Supplementary Figure Legends

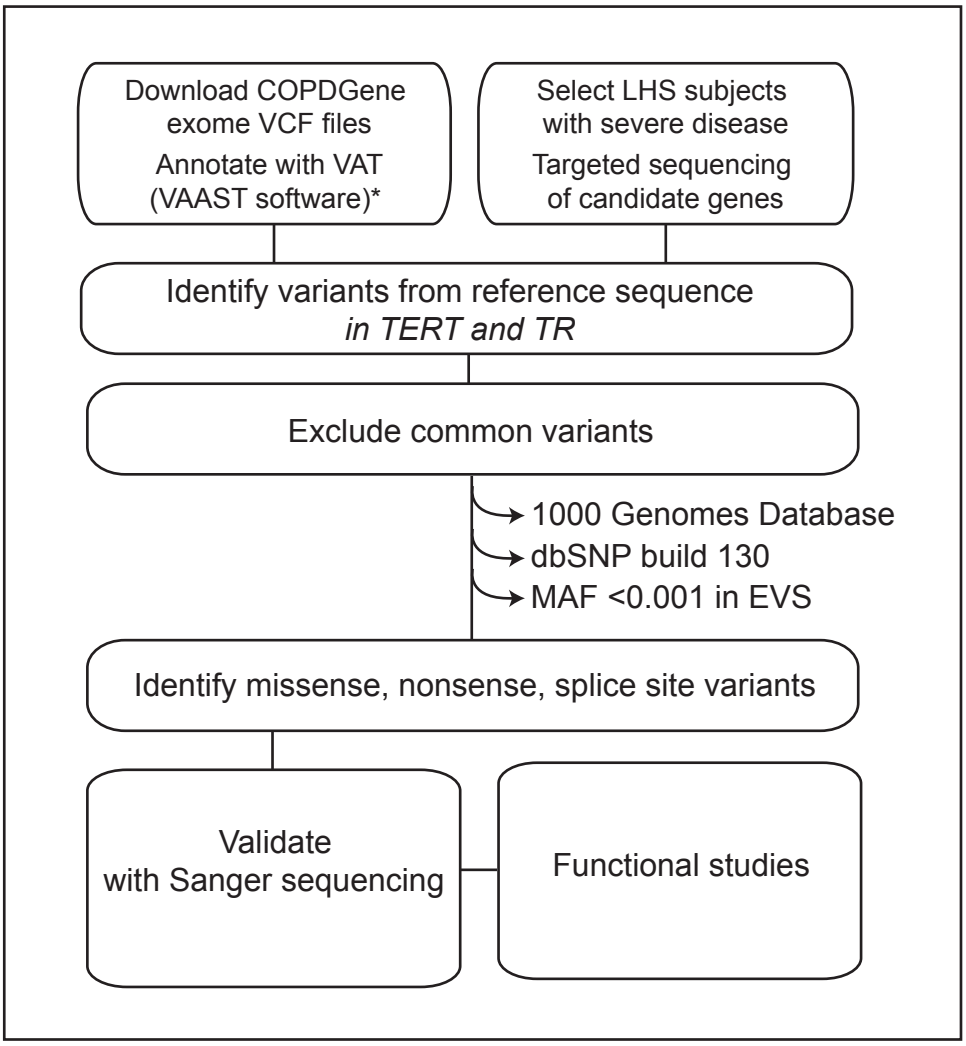
Supplementary Figure 1. Filtering strategy for identifying telomerase variants for functional analysis. Flow chart delineates a priori designed filtering strategy to identify rare telomerase variants in COPDGene and Lung Health Study (LHS). *Refers to publicly available VAAST software described in Yandell et al. *Genome Research* 2011. EVS refers to the Exome Variant Server, MAF to minor allele frequency and VCF to virtual contact file.

