ☐ None ☐ Mild ☐ Moderate ☐ Severe |
| Subpleural Sparing | ☐ No ☐ Yes |
| Reversed Halo | ☐ No ☐ Yes |
| Perilobular Opacities | ☐ No ☐ Yes |

| **9. Non-lung findings** | ☒ No ☐ Yes ☐ Analysis not performed |
|---|---|
| Extensive LAD | ☐ No ☐ Yes ☐ Analysis not performed |
| Pleural disease | ☐ No ☐ Yes ☐ Analysis not performed |
| Esophageal dilation | ☐ No ☐ Yes ☐ Analysis not performed |

| **10. Summary** | |
|---|---|
| UIP designation (new) | ☐ UIP ☐ Indeterminate for UIP ☐ Probable UIP ☐ Alternative diagnosis |
| UIP designation (old) | ☐ Definite ☐ Possible ☐ Inconsistent |
| Leading Diagnosis | |
| Alt. diagnosis 1 | |
| Alt. diagnosis 2 | |
| Confidence in diagnosis | ☐ High ☐ Intermediate ☐ Low |
| Notes | |
| Empty Fields | 13 |
| UIP discrepancy? | |
| >1 check selected | 0 |
| Actual Diagnosis | |

**OTHER DEFINITIONS**

**Severity**:
Mild: <10% lung involvement
Moderate: 10-50% lung involvement
Severe: >50% lung involvement
For mosaic perfusion and air trapping to be moderate or severe they must also be present bilaterally and in at least 3 lobes
**Bronchiectasis (traction or non-traction) severity:**
Calculate severity in each lobe as (0=none, 1=mild, 2=moderate, 3=severe)
The sum of all lobes determines overall severity:
Mild ≤3
Moderate 4-7
Severe ≥8
**Confidence in diagnosis:**
High: ≥90% likelihood
Intermediate: 51-89% likelihood
Low: ≤50% likelihood

**Figure E2.** Histopathology data collection form

# ILD HISTOPATHOLOGIC SCORING FORM

Name: _____
Last First

Biopsy date: _____ Biopsy site(s): ☐ RUL ☐ LUL ☐ TBBx ☐ RML ☐ Lingula ☐ Unknown ☐ RLL ☐ LLL ☐ Other ___

Pathologist: ☐ Jones ☐ Other: _____

## GENERAL OBSERVATIONS

*Low Magnification*

| | | | |
|---|---|---|---|
| 1. Heterogeneous distribution of abnormal areas | Yes | No | N/A |
| 2. Accentuation of fibrosis at the pleural surface | Yes | No | N/A |
| 3. Abnormalities airway centered | Yes | No | N/A |
| 4. Diffuse alveolar septal thickening is present | Yes | No | N/A |

*High Magnification*

| | | | |
|---|---|---|---|
| 1. Temporal heterogeneity | Yes | No | N/A |
| 2. Inflammation confined to areas of fibrosis | Yes | No | N/A |
| 3. Microscopic honeycombing | Yes | No | N/A |
| 4. Areas of normal lung | Yes | No | N/A |

## SPECIFIC FINDINGS (0 = ABSENT, 1 = MILD, 2 = MODERATE, 3 = MARKED)

| | | | | |
|---|---|---|---|---|
| 1. Fibroblast foci (interstitial young connective tissue) | 0 | 1 | 2 | 3 |
| 2. Organizing pneumonia (airway luminal granulation tissue | 0 | 1 | 2 | 3 |
| 3. Lymphocytic interstitial infiltrate in areas on non-fibrotic lung | 0 | 1 | 2 | 3 |
| 4. Alveolar macrophages | 0 | 1 | 2 | 3 |
| 5. Dense collagen fibrosis | 0 | 1 | 2 | 3 |
| 6. Granuloma/Giant cells | 0 | 1 | 2 | 3 |
| 7. Germinal centers | 0 | 1 | 2 | 3 |
| 8. Inorganic dust deposits | 0 | 1 | 2 | 3 |
| 9. Hemosiderin laden macrophages and intra-alveolar blood | 0 | 1 | 2 | 3 |
| 10. Eosinophilia/Eosinophilic abscess | 0 | 1 | 2 | 3 |
| 11. Airway-centered inflammation | 0 | 1 | 2 | 3 |
| 12. Small airways disease | 0 | 1 | 2 | 3 |
| 13. Emphysema | 0 | 1 | 2 | 3 |
| 14. Acute lung injury (hyaline membranes) | 0 | 1 | 2 | 3 |

**Figure E3.** Principal component analysis, discovery cohort. Black lines define the European subgroup.

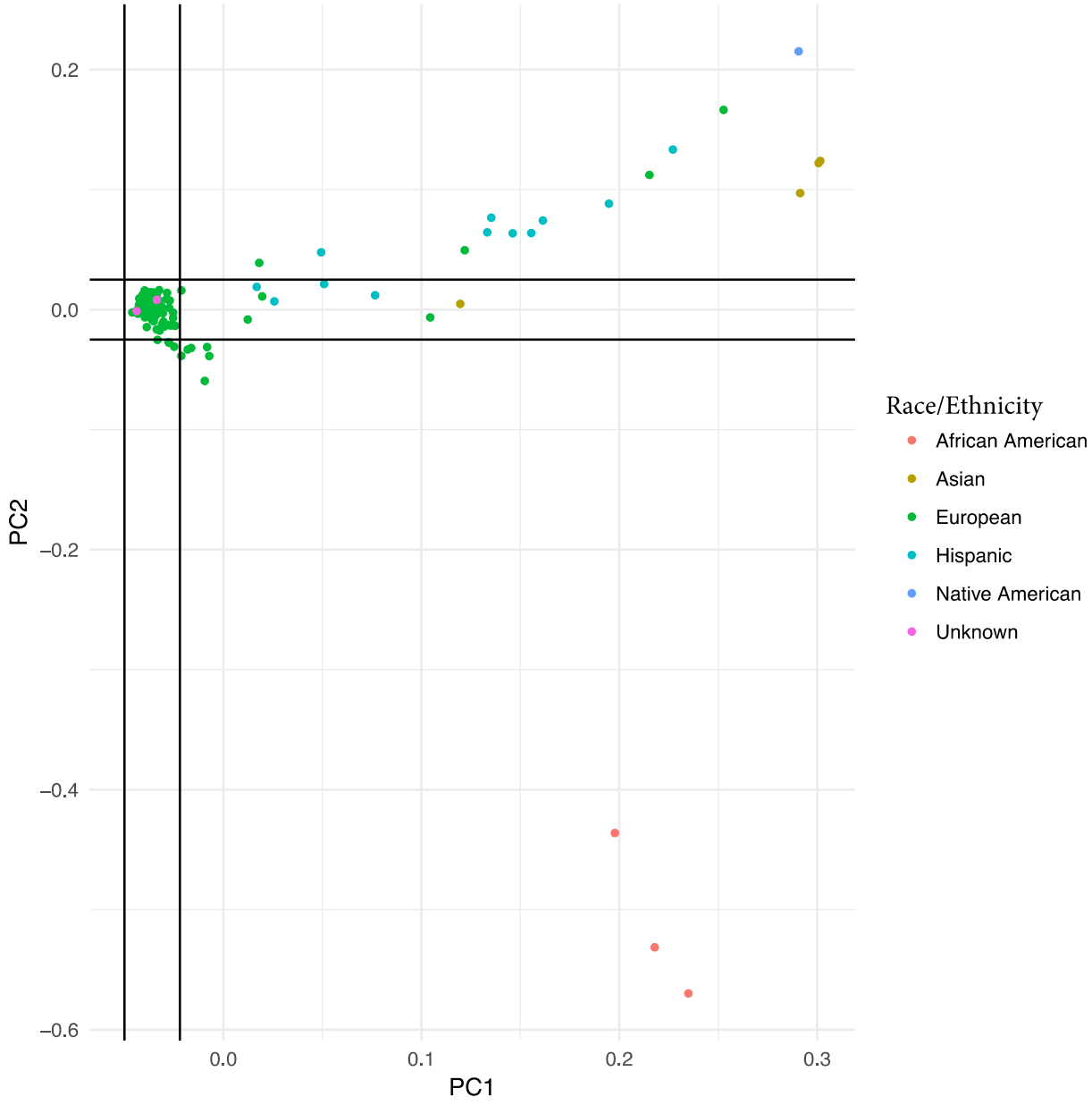

**Figure E4.** Principal component analysis, discovery cohort, restricted to the European subgroup, after excluding outliers.

