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SHORT REPORT

A common Alu insertion in the 3'UTR of *TMEM106B* is associated with risk of dementia

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Abstract

INTRODUCTION: Sequence variants in *TMEM106B* have been associated with an increased risk of developing dementia.

METHODS: As part of our efforts to generate a set of mouse lines in which we replaced the mouse *Tmem106b* gene with a human *TMEM106B* gene comprised of either a risk or protective haplotype, we conducted an in-depth sequence analysis of these alleles. We also analyzed transcribed *TMEM106B* sequences using RNA-seq data (AD Knowledge portal) and full genome sequences (1000 Genomes).

RESULTS: We identified an AluYb8 insertion in the 3' untranslated region (3'UTR) of the *TMEM106B* risk haplotype. We found this AluYb8 insertion in every risk haplotype analyzed, but not in either protective haplotypes or in non-human primates.

DISCUSSION: We conclude that this risk haplotype arose early in human development with a single Alu-insertion event within a unique haplotype context. This AluYb8 element may act as a functional variant in conferring an increased risk of developing dementia.

KEYWORDS
AluYb8 insertion, functional sequence variant, *TMEM106B* mouse models, *TMEM106B* protective haplotype, *TMEM106B* risk haplotype

Highlights

- We conducted an in-depth sequence analysis of (1) a risk and (2) a protective haplotype of the human *TMEM106B* gene.
- We also analyzed transcribed *TMEM106B* sequences using RNA-seq data (AD Knowledge Portal) and full genome sequences (1000 Genomes).
- We identified an AluYb8 insertion in the 3' untranslated region (3'UTR) of the *TMEM106B* risk haplotype. We found this AluYb8 insertion in every risk haplotype analyzed, but not in either protective haplotypes or in non-human primates.
- This AluYb8 element may act as a functional variant in conferring an increased risk of developing dementia.

1 | INTRODUCTION

A genome-wide association study published in 2010 identified a haplotype block containing the gene encoding lysosomal type II transmembrane protein 106B (*TMEM106B*) as a susceptibility locus for frontotemporal lobar degeneration (FTLD) with TAR DNA-binding protein (TDP-43) inclusions (FTLD-TDP).[1] The top tagging single nucleotide polymorphism (SNP) found in this study was rs1990622, with the minor G allele reducing the risk of developing FTLD-TDP dementia (odds ratio [OR] = 0.61) and the major A allele increasing risk (OR = 1.64). Association studies published the next year confirmed that the *TMEM106B* locus modified the risk of developing FTLD-TDP in patients with mutations in the gene encoding granulin (GRN), with the risk allele decreasing the age at onset by an average of 13 years and identified a coding SNP (rs3173615) in perfect linkage disequilibrium (LD) with rs1990622 SNP (D' = 1, R^2 = 1 in the CEU [Northern Europeans from Utah] reference population) that changes a single amino acid in the minor protective form of TMEM106B protein (T185S).[2] Studies published in 2014[3,4] reported that *TMEM106B* haplotypes also modify the risk of developing dementia in patients with the hexanucleotide repeat expansion mutation in C9ORF72 (homozygous protective haplotype OR = 0.33) but did not significantly modify the risk of developing motor neuron disease (OR = 0.85).[3] More recent studies have found that *TMEM106B* haplotypes modify the rate of cognitive decline in Parkinson's disease[5] and impact the severity of neuropathology found in *post mortem* brain tissue from patients with chronic traumatic encephalopathy (CTE, homozygous protective haplotype OR = 0.40)[6] and limbic-predominant age-related TDP-43 encephalopathy with hippocampal sclerosis pathology (LATE-NC + HS).[7]

The functional variant(s) in the *TMEM106B* haplotypes have not yet been conclusively identified. To date, rs3173615 is the only common coding variant identified in *TMEM106B*. A study found that the risk T185 TMEM106B protein isoform is degraded more slowly than the protective S185 isoform, leading to a 2-fold increase of T185 TMEM106B protein levels without impacting mRNA expression.[8] An alternative potential functional variant identified in part on *TMEM106B* expression studies in lymphoblastoid cell lines predicts that the differences in the non-coding SNP rs1990620 (very near rs1990622) differentially impacts chromatin structure and the transcription of this gene.[9]