Supplementary Figure 2. **Functional consequences of telomerase variant identified in COPDGene controls. A.** Gel image of telomeric DNA repeats generated from wild-type and variant telomerases reconstituted *in vivo* and immuno-purified. The total intensity of the DNA repeat products generated by TERT Arg653Cys shows similar activity as wild-type telomerase. A ^{32}P end-labeled 18mer oligonucleotide is included as an internal control for the recovery of DNA products. **B.** Northern blot for TR levels from immuno-purified telomerases and western blot for TERT expression in cells. Western blot performed with anti-FLAG and anti-GAPDH antibodies for ectopically expressed FLAG-tagged TERT and endogeneous GAPDH, respectively. **C.** Mean telomerase activity from four independent activity assays from two separate transfections. Enzymes were purified from cell lysates from two separate transfections and these experiments were done independent of those shown in Figure 1. Error bars represent standard error of the mean. P-values were calculated using Student's *t*-test and are two-sided.

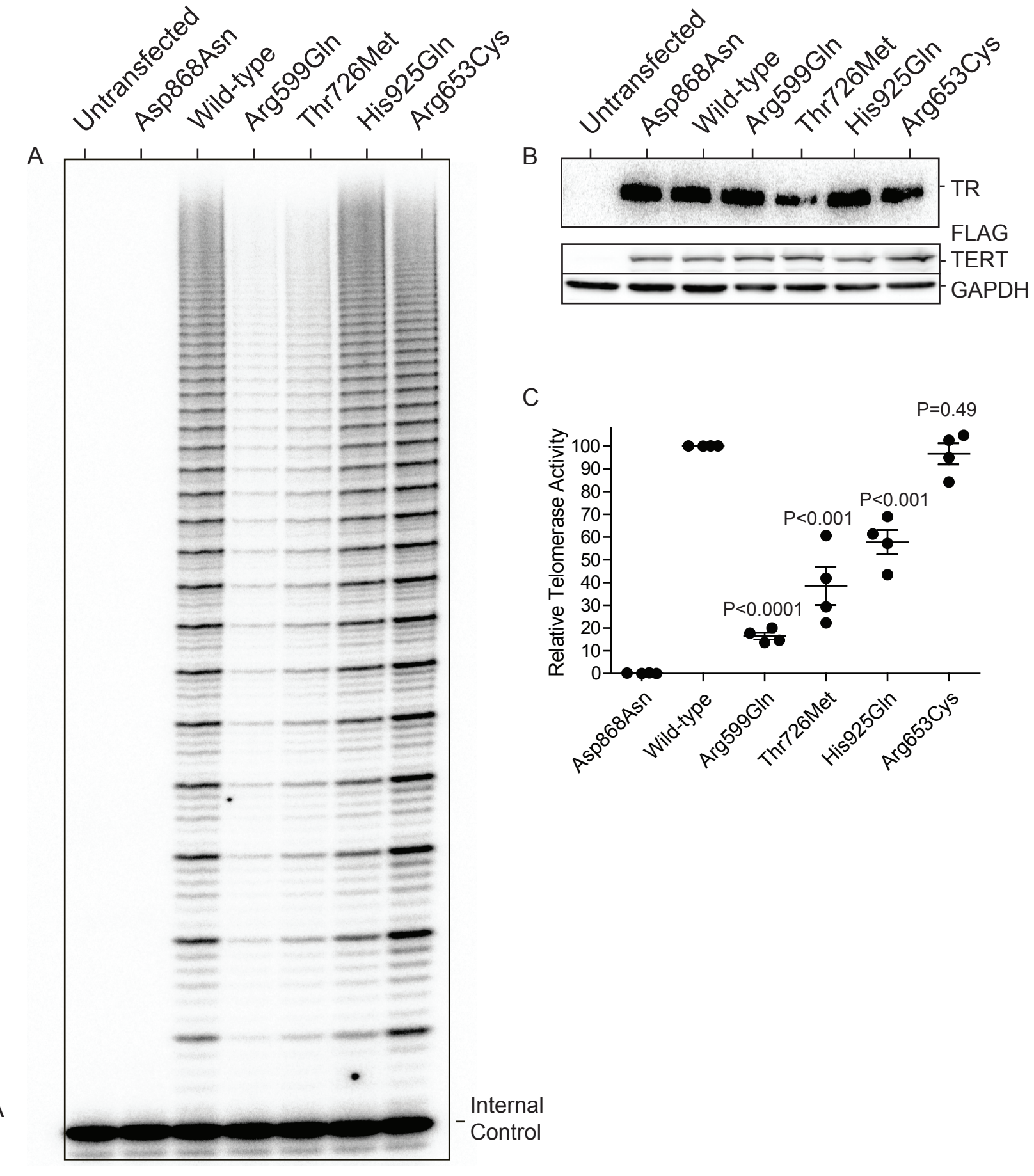
Supplementary Figure 3. Conservation of mutated residues in TERT. A. Mutations fall in conserved catalytic domains of the telomerase reverse transcriptase. **B.** Evolutionary conservation of TERT variants across seven species. Mutated residues are labeled above the alignment. Alignments were generated with the online tools Clustal Omega (http://www.ebi.ac.uk/Tools/msa/clustalo/) and BoxShade (http://www.ch.embnet.org/software/BOX_form.html).