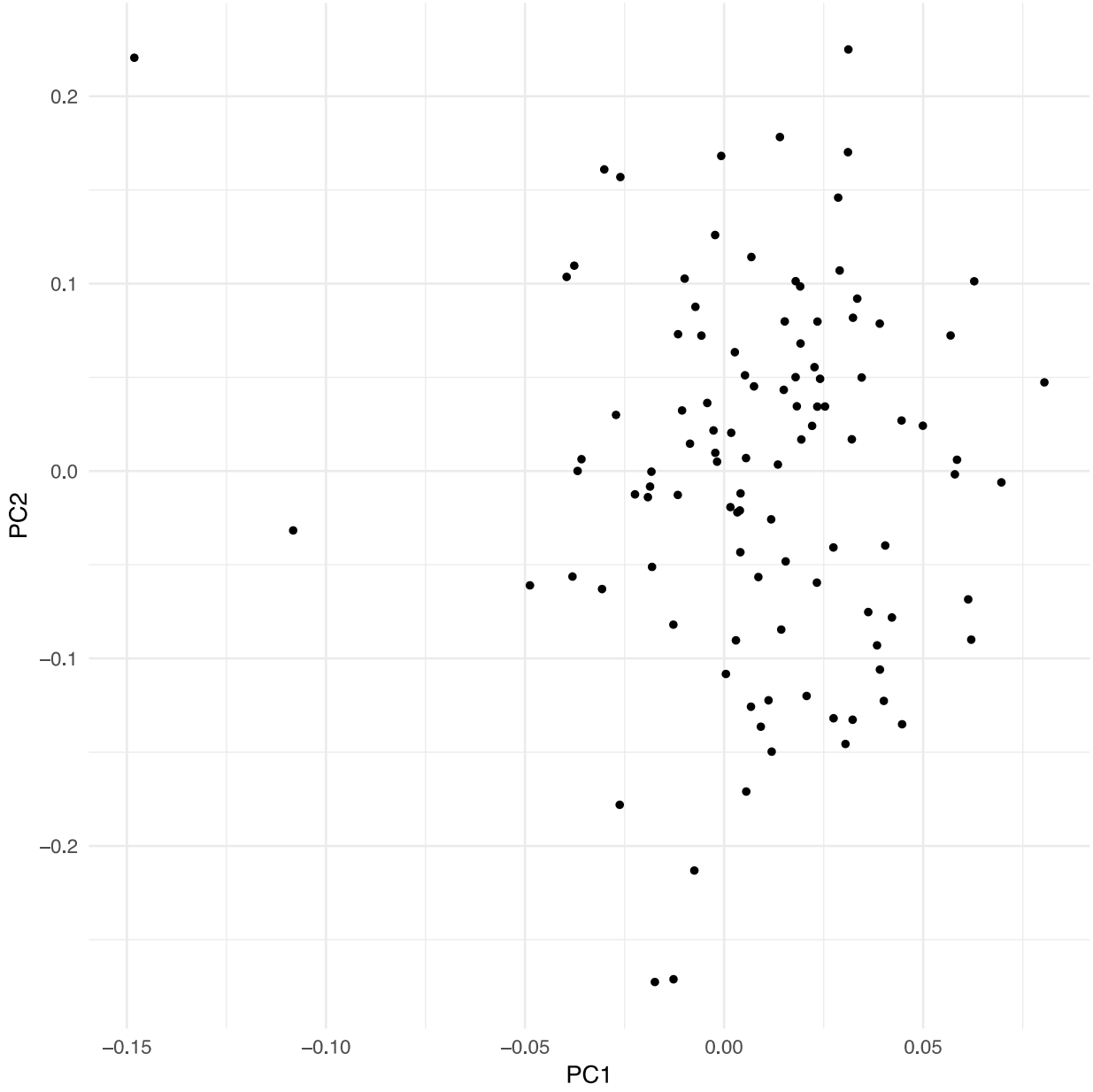

**Figure E5.** Principal component analysis, replication cohort. Black lines define the European subgroup.

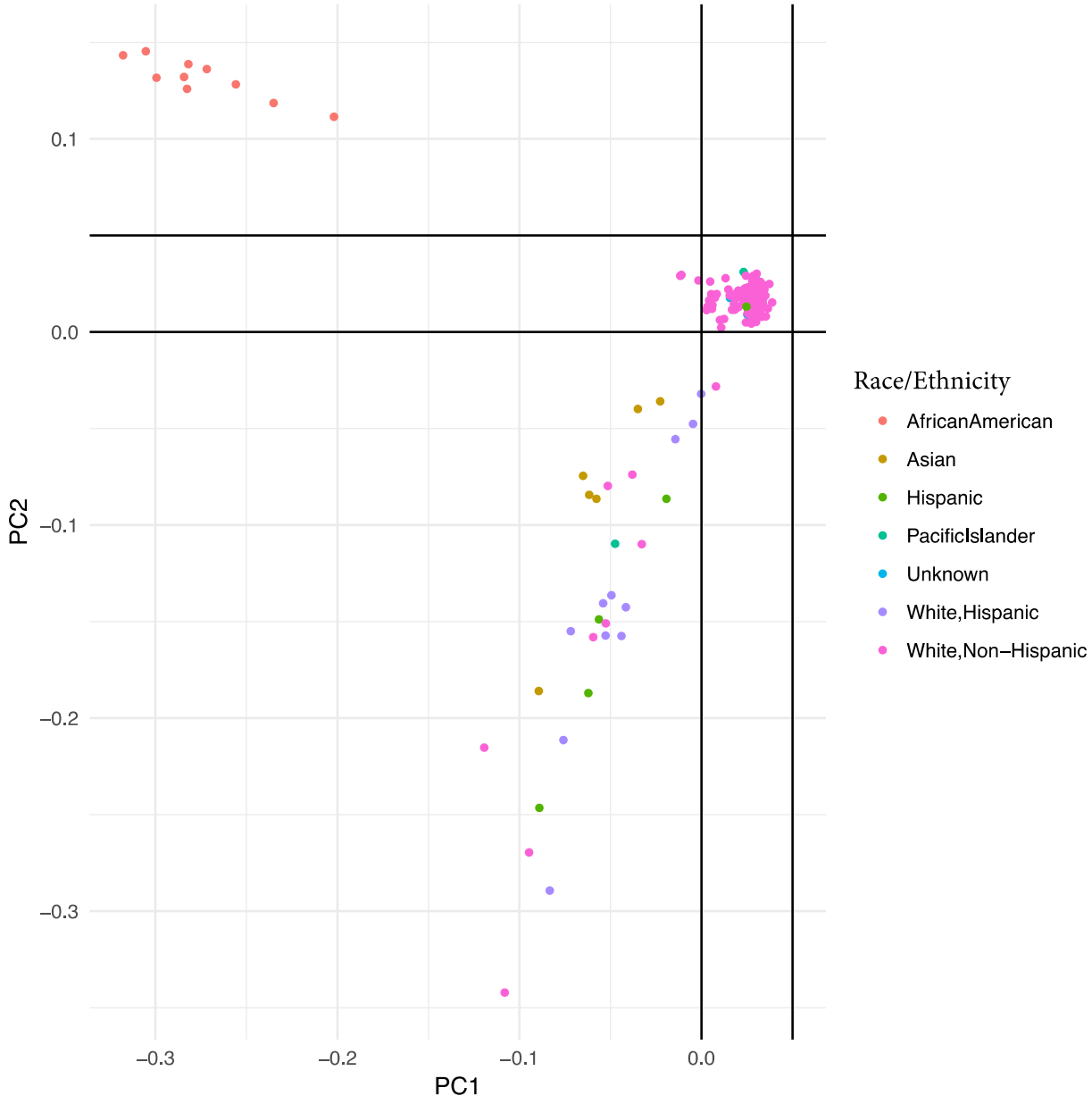

**Figure E6.** Principal component analysis, discovery cohort, restricted to the European subgroup, after excluding outliers.

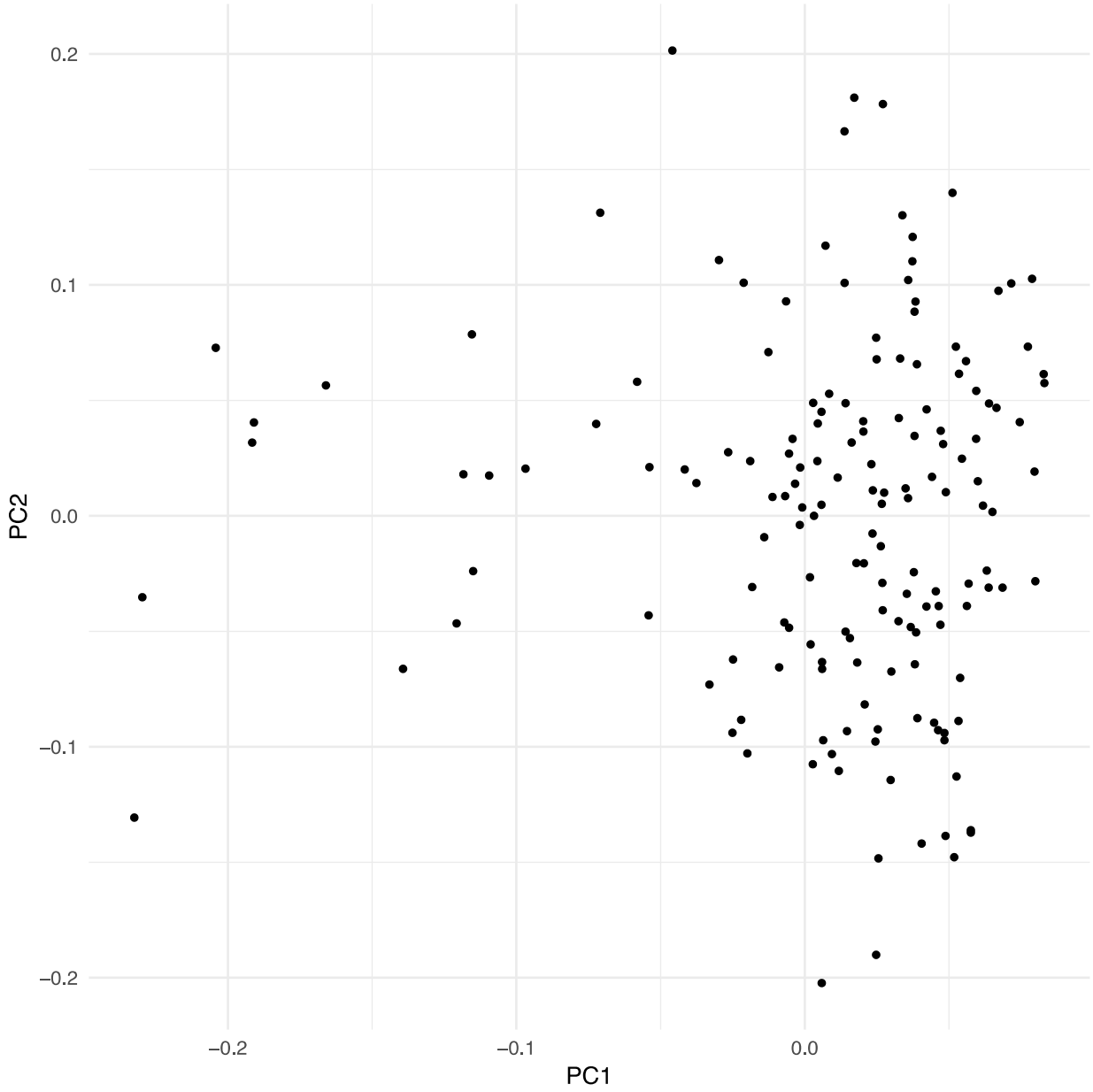

**Table E1.** Case-Control Analysis: Discovery Cohort

| | Cases Count | Cases Frequency | Controls Count | Controls Frequency | Odds Ratio | p-value |
|---|---|---|---|---|---|---|
| **TERC** | 0 | 0 | 1 | 0.0028 | NA | NA |
| **TERT** | 3 | 0.0256 | 0 | 0 | 23.72 | 0.0441 |
| **TINF2** | 0 | 0 | 2 | 0.0057 | 0.38 | 0.5502 |
| **PARN** | 2 | 0.0171 | 1 | 0.0028 | 4.2 | 0.1643 |
| **RTEL1** | 4 | 0.0427 | 4 | 0.0114 | 3.38 | 0.0582 |