Several recent studies evaluating brain tissue for fibrous TDP-43 instead found fibers made entirely or partially of TMEM106B.[10,11,12] TMEM106B has been shown to regulate lysosomal function,[13] suggesting a role for lysosomal pathways in the differential impacts of these two haplotypes on dementia risk and in its direct association with TDP-43 protein accumulations. Surprisingly, recent work has also shown that the TMEM106B protein can be present on the cell surface and can mediate SARS-CoV2 infection in cells.[14]

The potential functional variants in *TMEM106B* are all in perfect LD with rs1990622 (R^2 = 1) and so share the same statistical association with disease risk found for this tagging SNP in the association studies conducted to date. Additional experimental models are therefore needed to support the types of detailed mechanistic studies that will help to conclusively identify the functional variant(s) in these haplotypes and to elucidate at the molecular level precisely how *TMEM106B* impacts neuropathology. We are working to develop a set of mouse models in which we replaced the mouse *Tmem106b* gene with a human *TMEM106B* gene comprised of either a risk or a protective haplotype.[15] As part of these efforts, we fully sequenced the two *TMEM106B* genomic alleles introduced into these mouse lines and analyzed the sequence differences between these risk and protective haplotypes. We found an AluYb8 insertion in the risk haplotype allele that is not present in the protective haplotype allele.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. A risk haplotype in the *TMEM106B* gene is known to increase the risk of developing several forms of dementia, but the functional sequence variant(s) in this haplotype have not yet been identified. Moreover, animal models incorporating risk and protective haplotypes are not yet available. The relevant studies are appropriately cited.
2. **Interpretation**: We identified the sequence differences between the risk and protective haplotype alleles that we have incorporated into new *TMEM106B* Gene Replacement (GR) mouse models we are generating. We found that the risk haplotype contains an insertion of an AluYb8 that is not present in the protective haplotype.
3. **Future directions**: The GR mouse models incorporating the haplotypes described will allow us to evaluate the functional significance of the Alu element insertion and of other potential functional variants in modifying the risk of developing dementia.

2 | METHODS

2.1 | Bacterial artificial chromosome sequencing, variant calling, and visualization

Bacterial artificial chromosome (BAC) clones RP11-960B15 and CH17-22M18 containing the *TMEM106B* risk and protective haplotypes, respectively, were sequenced by the University of Minnesota Genomics Center using Illumina NovaSeq6000 with 2 × 150 bp reads. Raw sequences were mapped to the GRCh38/h38 human genome reference using Burrows-Wheeler Aligner (BWA) v0.7.17,[16] and Polymerase chain reaction (PCR) or optical duplicates were parked using Picard tools v2.19.9. These files were further processed with GATK v4.0.1[17] for base quality score recalibration and variant calling. Variants were filters using standard filtering parameters. For SNPs, the filtering criteria were QD < 2.0, FS > 60.0, SOR > 3.0,

ReadPosRankSum < −8.0, MQ < 40.0, and MQRankSum < −12.5. For indels, the filtering criteria were QD < 2.0, FS > 200.0, SOR > 10.0, and ReadPosRankSum < −20.0. Integrative Genomics Viewer (IGV) was used visually analyze bam files, variant calling files, and the Alu insertion in the 3'UTR of the risk haplotype. Assemblies for the risk and protective sequences BACs were completed using SPAdesv3.15.5. Contig sequences were then aligned and orientated using DS Gene from AccelrysGene.[18] Sequence data are available at GenBank (*TMEM106B* risk haplotype #PP879200 and protective haplotype #PP879201). The ethnic origin of the anonymous donors from which these BAC clones were ultimately derived is unknown (UNK).

2.2 | Human RNA-seq analysis

We analyzed whole transcriptome data from the Mayo Clinic Alzheimer's Disease Genetics Studies from the AD Knowledge Portal to determine whether the AluYb8 insertion was also present in additional genomes and expressed in brain tissue. This study contains RNA sequencing data from cerebellum and temporal cortex samples from North American Caucasian subjects with neuropathological diagnosis of AD, progressive supranuclear palsy (PSA), pathologic aging, or elderly controls without neurodegenerative diseases.[19] Only temporal cortex samples that were homozygous for the risk or protective haplotypes at SNP rs3173615 and rs1990622 were included in our analysis. Using the IGV, we visualized each RNA-seq Binary Alignment Map (BAM) file. BAM files were analyzed for protective or risk coding SNP and the presence or absence of the Alu insertion in the 3' UTR region (Figure S1 in supporting information).

