Global IPF Collaborative Network: a Platform for IPF Genetics

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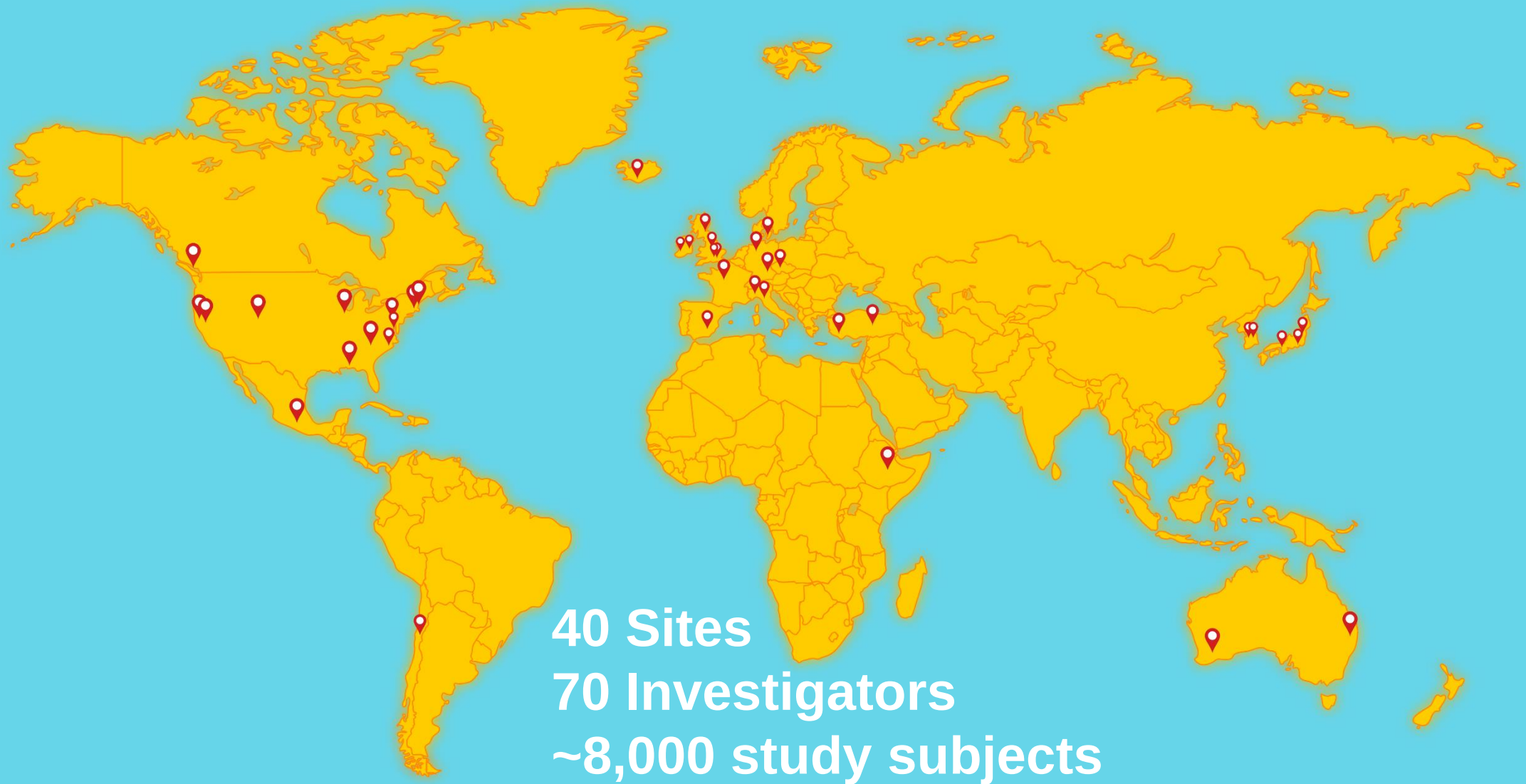
Global IPF Collaborative Network

- **Vision:** Further understand the genetics of IPF by collecting more than 10,000 ethnically diverse cases of IPF
  - Currently **30-40%** of the genetic risk of IPF is known in NHWs
- **Network**
  - >70 international investigators (40 sites)
  - Network members will participate in all publications
  - Network members have access to their site's genetic data

