Genetic findings in TDP-43 proteinopathies

	TMEM106B rs3173615 rs1990622	*GRN* rs5848	*ABCC9* rs704178	*KCNMB2* rs9637454	*APOE* ε4 haplotype
FTLD-TDP	GWAS	+	-*	-*	-*
HS-Aging	+	+	GWAS	GWAS	+
TDP-43 in elderly cohort	+	+			+
TDP-43 in AD	+	+*			+

GWAS = Evidence from genome-wide association study

+ = Evidence from candidate gene association study

- = No evidence from candidate gene association study

*** = unpublished**

Supplemental Table 1. Genetics of LATE-NC like phenotypes. Specific gene variants have been associated with risk for TDP-43 proteinopathy in aging. The neuropathologic phenotypes that have been the foci of prior studies have included frontotemporal lobar degeneration (FTLD-TDP), hippocampal sclerosis of aging (HS-Aging), TDP-43 proteinopathy in aging, and TDP-43 proteinopathy in those with comorbid Alzheimer's disease (AD). Note that two genes bearing disease-associated variants consistently associated with TDP-43 proteinopathy are *TMEM106B* and *GRN* (Baker *et al.* , 2006; Boeve *et al.* , 2006; Cruts *et al.* , 2006; Van Deerlin *et al.* , 2010); these were identified through gene-specific probes following the known associations between those genes and FTLD-TDP risk. *APOE* ε4 allele was previously associated with AD and Lewy body pathologies, but recent studies also showed *APOE* ε4 to be a risk factor in LATE-NC phenotype (Robinson *et al.* , 2018; Wennberg *et al.* , 2018; Yang *et al.* , 2018). Two genes that have been linked to LATE-NC like phenotype via GWAS studies are *ABCC9* and *KCNMB2* (Beecham *et al.* , 2014; Nelson *et al.* , 2014), both of which encode polypeptides that regulate potassium channels, but both of which require additional replication in other cohort studies.

Future biomarkers may enable specific combinatorial biomarker-based diagnoses

		Future biomarkers		Diagnoses
Aβ+	P-Tau+	α-Synuclein+	TDP-43+	
+	-	-	-	Presumed preclinical Alzheimer's disease (AD)
+	+	-	-	"Pure" AD
-	-	+	-	"Pure" Lewy body disease (LBD)
-	-	-	+	"Pure" LATE
+	+	+	-	AD+LBD
+	+	-	+	AD+LATE
+	+	+	+	AD+LBD+LATE
-		+	+	LBD+LATE
-	+	-	-	"Pure" Tauopathy
-	+	-	+	Tauopathy+LATE
-	+	+	-	Tauopathy+LBD

Supplemental Table 2. Future aging-related brain disease biomarkers may include a biomarker specific for TDP-43 proteinopathy (red column). This is a somewhat simplified representation that leaves off some diseases such as FTLD-TDP and vascular pathologies. However, with these biomarkers, one could ascertain most of the known common combinations of proteinopathies in aged persons' brains.