| **DKC1** | 1 | 0.0085 | 0 | 0 | NA | NA |
| **Combined** | 10 | 0.094 | 8 | 0.022 | 4.49 | 0.00173 |

**Table E2.** Case-Control Analysis: Replication Cohort (all cases compared to all ExAC)

| | Replication (n=209) | | ExAC (n=60,706) | | | |
|---|---|---|---|---|---|---|
| **Gene** | **Count** | **Frequency** | **Count** | **Frequency** | **OR (95%CI)** | **p-value** |
| TERC | 0 | 0 | 120 | 0.0019767 | NA | NA |
| TERT | 9 | 0.0430622 | 131 | 0.0021579 | 20.8 (9.2-41.5) | 1.65E-09 |
| TINF2 | 0 | 0 | 158 | 0.0026027 | NA | NA |
| PARN | 2 | 0.00956938 | 126 | 0.0020756 | 4.65 (0.55-17.3) | 0.719 |
| RTEL1 | 6 | 0.02870813 | 536 | 0.0088294 | 3.32 (1.20-7.39) | 0.0115 |
| DKC1 | 0 | 0 | 47 | 0.0007742 | NA | NA |
| **Combined** | **17** | **0.08133971** | **1118** | **0.0184166** | **4.71 (2.68-7.79)** | **1.87E-11** |