Global IPF Network Sites



U.S. Sites (N=14)

Institution	IPF samples w/ clinical data and DNA
National Jewish Hospital	246
Vanderbilt University	358
University of California San Francisco	508
Duke University	229
University of Pittsburgh	340
Inova Fairfax	19
Columbia University	113
University of Pennsylvania	351
University of Chicago	435
UC Davis	68
Brown University	23
University of Alabama Birmingham	7
Massachusetts General Hospital	9
Georgetown University	2

Total IPF Subjects w/ DNA: 7,793 (>1000 CT scans)

- **NHW – 71%**
- **Asian – 22%**
- **Hispanic – 3%**
- **African/AA – 1%**
- **Other/Unknown – 3%**

Outside U.S. Sites (N=26)

Institution	IPF samples w/ clinical data and DNA
University of Nottingham and Royal Brompton, UK	689
Bichat Hospital, Paris, France	153
University Hospital of Bellvitge, Spain	178
University of Western Australia	20
Cork University Hospital, Ireland	174
University of Edinburgh, Scotland	310
Landspitali Hospital, Iceland	86
National University of Ireland, Dublin	78
Helmholtz Zentrum München, Germany	109
University Medicine Essen - Ruhrlandklinik, Germany	53
Aarhus University Hospital, Denmark	123
Thomayer Hospital, Czech Republic	33
University of Genova, Italy	26
Ege University, Turkey	979
Gazi University, Turkey	15
GB Morgagni Hospital, Italy	107
University of British Columbia, Canada	30
Lung Foundation, Australia	129
Papworth Hospital, UK	147
National Inst. Respiratory Disease, Mexico	90
University of Chile	27
Tokyo National Hospital, Japan	43
Kini-Chuo Osaka, Japan	322
Tokyo Dental and Medical, Japan	57
Yonesi Severance Hospital, Korea	110
Asan Medical Center, Korea	997

ORIGINAL ARTICLE

Resequencing Study Confirms That Host Defense and Cell Senescence Gene Variants Contribute to the Risk of Idiopathic Pulmonary Fibrosis

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ORIGINAL ARTICLE

Idiopathic Pulmonary Fibrosis Is Associated with Common Genetic Variants and Limited Rare Variants

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ORIGINAL ARTICLE

A Polygenic Risk Score for Idiopathic Pulmonary Fibrosis and Interstitial Lung Abnormalities

Abstract

Rationale: In addition to rare genetic variants and the *MUC5B* locus, common genetic variants contribute to idiopathic pulmonary fibrosis (IPF) risk. The predictive power of common variants outside the *MUC5B* locus for IPF and interstitial lung abnormalities (ILAs) is unknown.

Objectives: We tested the predictive value of IPF polygenic risk scores (PRSs) with and without the *MUC5B* region on IPF, ILA, and ILA progression.

Methods: We developed PRSs that included (PRS-M5B) and excluded (PRS-NO-M5B) the *MUC5B* region (500-kb window around rs35705950-T) using an IPF genome-wide association study. We assessed PRS associations with area under the receiver operating characteristic curve (AUC) metrics for IPF, ILA, and ILA progression.

Measurements and Main Results: We included 14,650 participants (1,970 IPF; 1,068 ILA) from six multi-ancestry population-based and case–control cohorts. In cases excluded from genome-wide association study, the PRS-M5B (odds ratio [OR] per SD of the score, 3.1; $P = 7.1 \times 10^{-95}$) and PRS-NO-M5B (OR per SD, 2.8; $P = 2.5 \times 10^{-87}$) were associated with IPF. Participants in the top PRS-NO-M5B quintile had ~sevenfold odds for IPF compared with those in the first quintile. A clinical model predicted IPF (AUC, 0.61); rs35705950-T and PRS-NO-M5B demonstrated higher AUCs (0.73 and 0.7, respectively), and adding both genetic predictors to a clinical model yielded the highest performance (AUC, 0.81). The PRS-NO-M5B was associated with ILA (OR, 1.25) and ILA progression (OR, 1.16) in European ancestry participants.