2.3 | Global population analysis

The 1000 Genomes project data[20,21] were accessed on March 23, 2023. High coverage whole-genome sequencing samples were the only samples included in our analysis. We genotyped these samples based on rs3173615 using the IGV. Our sample set included five genomes homozygous for the risk haplotype, five genomes homozygous for the protective haplotype, and twelve genomes that were heterozygous for these haplotypes. Additional samples were analyzed from the Gambia dataset to identify a recombined haplotype block common in that population.

2.4 | Diversity, equity, and inclusion (DEI) statement

All RNA-seq data available from the AD knowledge portal was derived from samples taken from patients described as "North American Caucasian." Our full genome analysis included samples from the 1000 Genomes dataset from all global populations represented, including African, Asia, and Pacific Islander, to evaluate the prevalence this Alu insertion in these widely varied populations.

3 | RESULTS

3.1 | *TMEM106B* risk and protective haplotype sequencing and analysis

We used PCR and limited sequencing of polymorphic regions to identify the BAC clones RP11960B15 and CH17-22M18 as containing *TMEM106B* risk and protective haplotypes, respectively, and then used next-generation sequencing to obtain the full sequence of the *TMEM106B* region in these two clones. We analyzed and compared the syntenic 97 kb region from each sequence (Chr7:12185253 −12282003, assembly GRCH38.p14) that we have incorporated into our *TMEM106B*-GR (*TMEM106B*-GR) mouse lines.[15] The SNP and small insertions and deletions (INDEL) differences between these two haplotype sequences and the reference genome are listed in Table S1 in supporting information and are summarized for the transcribed region of *TMEM106B* in Figure 1A. We found that the BAC RP11-960B15 risk haplotype was essentially identical to the reference genomic sequence GRCh38.p14, which is also a risk haplotype, only differing by the slight expansion in a 12xT repeat tract in the reference genome to a 13xT tract in the risk haplotype sequenced (Figure 1A). On the other hand, we found that the CH17-22M18 protective haplotype was significantly different than the reference risk haplotype, with 193 SNP and 23 INDEL variants identified. By far the most striking sequence difference that we identified between the risk and protective haplotypes, however, is the insertion of a 316 bp AluYb8 element in the risk haplotype that is not present in the protective haplotype analyzed (Figure 1A,B). As shown in Figure 1B, this Alu element is inserted in the sense orientation into the 3' UTR of the longest *TMEM106B* isoform. As is typical of this type of insertion event,[22] the Alu element is flanked by a short, direct repeat of the insertion site sequence.

3.2 | Comparison to non-human primate haplotypes

We used Basic Local Alignment Search Tool (BLAST) alignment analysis to non-human primate genome sequences (i.e., chimpanzee, pygmy chimpanzee, gorilla, orangutan, gibbon, Rhesus, and green monkey) and found that none shared the *TMEM106B* AluYb8 insertion. Rather, each of these genomes share the Alu-negative insertion site found in the protective haplotype. This alignment is shown in Figure S2 in supporting information.

3.3 | Human RNA-seq analysis

We digitally genotyped samples from a Mayo RNA-seq study available from the AD Knowledge Portal based on tagging SNP rs1990622 and coding SNP rs3173615. We identified 15 *TMEM106B* data sets homozygous for the protective haplotypes and 15 sets homozygous for the risk haplotype samples and evaluated these sequence sets for the Alu insertion sequence in *TMEM106B* (Table 1). We found that all