**Table E3.** Case-Control Analysis: Replication Cohort (White/European individuals)

| | Replication (n=169) | | ExAC NFE (n=33,370) | | | |
|---|---|---|---|---|---|---|
| **Gene** | **Count** | **Frequency** | **Count** | **Frequency** | **OR (95%CI)** | **p-value** |
| TERC | 0 | 0 | 59 | 0.00176806 | NA | NA |
| TERT | 6 | 0.035503 | 69 | 0.00206773 | 17.8 (6.2-41.5) | 2.26E-06 |
| TINF2 | 0 | 0 | 96 | 0.00287684 | NA | NA |
| PARN | 2 | 0.0118343 | 67 | 0.00200779 | 5.95 (0.70-22.7) | 0.0475 |
| RTEL1 | 5 | 0.0295858 | 294 | 0.00881031 | 3.43 (1.09-8.26) | 0.0181 |
| DKC1 | 0 | 0 | 27 | 0.00080911 | NA | NA |
| **Combined** | **13** | **0.0769231** | **612** | **0.01833983** | **4.46 (2.31-7.91)** | **1.94E-08** |

Abbreviations: ExAC = Exome Aggregation Consortium v0.3.1; NFE = non-Finnish European; OR = odds ratio; CI = confidence interval

**Table E4.** Clinical, Radiographic, and Pathologic Data for Individuals with Qualifying Variants

| Gene | dbSNP | CHR | Position | REF | ALT | Effect | Exon | Protein | ExAC AF | ESP AF | PP2 | SIFT | CADD | Cohort | Race/Ethnicity | Exposure | FH | TL | HRCT features | Biopsy findings |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TERT | rs370445231 | 5 | 1260593 | G | A | missense | 12/16 | R951W | 8.26E-06 | Absent | D (0.999) | T (0.106) | 17.5 | Replication | Hispanic | Mold | Yes | 5559 | Incon: Mod fib, PBV, GGO | cfNSIP |
| TERT | rs775014633 | 5 | 1268538 | G | A | missense | 9/16 | A855V | 8.24E-06 | Absent | P (0.522) | T (0.199) | 7.4 | Discovery | White | Down | No | 5266 | Incon: Mod fib, UM, AT | PBF, PFGs |
| TERT | rs387907249 | 5 | 1278781 | G | A | missense | 6/16 | A716T | Absent | Absent | D (0.998) | D (0.0) | 23.1 | Discovery | White | Bird | Yes | 5055 | Incon: UM | fNSIP, PFGs |
| TERT | rs866282352 | 5 | 1279329 | G | A | missense | 5/16 | R698W | Absent | Absent | D (0.981) | D (0.008) | 23.1 | Discovery | White | Mold | No | 4248 | Incon: Mild fib, GGO, AT | PBI, OP, PFGs |
| TERT | n/a | 5 | 1280334 | G | T | missense | 4/16 | H592N | Absent | Absent | D (0.996) | D (0.005) | 23.7 | Replication | White | Unknown | No | 4312 | Incon: Mod fib, AT | Insufficient material |
| TERT | n/a | 5 | 1282488 | C | A | missense | 3/16 | K570N | Absent | Absent | D (0.965) | D (0.0) | 25.0 | Discovery | White | Bird | Yes | 4832 | Possible | cfNSIP, PFGs |
| TERT | n/a | 5 | 1282507 | G | A | missense | 3/16 | T564M | Absent | Absent | D (1.0) | D (0.0) | 26.5 | Replication | African American | Unknown | No | 5380 | Incon: Mod fib, UM, PBV, AT | LII, NNGs |
| TERT | n/a | 5 | 1293394 | C | T | missense | 2/16 | G498R | Absent | Absent | D (1.0) | D (0.0) | 25.5 | Replication | Hispanic | Down | No | 4783 | Incon: Mod fib, AT | No biopsy |
| TERT | rs34094720 | 5 | 1293652 | G | A | missense | 2/16 | H412Y | 0.0022 | 0.0043 | D (0.998) | D (0.007) | 20.2 | Discovery | Hispanic | Unknown | No | 6511 | Incon: Mild fib, AT | cNSIP |
| | | | | | | | | | | | | | | Discovery | White | Unknown | Yes | 5782 | Incon: Mod fib, GGO | cfNSIP, PFGs |
| | | | | | | | | | | | | | | Discovery | White | Unknown | No | 5486 | Incon: No fib, GGO, AT | No biopsy |
| | | | | | | | | | | | | | | Replication | White | Unknown | No | 5516 | Incon: Mild fib, UM | No biopsy |
| TERT | n/a | 5 | 1294393 | T | C | missense | 2/16 | S165G | Absent | Absent | P (0.734) | D (0.005) | 21.1 | Replication | White | Mold | No | 5415 | Incon: Sev fib, PBV, AT, CLN | UIP+PFGs |
| TERT | rs1060502990 | 5 | 1294549 | C | CG | frameshift | 2/16 | 112-113X | Absent | Absent | n/a | n/a | 15.9 | Replication | White | Mold | No | 4762 | Incon: No fib, GGO, AT | No biopsy |
| TERT | n/a | 5 | 1294656 | A | G | missense | 2/16 | L77P | Absent | Absent | D (0.0997) | D (0.028) | 23.8 | Replication | White | Unknown | No | 4493 | Possible | UIP+PFGs |
| TERT | n/a | 5 | 1294829 | C | T | missense | 1/16 | C54Y | Absent | Absent | D (1.0) | D (0.011) | 23.1 | Replication | White | Bird | No | 5010 | Incon: Sev fib, UM, PBV, AT | fNSIP |
| TERC | rs552679780 | 3 | 169765027 | C | T | n/a | n/a | n/a | Absent | Absent | n/a | n/a | 10.4 | Discovery | Asian | Unknown | Yes | 4850 | Incon: Mild fib, UM, GGO | BCF, LII, PFGs |
| PARN | rs377199187 | 16 | 14432695 | C | G | missense | 22/24 | R538P | 8.28E-05 | 3.63E-04 | P (0.928) | T (0.055) | 4.1 | Discovery | White | Unknown | No | 5863 | Incon: Mild fib, UM, PBV, GGO, AT | BCF, PFGs |
| PARN | n/a | 16 | 14554142 | T | C | missense | 20/24 | K443R | Absent | Absent | P (0.755) | T (0.167) | 25.5 | Replication | White | Bird | No | 5284 | Incon: Mod fib, UM, PBV, GGO, AT | cNSIP |
| PARN | rs774170618 | 16 | 14604184 | G | A | missense | 11/24 | R249C | 3.31E-05 | Absent | D (0.998) | D (0.016) | 31 | Discovery | White | Mold | No | 5683 | Incon: Mod fib, UM, PBV, AT | No biopsy |
| PARN | n/a | 16 | 14610777 | G | A | stop gained | 7/24 | Q141* | Absent | Absent | n/a | n/a | 31 | Replication | White | Bird | No | 5788 | Incon: Mod fib, UM | UIP+BM, upper lobe biopsy predominant |
| RTEL1 | rs151214675 | 20 | 63661882 | G | A | missense | 4/35 | A112T | 2.22E-04 | 2.33E-04 | D (0.998) | D (0.005) | 27.3 | Discovery | White | Down | No | 5767 | Incon: No fib, GGO, AT | No biopsy |
| | | | | | | | | | | | | | | Replication | White | MAC | No | 6216 | Incon: No fib, GGO, AT, CLN | PBI, NNGs |
| RTEL1 | n/a | 20 | 63672587 | G | T | missense | 9/35 | G244V | Absent | Absent | D (0.965) | D (0.003) | 27.8 | Discovery | White | Down | Yes | 5386 | Definite | SLB: cfNSIP, OP, PFGs; Explant: UIP+PFGs |
| RTEL1 | n/a | 20 | 63688042 | T | A | missense | 18/35 | F529L | Absent | Absent | P (0.85) | D (0.01) | 22.6 | Discovery | White | Mold | No | 6630 | Incon: Mod fib, UM, AT | No biopsy |
| RTEL1 | rs1035926074 | 20 | 63689829 | G | A | missense | 24/35 | R702H | Absent | Absent | D (1.0) | D (0.005) | 26.0 | Replication | White | Mold/Bird | No | 6490 | Possible | cfNSIP, PFGs |
| RTEL1 | rs775121139 | 20 | 63690303 | C | G | missense | 26/35 | P759A | 1.66E-05 | Absent | P (0.751) | D (0.021) | 9.5 | Replication | White | Unknown | No | 6139 | Incon: Mod fib, UM, GGO, AT | No biopsy |
| RTEL1 | rs772872062 | 20 | 63691764 | C | T | missense | 28/35 | S860F | 3.31E-05 | Absent | P (0.848) | T (0.137) | 19.8 | Replication | White | Unknown | Yes | 5273 | Incon: Mild fib, GGO, AT, CLN | cfNSIP, PFGs |
| RTEL1 | rs754727644 | 20 | 63692883 | A | T | missense | 23/35 | N911Y | Absent | Absent | B (0.271) | D (0.013) | 22.4 | Discovery | White | Unknown | No | 4839 | Possible | fNSIP, OP, PFGs |
| RTEL1 | rs753270617 | 20 | 63693161 | G | A | missense | 30/35 | R957Q | 8.28E-06 | Absent | D (0.996 | D (0.014) | 25.9 | Discovery | White | Down | No | 5091 | Incon: No fib, GGO, AT | cNSIP, PFGs |
| RTEL1 | rs759564073 | 20 | 63693208 | G | A | missense | 30/35 | G973R | 8.29E-06 | Absent | D (1.0) | D (0.003) | 25.9 | Replication | Unknown | Unknown | No | 5478 | Incon: Sev fib, PBV | UIP+LII+PFGs+BM |
| RTEL1 | rs367598119 | 20 | 63695356 | G | C | missense | 34/35 | K1176N | 1.67E-05 | Absent | P (0.501) | D (0.012) | 17.0 | Replication | White | Mold | No | 6636 | Incon: No fib, GGO, AT | cfNSIP, PFGs |
| DKC1 | rs146700772 | X | 154769233 | A | C | missense | 9/15 | S280R | 2.80E-04 | 1.50E-04 | P (0.519) | D (0.042) | 23.3 | Discovery | White | Unknown | No | 5243 | Incon: Mild fib, AT | cfNSIP, PFGs |