Supplementary Figure 4. Depth of coverage in next-generation sequence data. Percent coverage is shown as percent of sequences with 8X or greater coverage in the COPDGene (whole exome sequencing) and Lung Health Study cases (customized targeted panel). Eleven exomes were selected randomly for the COPDGene coverage analysis. For the Lung Health Study, the coverage reflects data from the 76 samples that passed quality control. The mean coverage calculation included exons and their flanking sequence. For *SERPINA1,* coverage included exon 6 and the 20 flanking nucleotides since this region represents the most common severe alpha-1 antitrypsin deficiency allele (PI*Z, rs28929474). Coverage from the COPDGene exomes was calculated from Binary Alignment/Map (BAM) files downloaded from the dbGaP portal.

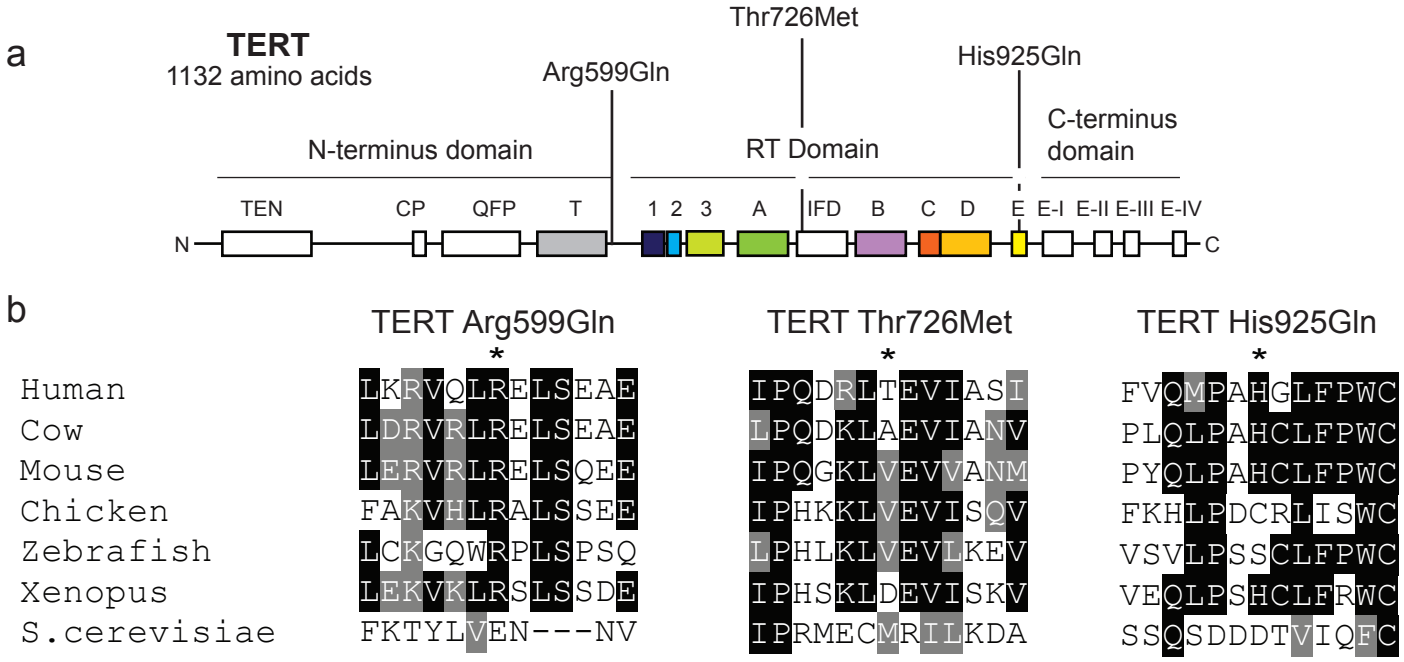
Supplementary Figure 1



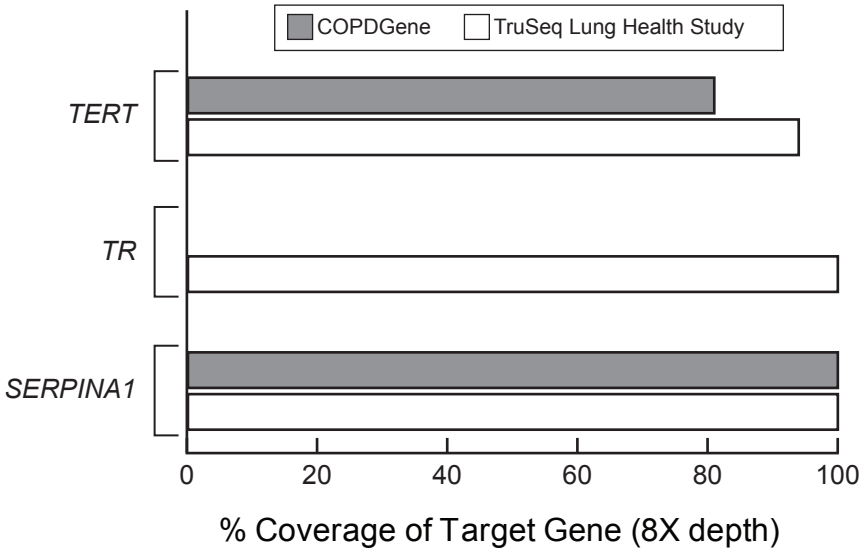
Supplementary Figure 2



Supplementary Figure 3



Supplementary Figure 4



Supplementary Table 1. Allele frequencies of rare *TERT* variants

Variant	1000 Genomes (n=1,092)	Mutli-ethnic Cohort (n=528)*	Other Controls (n=400)**	Exome Variant Server (n=6,503)	LHS Subjects (n=83)	Minor Allele Frequency
TERT **Arg599Gln CGG>CAG**	**0**	**0**	**0**	**1**	**0**	**5.8×10^{-5}**
TERT **Arg653Cys CGT>TGT†**	**0**	**0**	**0**	**1†**	**0**	**5.8×10^{-5}**
TERT **Thr726Met ACG>ATG**	**0**	**0**	**0**	**4††**	**0**	**2.3×10^{-4}**
TERT **His925Gln CAC>CAA**	**0**	**0**	**0**	**0**	**1**	**5.8×10^{-5}**

LHS, Lung Health Study; MAF, minor allele frequency

**TERT* sequence data from multi-ethnic cohort examined in Yamaguchi et al. *NEJM* 2005.
***DNA from these controls of European descent was obtained through the National Disease Research Interchange
†This variant was present in the COPDGene control group had comparable activity to wild-type telomerase
††This variant was reported previously in a child with aplastic anemia in Liang J et al. *Haematologica* 2006.