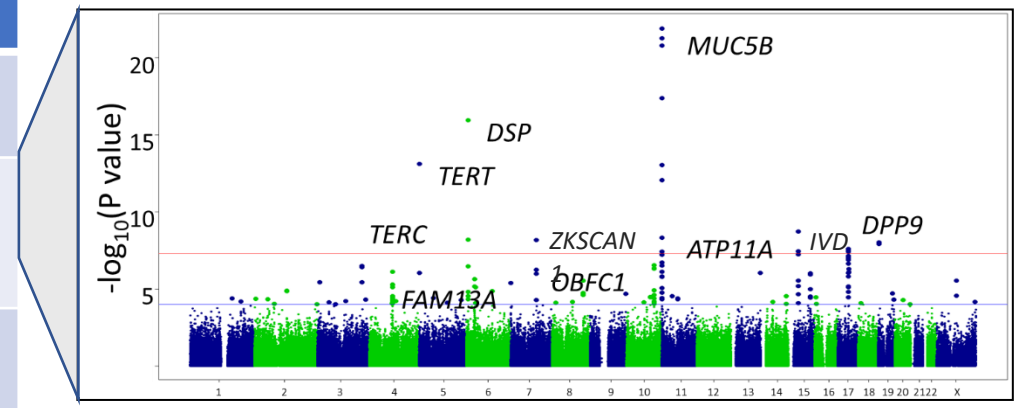
Conclusions: A common genetic variant risk score complements the *MUC5B* variant to identify individuals at high risk of interstitial lung abnormalities and pulmonary fibrosis.

Keywords: idiopathic pulmonary fibrosis; interstitial lung abnormalities; polygenic risk score; *MUC5B*

IPF GWAS
Among Asian Ancestries

Genome-wide association studies of IPF

Study	Population	Discovery Sample Size	Findings
Mushiroda, 2008	Japanese	159 cases 934 controls	*TERT*
Fingerlin, 2013	NHW	1,616 cases 4,683 controls	
Noth, 2013	NHW	542 cases 542 controls	11p15, 17q21
Fingerlin, 2016 *imputation*	NHW	1,616 cases 4,683 controls	DRB1*15:01, DQB1*06:02
Allen, 2017	NHW	602 cases 3,366 controls	*AKAP13*
Allen, 2020	NHW	Meta-analysis	*KIF15*, *MAD1L1*, *DEPTOR*



GWAS of IPF among Asian ancestry

Global IPF Network

- Asian countries (South Korea, Taiwan) report incidences of IPF, similar to that of European countries, on average
- The Global IPF Network has collected >2,700 samples from individuals of Asian ancestry, including IPF and control samples.
- Now possible to investigate genetics of IPF among Asians

- Are IPF risk variants in Asian patients shared/distinct from those in NHW populations?

