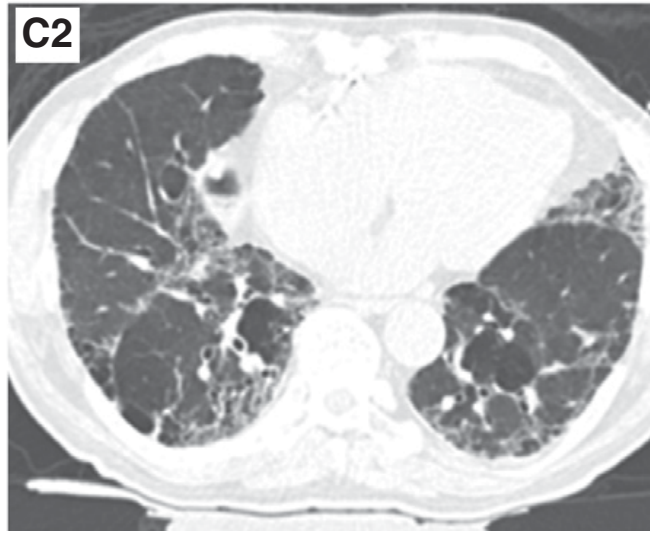
Integration of a *MUC5B* Promoter Variant and a Polygenic Risk Score for IPF and ILA

Matthew Moll, M.D., M.P.H.
Channing Division of Network Medicine
Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital, Boston, MA

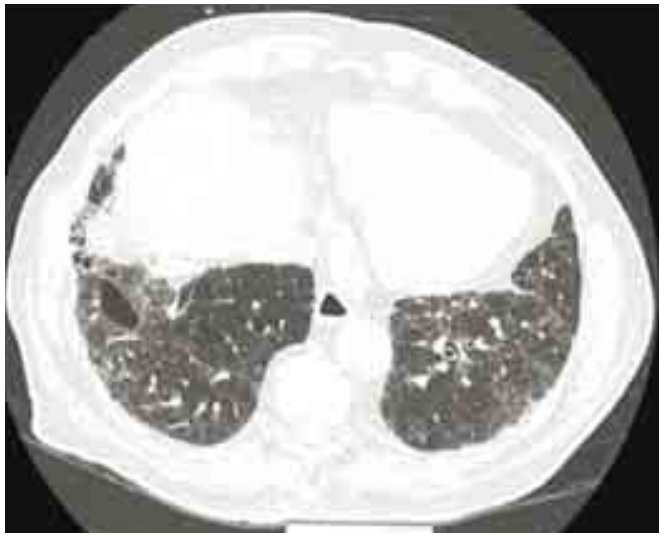
Hypothesis

- Idiopathic pulmonary fibrosis (IPF) characterized by progressive lung scarring and death - early disease detection is paramount.
- Chest computed tomographic imaging can detect ILA, which may progress to IPF.
- *MUC5B* promoter variant rs35705950 is common (MAF [Europeans]=0.11) and of large effect size conferring risk for both IPF (OR 6-13, heterozygotes) and ILA (OR 2-3)
- We hypothesized that an IPF polygenic risk score (PRS) excluding the *MUC5B* region would add complementary predictive value to the *MUC5B* variant for IPF and ILA.

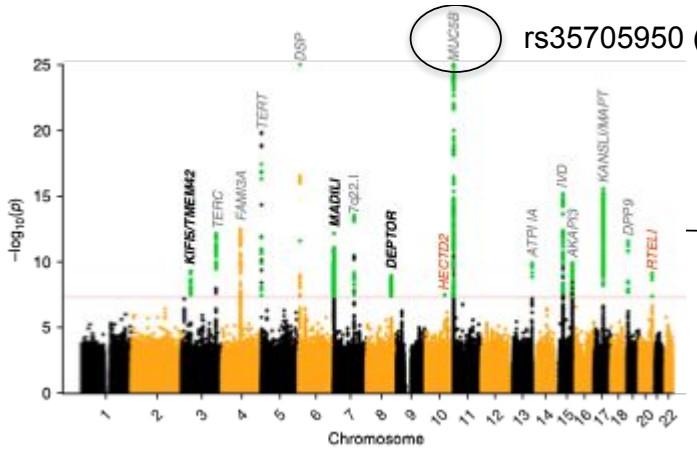
Idiopathic Pulmonary Fibrosis (IPF)



Interstitial Lung Abnormalities (ILA)



Study Design



Summary statistics from GWAS of IPF (Allen et al., *AJRCCM*, 2019).