Footnote, by column:

1. Gene: TERT = telomerase reverse transcriptase; TERC = telomerase RNA component; PARN = poly(A)-specific ribonuclease; RTEL1 = regulator of telomere elongation helicase 1; DKC1 = dyskerin pseudouridine synthase 1
2. dbSNP = database of short genetic variations identifiers, build 150, release July 10, 2017
3. CHR = chromosome number
4. Position = genomic position, human genome version 38
5. REF = reference genome allele
6. ALT = alternate allele
7. Effect = genomic effect
8. Exon = exon number/total exons
9. Protein = effect on protein
10. ExAC AF = Exome Aggregation Consortium allele frequency
11. ESP AF = Exome sequencing project allele frequency
12. PP2 = Polyphen-2 prediction of effect on protein function, format: D = probably damaging, P = possibly damaging, B = benign (hdiv score)

13. SIFT = Sorting Intolerant From Tolerant prediction of effect on protein function, format: D = damaging, T = tolerated (score)
14. CADD = Combined Annotation Dependent Depletion score; score 10 or greater indicates top 10% of most deleterious in genome and score 20 or greater indicates top 1%
15. Cohort: cohort in which variant was identified
16. Race/Ethnicity: self-reported race/ethnicity
17. Exposure: exposure clinically suspected to be causing hypersensitivity pneumonitis
18. FH = family history of interstitial lung disease
19. TL = telomere length in base pairs
20. HRCT features: high-resolution computed tomography features; abbreviations: Incon = inconsistent with usual interstitial pneumonia pattern; Possible = possible usual interstitial pneumonia pattern; Definite = definite usual interstitial pneumonia pattern; Mod = moderate; Sev = severe; fib = fibrosis; PBV = peribronchovascular distribution; GGO = ground glass opacities; UM = upper-mid lung distribution; AT = air-trapping; CLN = centrilobular nodules
21. Biopsy findings: c = cellular, f = fibrotic, cf = cellular and fibrotic, NSIP = non-specific interstitial pneumonia; PBF = peribronchiolocentric fibrosis; PFGs = poorly formed granulomas; PBI = peribronchiolar inflammation; OP = organizing pneumonia; LII = lymphocytic interstitial inflammation; NNGs = non-necrotizing granulomas; UIP = usual interstitial pneumonia; BCF = bronchiolocentric fibrosis; BM = bronchiolar metaplasia; SLB = surgical lung biopsy, Explant = explanted lung

**Table E5.** Phenotypes associated with qualifying variants

| Gene | dbSNP | CHR | Position | REF | ALT | Protein | ClinVar (OMIM); Clinical Significance |
|---|---|---|---|---|---|---|---|
| TERT | rs370445231 | 5 | 1260593 | G | A | R951W | None |
| TERT | rs775014633 | 5 | 1268538 | G | A | A855V | Idiopathic fibrosing alveolitis, chronic form (178500); Uncertain Significance<br>Dyskeratosis congenita, autosomal dominant, 2 (613989); Uncertain Significance |
| TERT | rs387907249 | 5 | 1278781 | G | A | A716T | Pulmonary fibrosis and/or bone marrow failure, telomere-related, 1 (614742); Pathogenic |
| TERT | rs866282352 | 5 | 1279329 | G | A | R698W | None |
| TERT | n/a | 5 | 1280334 | G | T | H592N | |
| TERT | n/a | 5 | 1282488 | C | A | K570N | |
| TERT | n/a | 5 | 1282507 | G | A | T564M | |
| TERT | n/a | 5 | 1293394 | C | T | G498R | |
| TERT | rs34094720 | 5 | 1293652 | G | A | H412Y | Conflicting interpretations for pathogenicity from Benign to Pathogenic for: Idiopathic fibrosing alveolitis, chronic form; Aplastic Anemia; Dyskeratosis congenita, autosomal dominant, 2; Dyskeratosis congenita, autosomal recessive, 4; Pulmonary fibrosis and/or bone marrow failure, telomere-related, 1; Dyskeratosis Congenita, Recessive |
| TERT | n/a | 5 | 1294393 | T | C | S165G | |
| TERT | rs1060502990 | 5 | 1294549 | C | CG | 112-113X | Idiopathic fibrosing alveolitis, chronic form (178500); Pathogenic<br>Dyskeratosis congenita, autosomal dominant, 2 (613989); Pathogenic |
| TERT | n/a | 5 | 1294656 | A | G | L77P | |
| TERT | n/a | 5 | 1294829 | C | T | C54Y | |
| TERC | rs552679780 | 3 | 169765027 | C | T | n/a | None |
| PARN | rs377199187 | 16 | 14432695 | C | G | R538P | Dyskeratosis congenita, autosomal recessive 6 (616353); Uncertain Significance<br>Pulmonary fibrosis and/or bone marrow failure, telomere-related, 4 (616371); Uncertain Significance |
| PARN | n/a | 16 | 14554142 | T | C | K443R | |
| PARN | rs774170618 | 16 | 14604184 | G | A | R249C | None |
| PARN | n/a | 16 | 14610777 | G | A | Q141* | |
| RTEL1 | rs151214675 | 20 | 63661882 | G | A | A112T | None |
| RTEL1 | n/a | 20 | 63672587 | G | T | G244V | |
| RTEL1 | n/a | 20 | 63688042 | T | A | F529L | |
| RTEL1 | rs1035926074 | 20 | 63689829 | G | A | R702H | Dyskeratosis congenita, autosomal recessive, 5 (615190); Uncertain Significance<br>Pulmonary fibrosis and/or bone marrow failure, telomere-related, 3 (616373); Uncertain Significance |
| RTEL1 | rs775121139 | 20 | 63690303 | C | G | P759A | None |
| RTEL1 | rs772872062 | 20 | 63691764 | C | T | S860F | None |
| RTEL1 | rs754727644 | 20 | 63692883 | A | T | N911Y | None |
| RTEL1 | rs753270617 | 20 | 63693161 | G | A | R957Q | None |
| RTEL1 | rs759564073 | 20 | 63693208 | G | A | G973R | None |
| RTEL1 | rs367598119 | 20 | 63695356 | G | C | K1176N | None |
| DKC1 | rs146700772 | X | 154769233 | A | C | S280R | Dyskeratosis congenita X-linked (305000); Pathogenic |