GLOBAL IPF NETWORK

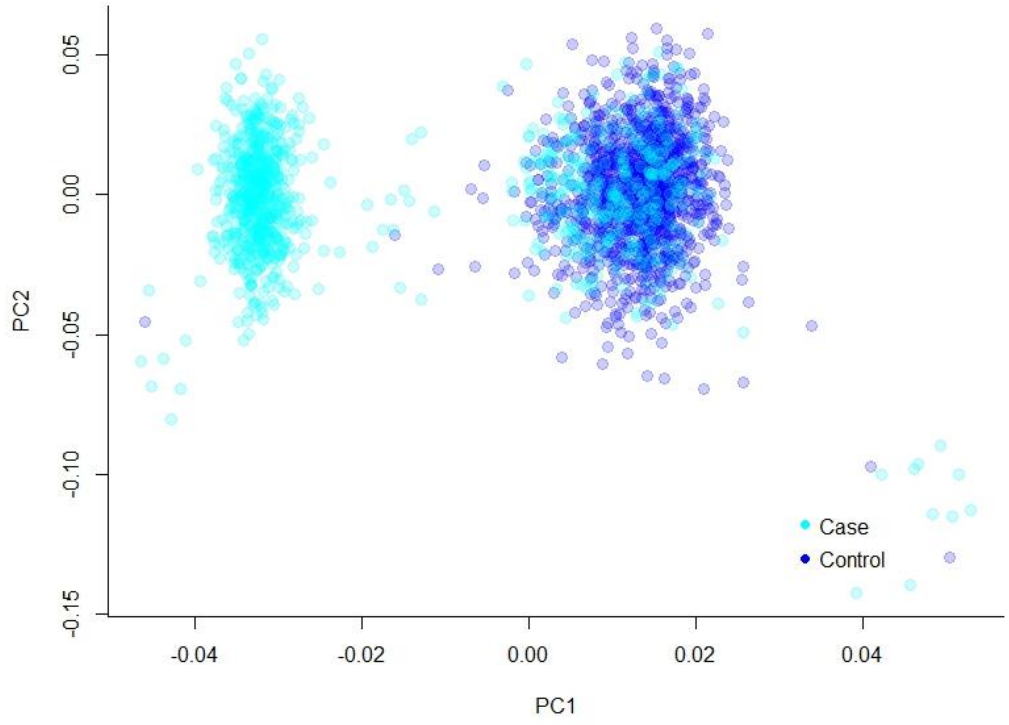
Asian study population from 2023

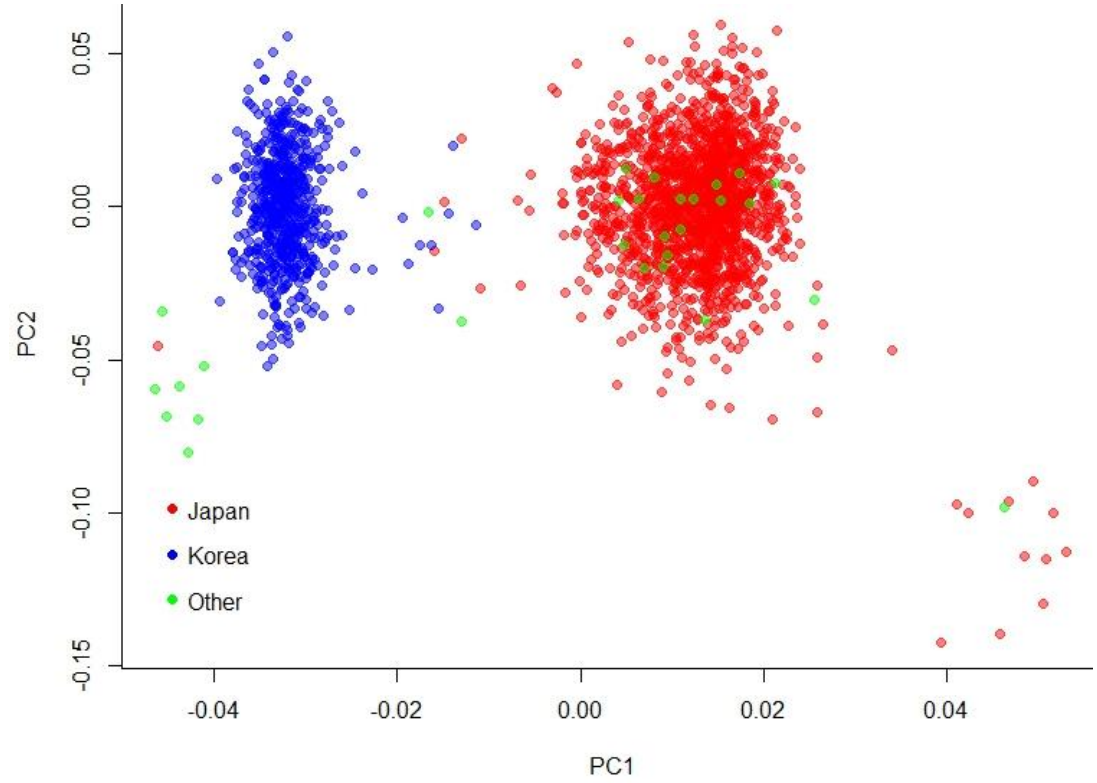
- Available IPF and controls samples, genotyped on MEGA chip

	Controls	Cases
Japanese	1262	341
Korean	1	628
Other-Asian	4	25

- Confounding between disease status and country of origin
  - ➢ Significant differences between cases and controls could be attributed to differences in genetic ancestry
  - ➢ **Examine PCs**