Exclude 500 Kb around rs35705950

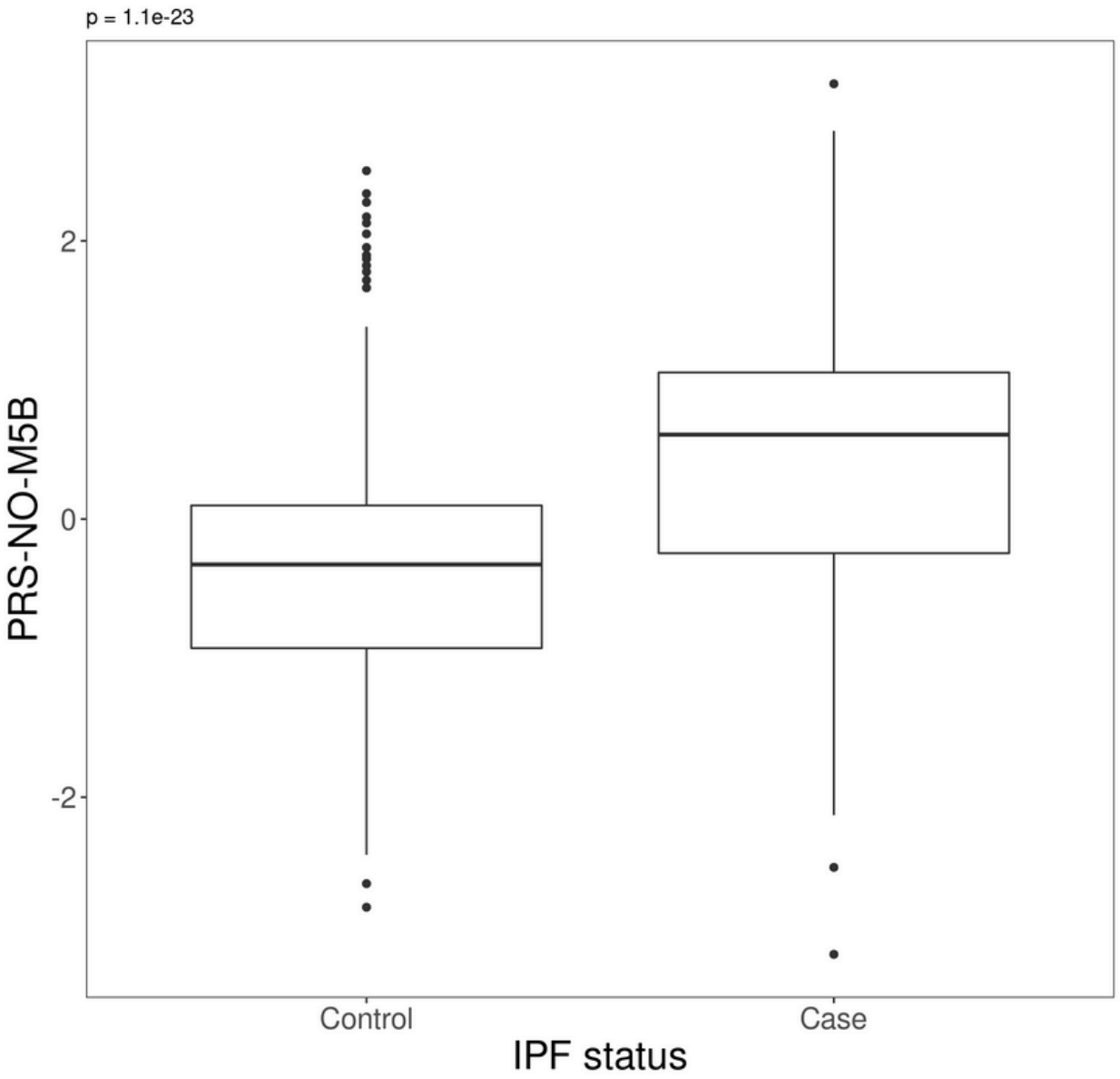
Train polygenic risk score (PRS) using lassosum (Mak et al, *Genet Epidemiol.* 2017) (PRS-NO-M5B)