1. ClinVar database, searched on 04/26/2019.
2. OMIM = Online Mendelian Inheritance in Man database number

**Table E6.** Comparison of clinical features by telomere variant status

| | Discovery Cohort | | | | | | Replication Cohort | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All Patients | | | European Ancestry | | | All Patients | | | European Ancestry | | |
| **Characteristic** | **No Variant** | **Variant** | **p-value** | **No Variant** | **Variant** | **p-value** | **No Variant** | **Variant** | **p-value** | **No Variant** | **Variant** | **p-value** |
| N | 128 | 16 | | 93 | 12 | | 192 | 17 | | 148 | 11 | |
| Age in Years, mean (SD) | 63.6 (11.0) | 62.4 (13.0) | 0.70 | 64.3 (10.7) | 60.1 (12.5) | 0.21 | 65.1 (10.3) | 65.4 (10.7) | 0.92 | 65.7 (9.6) | 67.7 (9.3) | 0.53 |
| Male sex, n (%) | 53 (41.4%) | 6 (37.5%) | 1.00 | 39 (42%) | 5 (42%) | 1.00 | 85 (44.3%) | 6 (35.3%) | 0.61 | 69 (46.6%) | 6 (54.5%) | 0.76 |
| Race, n (%) | | | 0.81 | | | 1.00 | | | 0.39 | | | 0.44 |
| African American | 3 (2.3%) | 0 (0.0%) | | | | | 9 (4.7%) | 1 (5.9%) | | | | |
| Asian | 3 (2.3%) | 1 (6.2%) | | | | | 4 (2.1%) | 0 (0.0%) | | | | |
| European | 107 (83.6%) | 14 (87.5%) | | 90 (97%) | 12 (100%) | | 157 (81.8%) | 12 (70.6%) | | 141 (95.3%) | 10 (90.9%) | |
| Hispanic | 12 (9.4%) | 1 (6.2%) | | 1 (1%) | 0 (0%) | | 15 (7.8%) | 3 (17.6%) | | 3 (2.0%) | 0 (0.0%) | |
| Other or Unknown | 3 (2.3%) | 0 (0.0%) | | 2 (2%) | 0 (0%) | | 7 (3.6%) | 1 (5.9%) | | 4 (2.7%) | 1 (9.1%) | |
| Family history, n (%) | 7 (5.5%) | 5 (31.2%) | 0.004 | 6 (6%) | 4 (33%) | 0.015 | 12 (6.2%) | 2 (11.8%) | 0.32 | 11 (7.4%) | 0 (0.0%) | 1.00 |
| Ever-smoker, n (%) | 66 (53.7%) | 7 (43.8%) | 0.60 | 49 (54%) | 6 (50%) | 1.00 | 102 (53.1%) | 7 (41.2%) | 0.45 | 80 (54.1%) | 6 (54.5%) | 1.00 |
| Known exposure, n (%) | 90 (70.3%) | 9 (56.2%) | 0.26 | 67 (72%) | 8 (67%) | 0.74 | 132 (68.8%) | 10 (58.8%) | 0.42 | 99 (66.9%) | 6 (54.5%) | 0.51 |
| Exposure type, n (%) | | | 0.71 | | | 0.83 | | | 0.17 | | | 0.48 |
| Avian | 63 (49.2%) | 6 (37.5%) | | 47 (51%) | 5 (42%) | | 84 (43.8%) | 4 (23.5%) | | 64 (43.2%) | 3 (27.3%) | |
| Mold | 23 (18.0%) | 3 (18.8%) | | 16 (17%) | 3 (25%) | | 41 (21.4%) | 4 (23.5%) | | 28 (18.9%) | 2 (18.2%) | |
| Other | 4 (3.1%) | 0 (0.0%) | | 4 (4%) | 0 (0%) | | 7 (3.6%) | 2 (11.8%) | | 7 (4.7%) | 1 (9.1%) | |
| Unknown | 38 (29.7%) | 7 (43.8%) | | 26 (28%) | 4 (33%) | | 60 (31.2%) | 7 (41.2%) | | 49 (33.1%) | 5 (45.5%) | |
| FVC % predicted, mean (SD) | 68.1 (19.1) | 61.0 (17.0) | 0.16 | 69.7 (20.5) | 54.9 (14.2) | 0.017 | 66.2 (17.9) | 57.5 (20.1) | 0.057 | 68.0 (18.0) | 58.9 (19.1) | 0.11 |
| DLCO % predicted, mean (SD) | 47.6 (16.4) | 43.4 (17.9) | 0.34 | 48.0 (15.9) | 44.8 (20.2) | 0.54 | 59.8 (21.5) | 49.7 (14.6) | 0.077 | 60.0 (21.5) | 54.4 (13.3) | 0.42 |
| MUC5B genotype, n (%) | | | 0.34 | | | 0.31 | | | 0.15 | | | 0.61 |
| G/G | 70 (58.3%) | 11 (68.8%) | | 49 (56%) | 8 (67%) | | 104 (54.5%) | 10 (58.8%) | | 77 (52.4%) | 6 (54.5%) | |
| G/T | 46 (38.3%) | 4 (25.0%) | | 36 (41%) | 3 (25%) | | 81 (42.4%) | 5 (29.4%) | | 64 (43.5%) | 4 (36.4%) | |
| T/T | 4 (3.3%) | 1 (6.2%) | | 3 (3%) | 1 (8%) | | 6 (3.1%) | 2 (11.8%) | | 6 (4.1%) | 1 (9.1%) | |
| G/T or T/T | 50 (42.4%) | 5 (31.2%) | 0.43 | 39 (45%) | 4 (33%) | 0.54 | 87 (45.5%) | 7 (41.2%) | 0.80 | 70 (47.6%) | 5 (45.5%) | 1.00 |
| Telomere length in bp, median (IQR) | 6139 (5639-6573) | 5447 (4996-5989) | 0.004 | 6048 (5615-6607) | 5447 (5141-5940) | 0.012 | 6090 (5716-6377) | 5415 (5010-5788) | <0.001 | 6081 (5716-6371) | 5478 (4763-6139) | 0.007 |