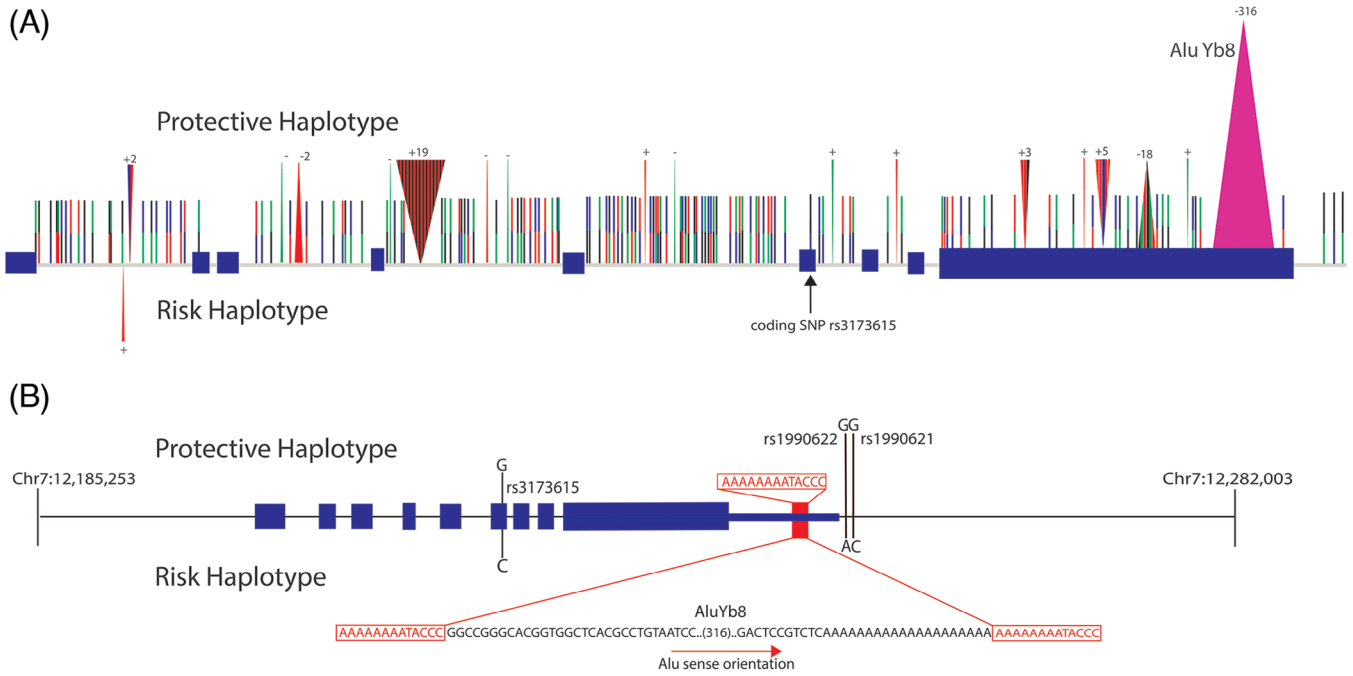

FIGURE 1 *TMEM106B* risk and protective haplotype characterization. A, Visual representation of variants identified in the risk and protective haplotypes within the transcribed region of *TMEM106B* compared to the genome reference sequence (GRCH38.p14). Exons in the *TMEM106B* gene are indicated by blue boxes. Significant SNP polymorphisms between the two haplotypes are shown. Wedges = INDELs (# of bases added or lost is shown), Lines = SNPs; Red = A, Black = G, Green = T, Blue = C. B, Visual representation of the entire region of the risk and protective haplotypes analyzed (Chr7:12185253–12282003. GRCH38.p14). A 13 bp direct repeat duplication at the AluYb8 insertion site is shown in red, with the head and tail ends of the Alu element sequence in black letters. This insertion site and Alu element are transcribed in the longer 3'UTR generated by transcripts that terminate at the secondary distal alternative polyA site of *TMEM106B*. SNP, single nucleotide polymorphism; UTR, untranslated region.

the risk haplotype datasets contained the AluYb8 insertion identified in our BAC clone haplotype, and that all the reads from the 15 protective haplotype samples contained the insertion site sequence without the Alu insertion.

3.4 | Global population analysis

We randomly selected a set of whole-genome sequencing data from the 1000 Genomes database from individuals from a range of geographically diverse populations. We found five genomes that were homozygous for the risk haplotype, five genomes homozygous for the protective haplotype, and twelve genomes heterozygous for the *TMEM106B* risk allele (Table 2). We found that none of the five genomes homozygous for the protective haplotype contained the Alu insertion, that all five of the genomes homozygous for the risk allele only contained sequence reads with the Alu insertion, and as expected, found the Alu insertion in half of all sequence reads from all 12 heterozygous samples.