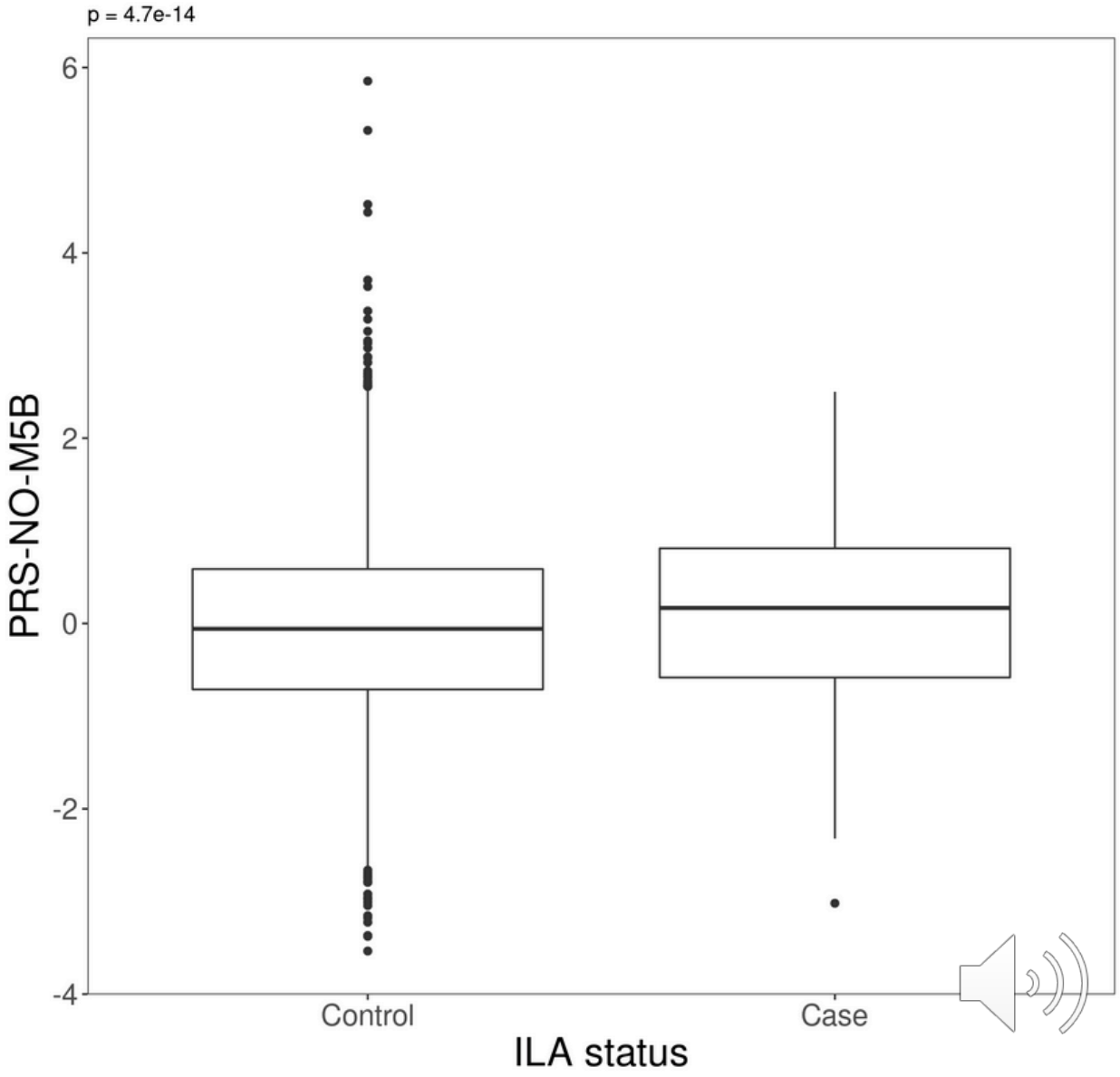
Train composite risk score of PRS+M5B using 10-fold cross-validation (100 bootstraps) in Lung Tissue Research Consortium (LTRC) IPF cases and controls

Test associations of PRS-NO-M5B, M5B, PRS+M5B with IPF in LTRC and ILA in Genetic Epidemiology of COPD (COPDGene) study. Covariates: age, sex, pack-years of smoking

Area-under-the-receiver-operating-curve (AUC) analyses
Quantify phenotypic variance (Nagelkerke R^2) analyses