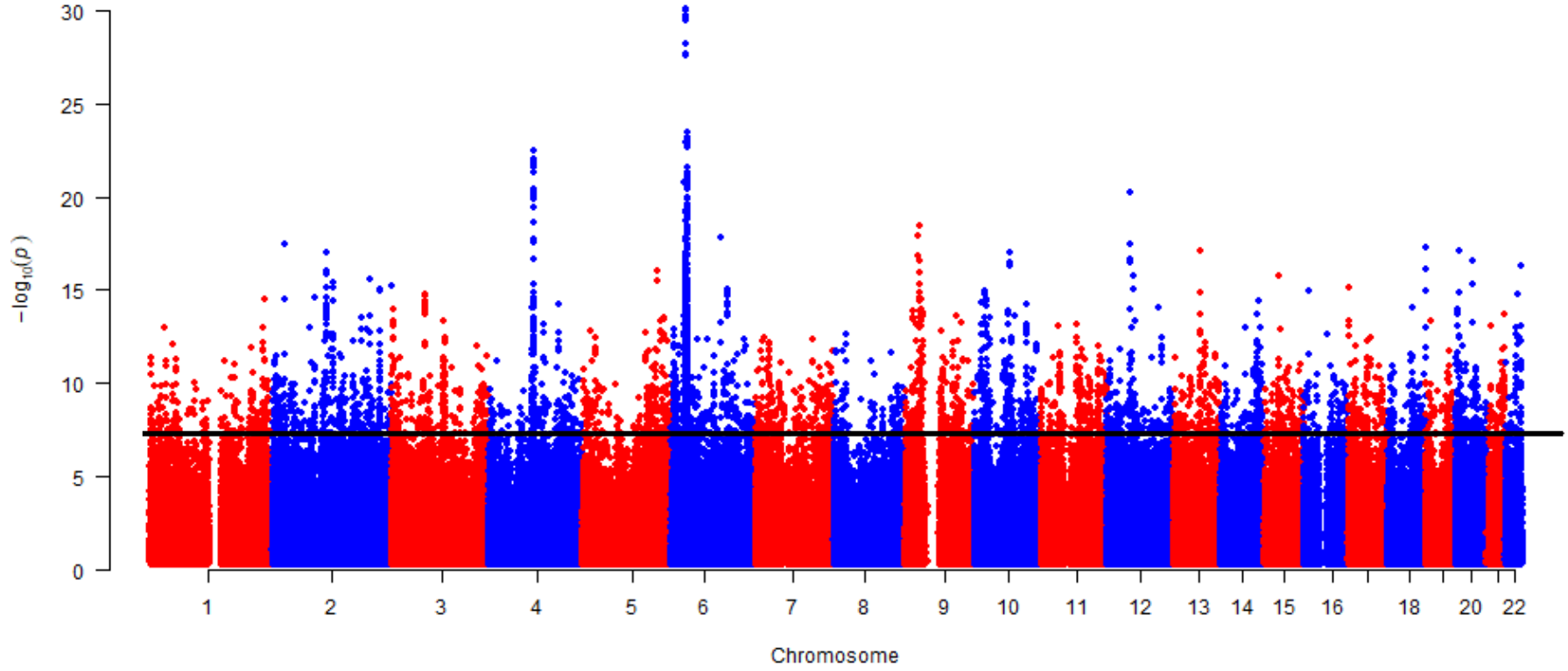
PCs show confounding between disease and genetic ancestry