**Table E7.** Comparison of radiologic features by telomere variant status

| | Discovery | | | | | | | Replication | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | All Patients | | | European | | | All Patients | | | | European | | |
| Factor | Total | No Variant | Variant | p-value | No Variant | Variant | p-value | Total | No Variant | Variant | p-value | No Variant | Variant | p-value |
| Number with CT scored | 134 | 119 | 15 | n/a | 86 | 11 | n/a | 204 | 187 | 17 | | 143 | 11 | |
| UIP pattern, n (%) | | | | 0.16 | | | 0.32 | | | | 0.74 | | | 0.61 |
| Definite | 5 (3.7%) | 4 (3.4%) | 1 (6.7%) | | 3 (3%) | 1 (9%) | | 13 (6.4%) | 12 (6.5%) | 1 (5.9%) | | 7 (4.9%) | 1 (9.1%) | |
| Possible | 12 (9.0%) | 9 (7.6%) | 3 (20.0%) | | 5 (6%) | 1 (9%) | | 16 (7.9%) | 14 (7.6%) | 2 (11.8%) | | 13 (9.2%) | 1 (9.1%) | |
| Inconsistent | 117 (87.3%) | 106 (89.1%) | 11 (73.3%) | | 78 (91%) | 9 (82%) | | 173 (85.6%) | 159 (85.9%) | 14 (82.4%) | | 122 (85.9%) | 9 (81.8%) | |
| Definite/Possible | 17 (12.7%) | 13 (10.9%) | 4 (26.7%) | 0.100 | 8 (9%) | 2 (18%) | 0.32 | 29 (14.4%) | 26 (14.1%) | 3 (17.6%) | 0.72 | 20 (14.1%) | 2 (18.2%) | 0.66 |
| Fibrosis, n (%) | | | | 0.90 | | | 1.00 | | | | 0.43 | | | 0.20 |
| None | 24 (17.9%) | 21 (17.6%) | 3 (20.0%) | | 15 (17%) | 2 (18%) | | 30 (14.9%) | 27 (14.6%) | 3 (17.6%) | | 22 (15.5%) | 3 (27.3%) | |
| Mild | 48 (35.8%) | 42 (35.3%) | 6 (40.0%) | | 30 (35%) | 4 (36%) | | 39 (19.3%) | 38 (20.5%) | 1 (5.9%) | | 28 (19.7%) | 0 (0.0%) | |
| Moderate | 54 (40.3%) | 49 (41.2%) | 5 (33.3%) | | 35 (41%) | 4 (36%) | | 110 (54.5%) | 100 (54.1%) | 10 (58.8%) | | 77 (54.2%) | 6 (54.5%) | |
| Severe | 8 (6.0%) | 7 (5.9%) | 1 (6.7%) | | 6 (7%) | 1 (9%) | | 23 (11.4%) | 20 (10.8%) | 3 (17.6%) | | 15 (10.6%) | 2 (18.2%) | |
| Moderate/Severe | 62 (43.1%) | 56 (43.8%) | 6 (37.5%) | 0.79 | 41 (44%) | 5 (42%) | 1.00 | 133 (65.8%) | 120 (64.9%) | 13 (76.5%) | 0.43 | 92 (64.8%) | 8 (72.7%) | 0.75 |
| Honeycombing, n (%) | 22 (16.4%) | 18 (15.1%) | 4 (26.7%) | 0.27 | 16 (19%) | 3 (27%) | 0.45 | 40 (19.8%) | 36 (19.5%) | 4 (23.5%) | 0.75 | 25 (17.6%) | 3 (27.3%) | 0.42 |
| Traction bronchiectasis, n (%) | 97 (72.4%) | 87 (73.1%) | 10 (66.7%) | 0.56 | 64 (74%) | 8 (73%) | 1.00 | 158 (78.2%) | 144 (77.8%) | 14 (82.4%) | 1.00 | 110 (77.5%) | 8 (72.7%) | 0.71 |
| Upper-middle lung distribution, n (%) | 47 (35.1%) | 43 (36.1%) | 4 (26.7%) | 0.57 | 34 (40%) | 3 (27%) | 0.52 | 56 (32.0%) | 51 (31.7%) | 5 (35.7%) | 0.77 | 35 (28.7%) | 4 (50.0%) | 0.24 |
| Peribronchovacular distribution, n (%) | 69 (51.5%) | 62 (52.1%) | 7 (46.7%) | 0.79 | 43 (50%) | 6 (55%) | 1.00 | 93 (53.1%) | 87 (54.0%) | 6 (42.9%) | 0.58 | 67 (54.9%) | 3 (37.5%) | 0.47 |
| Ground glass opacities, n (%) | 61 (45.5%) | 57 (47.9%) | 4 (26.7%) | 0.17 | 37 (43%) | 3 (27%) | 0.52 | 108 (53.5%) | 101 (54.6%) | 7 (41.2%) | 0.32 | 80 (56.3%) | 5 (45.5%) | 0.54 |
| Mosaic perfusion or air-trapping, n (%) | 76 (56.7%) | 69 (58.0%) | 7 (46.7%) | 0.42 | 55 (64%) | 6 (55%) | 0.53 | 129 (63.9%) | 117 (63.2%) | 12 (70.6%) | 0.61 | 94 (66.2%) | 7 (63.6%) | 1.00 |