PRS-NO-M5B is Associated With IPF and ILA



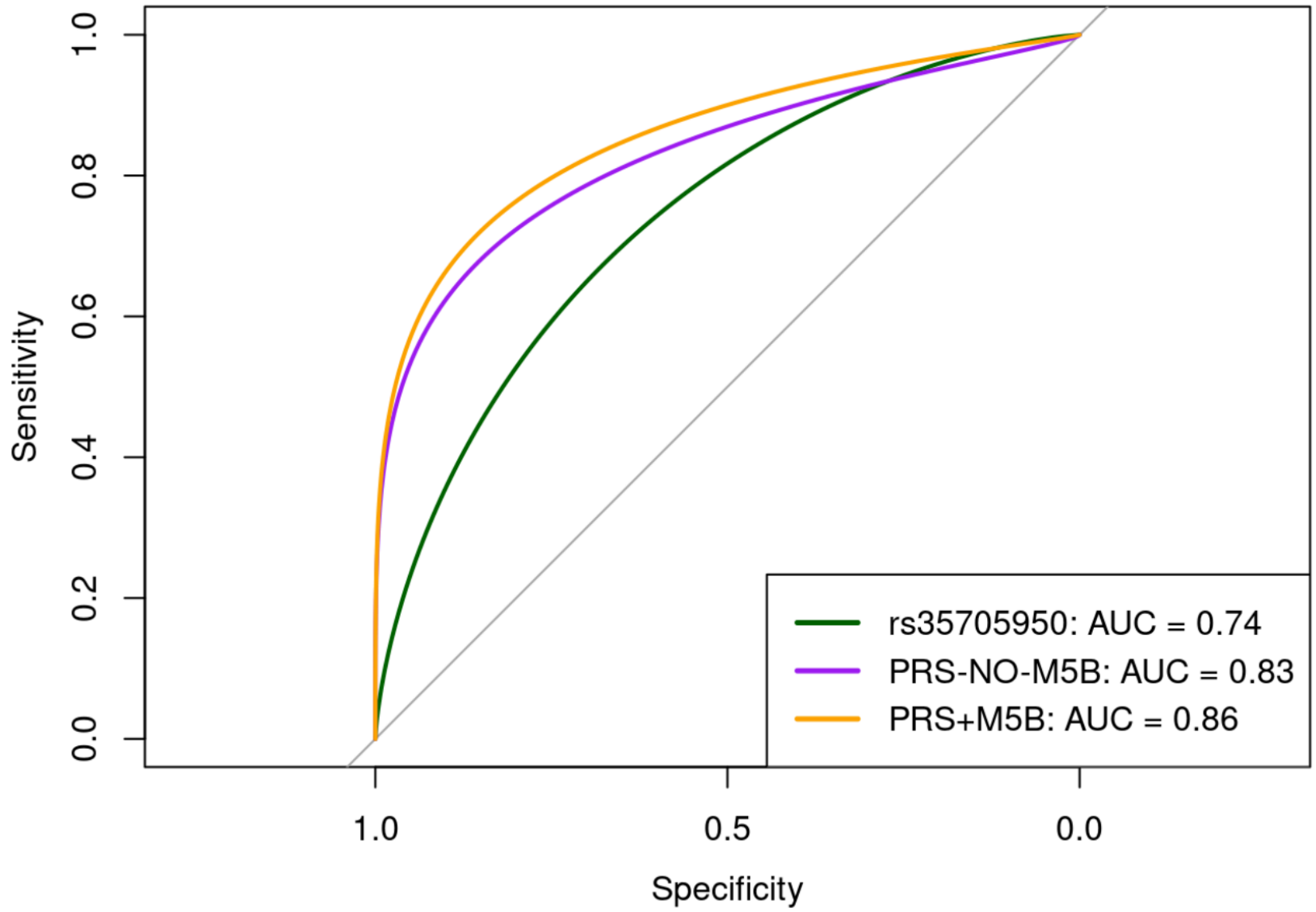


IPF PRS is Associated with IPF in LTRC

variable	Model 1		Model 2	
	adj. OR (95% CI)	p	adj. OR (95% CI)	p
PRS-NO-M5B	4.7 (3.2-6.8)	2.30E-15	NA	NA
rs35705950	3.6 (2.3-5.8)	7.00E-08	NA	NA
PRS-NO-M5B X rs35705950	0.87 (0.48 - 1.6)	0.66	NA	NA
PRS+M5B	NA	NA	18 (10 - 30)	5.00E-26

Model 1: PRS-NO-M5B, rs35705950, and interaction term, adjusted for age, sex, pack-years of smoking, and 10 principal components of genetic ancestry.
Model 2: PRS+M5B composite score, adjusted for age, sex, pack-years of smoking, and 10 principal components of genetic ancestry.

IPF PRS Predicts IPF in an External Cohort



IPF PRS is Associated with ILA in COPDGene

variable	adj. OR (95% CI)	p
PRS-NO-M5B	1.2 (1.1-1.3)	2.60E-03
rs35705950	2.4 (1.9-3.1)	6.30E-13
PRS+M5B	1.8 (1.4-2.2)	7.50E-08

Models adjusted for age, sex, pack-years of smoking and first 5 principal components of genetic ancestry.

Conclusions

- An IPF PRS exclusive of rs35705950 was complementary to rs35705950 predicting IPF, but not ILA
- IPF and ILA demonstrate overlapping, but not identical, polygenic risk
- Further investigation into the optimal modeling of the unusual genetic architecture of IPF is needed.