GWAS Results

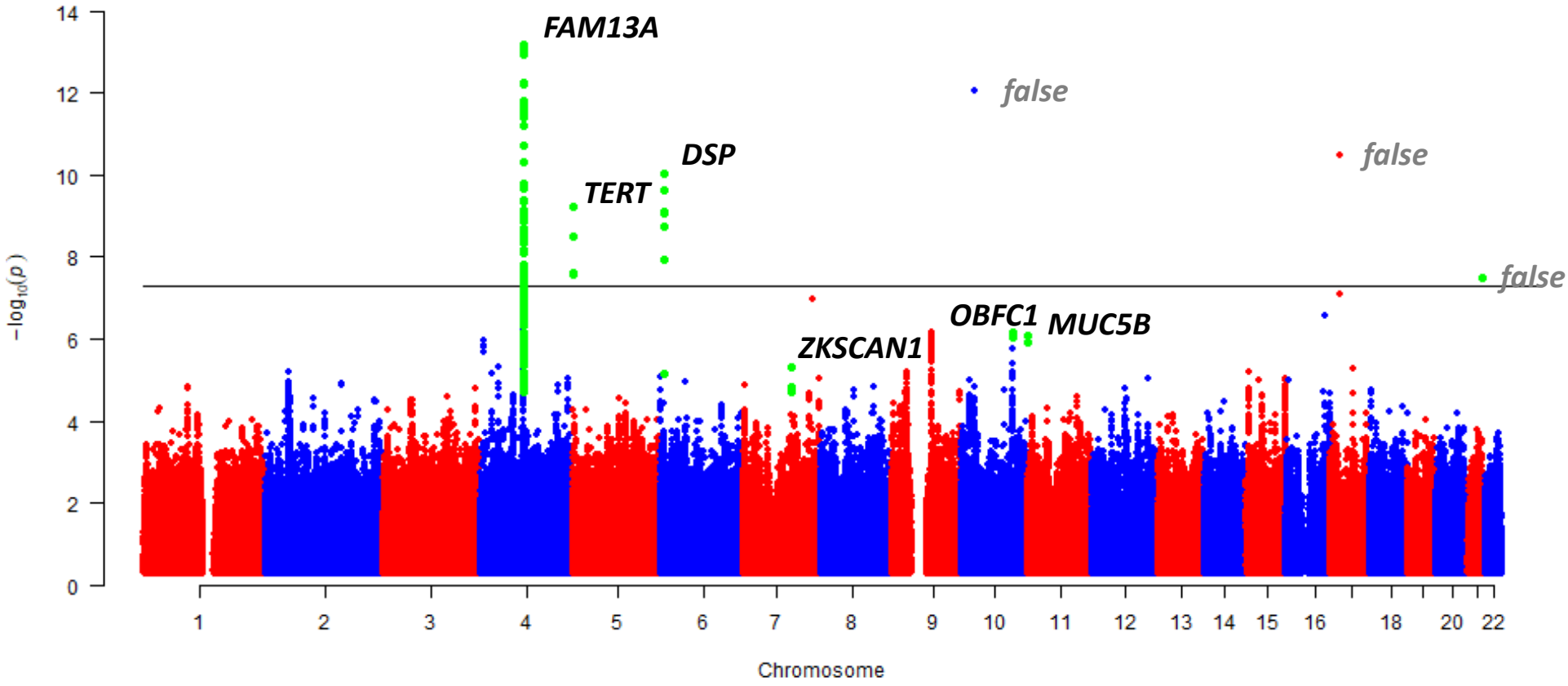
Korean and Japanese cohorts combined



- Excess genomic inflation

Meta-analysis

Adding external Korean controls

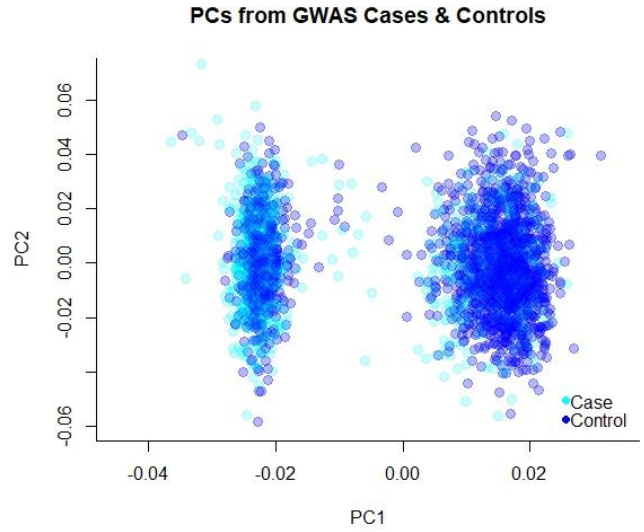


- Unable to differentiate false-positives vs. true positives

New meta-analysis

with internally genotyped Korean controls

- Genotyped ~500 additional Korean controls
- Combined with Japanese + Korean cases
- Imputed genotypes to 1000Genomes EAS population
- Japan + Korea meta-analysis