**Table E8.** Comparison of pathologic features by telomere variant status

| | | All | | | European | | |
|---|---|---|---|---|---|---|---|
| **Feature** | **Total** | **No Variant** | **Variant** | **p-value** | **No Variant** | **Variant** | **p-value*** |
| N | 110 | 98 | 12 | | 78 | 8 | |
| Microscopic honeycombing | 24 (22.0%) | 20 (21%) | 4 (33%) | 0.30 | 16 (21%) | 3 (38%) | 0.37 |
| Heterogenous distribution | 75 (68.2%) | 65 (66%) | 10 (83%) | 0.33 | 52 (67%) | 8 (100%) | 0.099 |
| Subpleural accentuation | 28 (25.9%) | 23 (24%) | 5 (42%) | 0.29 | 19 (25%) | 4 (50%) | 0.21 |
| Airway centered | 80 (73.4%) | 70 (72%) | 10 (83%) | 0.51 | 55 (71%) | 7 (88%) | 0.44 |
| Dense collagen fibrosis | | | | 0.66 | | | 0.92 |
| None | 26 (23.6%) | 24 (24%) | 2 (17%) | | 19 (24%) | 1 (12%) | |
| Mild | 36 (32.7%) | 33 (34%) | 3 (25%) | | 28 (36%) | 3 (38%) | |
| Moderate | 20 (18.2%) | 18 (18%) | 2 (17%) | | 12 (15%) | 1 (12%) | |
| Marked | 28 (25.5%) | 23 (23%) | 5 (42%) | | 19 (24%) | 3 (38%) | |
| Any | 84 (76.4%) | 74 (76%) | 10 (83%) | 0.73 | 59 (76%) | 7 (88%) | 0.67 |
| Moderate-Marked | 48 (43.6%) | 41 (42%) | 7 (58%) | 0.36 | 31 (40%) | 4 (50%) | 0.71 |
| Interstitial granulomas | | | | 0.97 | | | 0.84 |
| None | 32 (29.1%) | 29 (30%) | 3 (25%) | | 21 (27%) | 1 (12%) | |
| Mild | 19 (17.3%) | 17 (17%) | 2 (17%) | | 12 (15%) | 1 (12%) | |
| Moderate | 29 (26.4%) | 26 (27%) | 3 (25%) | | 23 (29%) | 3 (38%) | |
| Marked | 30 (27.3%) | 26 (27%) | 4 (33%) | | 22 (28%) | 3 (38%) | |
| Any | 78 (70.9%) | 69 (70%) | 9 (75%) | 1.00 | 57 (73%) | 7 (88%) | 0.67 |
| Moderate-Marked | 59 (53.6%) | 52 (53%) | 7 (58%) | 0.77 | 45 (58%) | 6 (75%) | 0.46 |
| Lymphocytic infiltration | | | | 0.96 | | | 1.00 |
| None | 16 (14.8%) | 15 (16%) | 1 (8%) | | 9 (12%) | 1 (12%) | |
| Mild | 34 (31.5%) | 30 (31%) | 4 (33%) | | 24 (32%) | 3 (38%) | |
| Moderate | 52 (48.1%) | 45 (47%) | 7 (58%) | | 37 (49%) | 4 (50%) | |
| Marked | 6 (5.6%) | 6 (6%) | 0 (0%) | | 6 (8%) | 0 (0%) | |
| Any | 92 (85.2%) | 81 (84%) | 11 (92%) | 0.69 | 67 (88%) | 7 (88%) | 1.00 |
| Moderate-Marked | 58 (53.7%) | 51 (53%) | 7 (58%) | 0.77 | 43 (57%) | 4 (50%) | 0.73 |
| Fibroblastic foci | | | | 0.004 | | | 0.019 |
| None | 69 (63.3%) | 65 (67%) | 4 (33%) | | 54 (70%) | 3 (38%) | |
| Mild | 31 (28.4%) | 27 (28%) | 4 (33%) | | 21 (27%) | 3 (38%) | |
| Moderate | 8 (7.3%) | 5 (5%) | 3 (25%) | | 2 (3%) | 1 (12%) | |
| Marked | 1 (0.9%) | 0 (0%) | 1 (8%) | | 0 (0%) | 1 (12%) | |
| Any | 40 (36.7%) | 32 (33%) | 8 (67%) | 0.029 | 23 (30%) | 5 (62%) | 0.11 |
| Moderate-Marked | 9 (8.3%) | 5 (5%) | 4 (33%) | 0.008 | 2 (3%) | 2 (25%) | 0.043 |
| Small airway disease | | | | 0.75 | | | 0.22 |
| None | 15 (14.0%) | 14 (15%) | 1 (9%) | | 11 (14%) | 1 (12%) | |
| Mild | 50 (46.7%) | 43 (45%) | 7 (64%) | | 37 (49%) | 6 (75%) | |
| Moderate | 32 (29.9%) | 30 (31%) | 2 (18%) | | 22 (29%) | 0 (0%) | |
| Marked | 10 (9.3%) | 9 (9%) | 1 (9%) | | 6 (8%) | 1 (12%) | |
| Any | 92 (86.0%) | 82 (85%) | 10 (91%) | 1.00 | 65 (86%) | 7 (88%) | 1.00 |
| Moderate-Marked | 42 (39.3%) | 39 (41%) | 3 (27%) | 0.52 | 28 (37%) | 1 (12%) | 0.25 |

*Trends in associations between variant status and semi-quantitative categories were evaluated using a multinomial logistic regression model.

**Table E9.** Coverage statistics for candidate genes

| | Discovery Cohort | | Replication Cohort | |
|---|---|---|---|---|
| GENE | Median | Minimum | Median | Minimum |
| DKC1 | 28 | 8 | 35 | 29 |
| PARN | 28 | 20 | 29 | 25 |
| RTEL1 | 37 | 23 | 35 | 30 |
| TERC | 32 | 22 | 51 | 15 |
| TERT | 36 | 23 | 40 | 30 |
| TINF2 | 29 | 20 | 44 | 31 |

Footnote:

1. Median = median of median coverage per exon across samples in read depth
2. Minimum = median of minimum coverage per exon across samples in read depth

**Table E10.** Comparison of variant inclusion criteria and variant frequencies between the current study and prior studies of telomere-related gene variants in idiopathic pulmonary fibrosis and rheumatoid arthritis-associated interstitial lung disease

| Study | Genes included | MAF cut-off | Predicted effects | Frequency in Cases from Reference Study | Frequency in Controls from Reference Study | Frequency in non-Hispanic White Cases from Discovery Cohort in Current Study | Frequency in non-Hispanic White Cases from Replication Cohort in Current Study |
|---|---|---|---|---|---|---|---|
| Ley et al (current study) | TERT, TERC, PARN, RTEL1, TINF2, DKC1 | 0.005 | 1. LoF<br>2. PP2 – at least possibly damaging<br>3. SIFT- deleterious | n/a | n/a | n/a | n/a |
| Petrovski et al (Reference 29) | Whole Exome | 0.0005 cases/controls AND absent in Exome Variant Server and ExAC | 1. LoF<br>2. PP2- at least probably damaging | TERT = 0.0496<br>RTEL1 = 0.0229<br>PARN = 0.0267<br>Combined = 9.9% | TERT = 0.0014<br>RTEL1 = 0.0<br>PARN = 0.0012<br>Combined = 0.26% | TERT = 0.0248<br>RTEL1 = 0.0083<br>PARN = 0.0<br>Combined = 3.3% | TERT = 0.0237<br>RTEL1 = 0.0059<br>PARN = 0.0059<br>Combined = 3.6% |
| Juge et al (Reference 31) | ABCA3, PARN, RTEL1, SFTPA2, SFTPC, TERT | 0.01 | 1. PP2 probably damaging or SIFT deleterious<br>2. GERP >=2<br>3. CADD >=10 | TERT = 0.0741<br>RTEL1 = 0.0370<br>PARN = 0.123<br>Combined = 12.3% | TERT = 0.0168<br>RTEL1 = 0.0139<br>PARN = 0.0069<br>Combined = 3.8% | TERT = 0.0413<br>RTEL1 = 0.0413<br>PARN = 0.0083<br>Combined = 8.3% | TERT = 0.0355<br>RTEL1 = 0.0296<br>PARN = 0.0118<br>Combined = 7.7% |
| Dressen et al (Reference 30) | Whole Genome | 0.01 | PP2 >=0.5 OR high-impact | TERT = 0.0424<br>RTEL1 = 0.0305<br>PARN = 0.0124<br>Combined = 8.5% | TERT = 0.01<br>RTEL1 = 0.0176<br>PARN = 0.001<br>Combined = 2.9% | TERT = 0.0496<br>RTEL1 = 0.0331<br>PARN = 0.0165<br>Combined = 9.9% | TERT = 0.0355<br>RTEL1 = 0.0355<br>PARN = 0.0118<br>Combined = 8.3% |

Abbreviations: MAF = minor allele frequency, ExAC = Exome Aggregation Consortium, LoF = loss of function, PP2 = polyphen-2, SIFT = Sorting Intolerant from Tolerant, GERP = Genomic Evolutionary Rate Profiling score, CADD = Combined Annotation Dependent Depletion score