Supplementary Table 2. Clinical features of subjects with *TERT* mutations in the COPDGene and Lung Health Studies

Age at Diagnosis (y)	Age at Enrollment (y)	Gender	Mutation	Parent Study	Smoking History (pack-years)	BMI (kg/m2)	Pulmonary Function Tests			CT Findings	Resting saturation (%) (Hours on oxygen)	Co-morbidities
							FEV_1 (L/s, %)	FVC (L, %)	FEV_1/FVC (%, %)			
46	41	F	*TERT* His925Gln CAC>CAA	Lung Health Study	18*	21.3	1.34 (47)	2.79 (79)	48 (58)	-	-	-
49	57 *(d. 62)*	F	*TERT* Arg599Gln CGG>CAG	COPDGene	43	19.4	0.45 (20)	1.65 (56)	27 (35)	Emphysema (30%) Interstitial abnormality Bronchiectasis Expiratory air trapping	82 (24 h)	Pneumothorax
53	57	F	*TERT* Thr726Met ACG>ATG	COPDGene	48	18.9	0.69 (26)	2.16 (63)	31 (41)	Emphysema (40%)	95 (6 h)	Stomach ulcers Vertebral fractures Osteoporosis Congestive Heart Failure

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity

*Smoking history was recorded at study enrollment; pulmonary functions are from year 5 of study.

Supplementary Table 3. Minor allele frequency of *TERT* Variants found in COPDGene and LHS subjects*

Variant** (chr5)	COPDGene Controls (n=206)	COPDGene Cases (n=209)	Lung Health Study (n=83)	Previous report	NCBI submitted SNP number
g.1295060G>A p.Arg15Arg	0	0	0.012	-	1477761192
g.1295018C>T p.Arg29Arg	0	0	0.012	-	1477761156
g.1294166C>T p.Ala279Thr	0.032	0.041	0.06	rs61748181	1477761119
g.1294086C>T p.Ala305Ala	0.279	0.275	0.446	rs2736098	1477761081
g.1293767G>A p.His412Tyr	0.002	0.002	0.012	rs34094720	1477761044
g.1280411T>C p.Ala604Ala	0.007	0	0.012	rs33959226	1477760829
g.1280387G>C p.Ala612Ala	0	0	0.012	rs34170122	1477760794
g.1279505G>A p.Gly677Gly	0.012	0.012	0.036	rs33956095	1477760682
g.1279439G>A p.Ala699Ala	0.012	0.005	0	rs33963617	-
g.1279430C>T p.Pro702Pro	0	0	0.012	rs151055240	1477760646
g.1278888,G,A p.Asp718Asp	0	0.003	0	-	-
g.1278804C>T p.Val746Val	0	0	0.012	-	1477760573
g.1271254G>A p.His816His	0	0.003	0	-	-
g.1268700C>T p.Thr839Thr	0	0.003	0	rs140124989	-
g.1264611C>T p.Thr917Thr	0	0.003	0	-	-
g.1264587G>A p.His925His	0	0	0.012	rs34528119	1477760502
g.1260708G>T p.Arg951Arg	0	0.003	0	-	-
g.1255520G>A p.His1013His	0.104	0.1	0.181	rs33954691	1477760465
g.1255454G>A p.Val1035Val	0.005	0.005	0	rs181612536	-
g.1254594C>T p.Ala1062Thr	0.014	0.022	0.036	rs35719940	1477760428
g.1253918C>T p.Pro1108Pro	0.019	0.029	0.108	rs35033501	1477760388

*No SNPs in *TR* were identified.
**Coordinates refer to hg19 version of the genome.