We found that the SNP frequency data from samples identified as "African" appeared to indicate recombined haplotypes that disrupt the perfect LD between the coding SNP rs3173615 and the tagging SNP rs1990622. Within the African samples, the population with the least LD between these two markers is the Jola samples from the Gambia population ($r^2 = 0.46$). We found through analysis of genotyping data that the decreased LD in this population is largely due to a single common recombined haplotype derived from a recombination between the risk and protective haplotypes. In this recombined haplotype, the polymorphisms from rs3173615 (chr7: 12229791) to rs7797705 (chr7:12238147) are from the risk haplotype, whereas those from rs1548884 (chr7:12240135) to rs1990622 (Chr7:12244161) are the protective haplotype. We identified five individuals in the Jola dataset homozygous for this recombined haplotype (e.g., SC_GMJOL5309934 and SC_GMJOL5309918 from a mother/daughter pair of samples), analyzed the genomic sequences from this recombined allele in these homozygous samples, and found that they contain the Alu-negative insertion site from the protective haplotype. We also analyzed from the Jola population an additional three genomes homozygous for the risk haplotype and three genomes homozygous for the protective haplotype and again found the Alu insertion only in the risk haplotypes (Table 2).

4 | DISCUSSION

In this study we present our findings from an in-depth sequence characterization of the pair of *TMEM106B* protective/risk haplotypes that we have introduced into our matched set of *TMEM106B*-GR mouse

TABLE 1 Human RNA-seq data.

Sample number	Disease phenotype	rs3173615	ALU	
1015	AD	C/C	+/+	Risk
11,265	CON	C/C	+/+	
11,289	CON	C/C	+/+	
11,300	PSA	C/C	+/+	
11,311	CON	C/C	+/+	
11,357	PSP	C/C	+/+	
11,371	UNK	C/C	+/+	
11,394	PSA	C/C	+/+	
11,424	PA	C/C	+/+	
11,440	PSA	C/C	+/+	
11,449	PSA	C/C	+/+	
11,249	PSA	C/C	+/+	
11,321	CON	C/C	+/+	
11,398	PSA	C/C	+/+	
11,497	AD	C/C	+/+	
11,469	CON	G/G	–/–	Protective
1203	AD	G/G	–/–	
1302	CON	G/G	–/–	
1052	AD	G/G	–/–	
11,322	CON	G/G	–/–	
11,372	PSA	G/G	–/–	
11,396	CON	G/G	–/–	
11,410	UNK	G/G	–/–	
1929	UNK	G/G	–/–	
732	AD	G/G	–/–	
894	AD	G/G	–/–	
966	AD	G/G	–/–	
1104	AD	G/G	–/–	
11,457	PSA	G/G	–/–	
1275	AD	G/G	–/–	

Note: RNA-seq data from 30 patients with various neurological disorders available through the Mayo Clinic Alzheimer's Disease Genetics Studies from the AD Knowledge Portal were genotyped based on coding SNP rs3173615 and rs1990622. All risk haplotype samples were positive for the AluYb8 insertion.
Abbreviations: AD, Alzheimer's disease; CON, control; PA, Parkinson's disease; PSA, progressive supranuclear palsy; SNP, single nucleotide polymorphism; UNK, unknown.

TABLE 2 1000 Genomes dataset.

Sample	Region	rs3173615	ALU
HGDP00664	Middle East	C/G	+/–
HGDP00823	Middle East	G/G	–/–
HGDP01256	Middle East	C/G	–/+
HGDP00723	Middle East	C/C	+/+
HGDP01286	Africa (Senegal)	G/G	–/–
HGDP01036	Africa (Namibia)	G/G	–/–
HGDP00994	Africa (Bantu)	C/G	–/+
HGDP00993	Africa (Bantu)	C/G	–/+
HGDP00982	Africa (Congo)	G/G	–/–
HGDP01099	China (Tuija)	C/G	–/+
HGDP01096	China (Tuija)	C/G	–/+
HGDP00491	Oceania	G/G	–/–
HGDP00655	Oceania	C/C	+/+
HGDP00662	Oceania	C/G	–/+
HGDP00788	Oceania	C/C	+/+
HGDP00541	Oceania	C/G	–/+
HGDP00843	Brazil (Surui)	C/G	–/+
HGDP01043	Mexico (Pima)	C/G	–/+
HGDP01037	Mexico (Oima)	C/C	+/+
ERR1347710	European	C/G	–/+
ERR759318	European	C/G	–/+
SC_GMJOL5309922	Gambia (Jola)	G/G	–/–
SC_GMJOL5309914	Gambia (Jola)	C/C	+/+
SC_GMJOL5309930	Gambia (Jola)	C/C	+/+
SC_GMJOL5309941	Gambia (Jola)	G/G	–/–
SC_GMJOL539	Gambia (Jola)	G/G	–/–

Note: Twenty-six samples from diverse populations world-wide were analyzed from the 1000 Genomes dataset. Samples were genotyped using SNP rs3173615. The AluYb8 insertion was found in all risk heterozygous and homozygous samples. Green = protective, Yellow = risk.
Abbreviation: SNP, single nucleotide polymorphism.

lines.[15] We sequenced and analyzed these protective and risk haplotypes from BAC clones and identified an AluYb8 insertion in the 3' UTR of *TMEM106B*. The Alu element is inserted in the sense direction and differs from the consensus AluYb8 sequence[22] at four base pair. We did not find this Alu insertion sequence in the primate sequences that we analyzed. This finding together with the fact that the other major *TMEM106B* haplotype does not contain the Alu sequence strongly suggests that this insertion event occurred after the divergence from our last common primate ancestor. We evaluated transcribed *TMEM106B* sequences and full genome sequences from a range of global populations and consistently saw the Alu insertion in the risk haplotype sequence and absent from the protective.

Allele frequency of the risk SNPs rs1990622-A and rs3173615-C range from 26% to 60% in global populations (Table 3). We note that the allele frequencies for these two SNPs are essentially identical in all populations except those identified in this study as "African," with a particularly large disruption in LD in the Jola samples from the Gambia population ($r^2 = 0.46$). We identified a haplotype common in this population derived from a recombination between the risk and protective haplotypes, with risk SNPs linked to the coding SNP rs3173615 and protective SNPs linked to the tagging SNP rs1990622. As expected, this recombined allele also contains the Alu-negative insertion site from the protective haplotype present in this portion of that haplotype.

TABLE 3 Global allele frequency.

Population	rs3173615-C	rs1990622-A	AluYb8 frequency
European	0.60	0.60	0.60
African	0.31	0.26	0.26
East Asian	0.34	0.34	0.34
South Asian	0.36	0.36	0.36
American	0.44	0.45	0.45

Note: Allele frequency in global populations of risk alleles rs3173615-C and rs1990622-A identified in the 10,000 Genomes project data. 22, 23 estimated AluYb8 frequency based on tagging SNP rs1990622.
Abbreviation: SNP, single nucleotide polymorphism.

The Alu insertion site and the tagging SNP rs1990622 are therefore in perfect LD even in this African population that exhibits the lowest LD scores between rs3173615 and rs1990622. We conclude that the Alu insertion in the risk haplotype occurred early in human development in a single molecular event and is now one of the two major *TMEM106B* haplotypes in all populations globally. Each of these two *TMEM106B* haplotype alleles is likely to offer a significant selective evolutionary advantage over other ancestral variants, but neither has come to fully predominate in any modern human population.

Alu elements are one of the most common transposable elements in the human genome. The AluY subfamily is most recently integrated in the human genome and makes up < 10% of the Alu insertions in the human genome.[23] Alu insertions often cause disease by disrupting a coding region or a splice signal. For example, Alu insertions in *BRCA1* can cause hereditary breast cancer,[24] and Alu insertions in *GLA* can cause cardiac diseases.[25] Although we do not yet have evidence that the AluYb8 insertion in the 3' UTR of the risk haplotype has a functional impact on the *TMEM106B* gene in this haplotype, the 3'UTR region of genes often plays a role in transcriptional regulation[26] and this insertion may impact the expression of protein from this transcript.

The *TMEM106B*-GR mouse model set we are developing[15] will allow us to directly evaluate the molecular impacts of the AluYb8 insertion that we identified and report here, as well as those of the other putative functional sequence variations. One of the two *TMEM106B*-GR lines that we have made to date carries the risk haplotype in place of the syntenic *Tmem106b* region of the mouse genome, and the other matched line carries the protective haplotype (Figure 1). We are currently generating additional matched lines in which we modify the sequence in the risk haplotype by (1) deleting the AluYb8 sequence, or (2) converting the rs3173615 SNP from C to G and will assess the impacts of these sequence variants on *TMEM106B* endophenotypes in these lines.

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CONFLICT OF INTEREST STATEMENT

None. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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