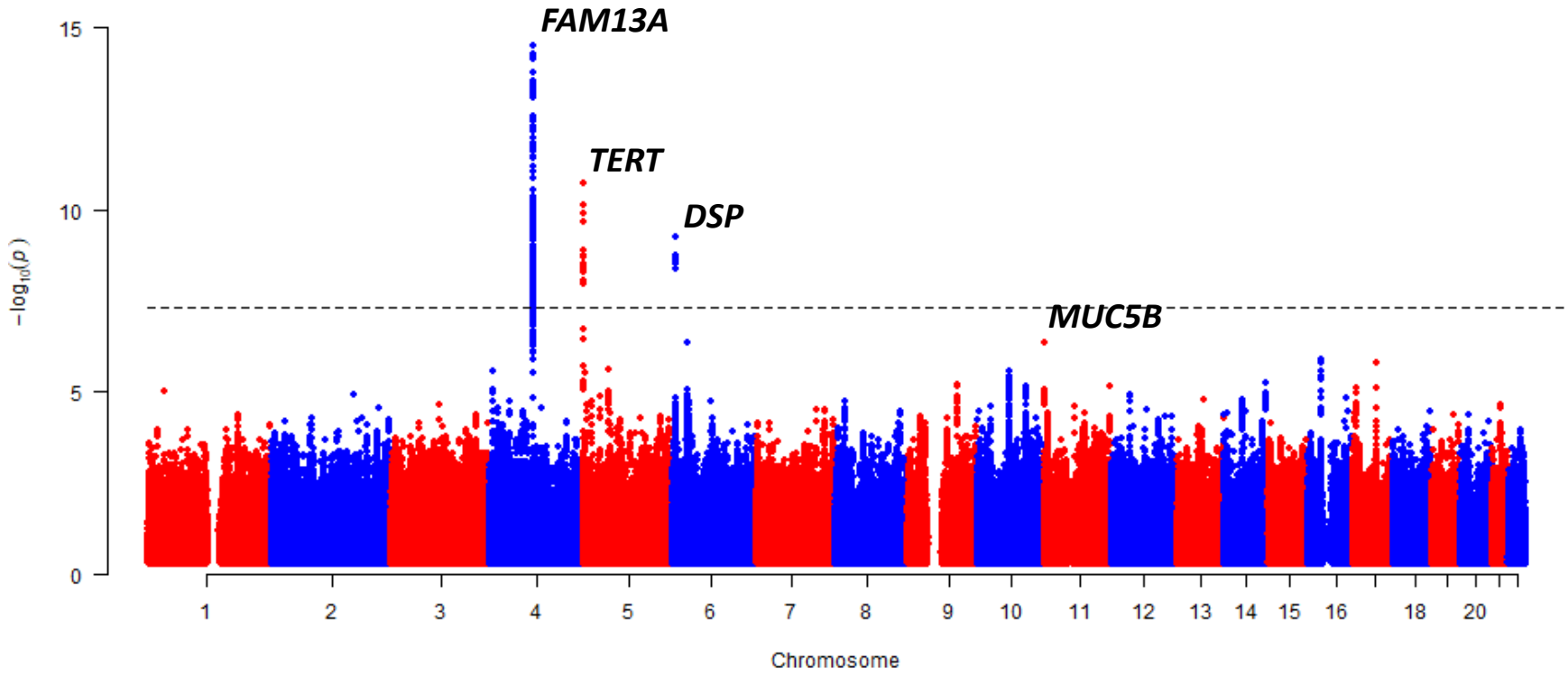


Final Study Cohorts

	Japanese		Korean	
	Case	**Control**	**Case**	**Controls**
N	359	1272	667	451
Female, N (%)	80 (22)	514 (40)	147 (22)	102 (23)
Age, Mean (SD)	70.1 (9.1)	38.5 (11.5)	65.9 (8.5)	50.7 (7.8)

New meta-analysis

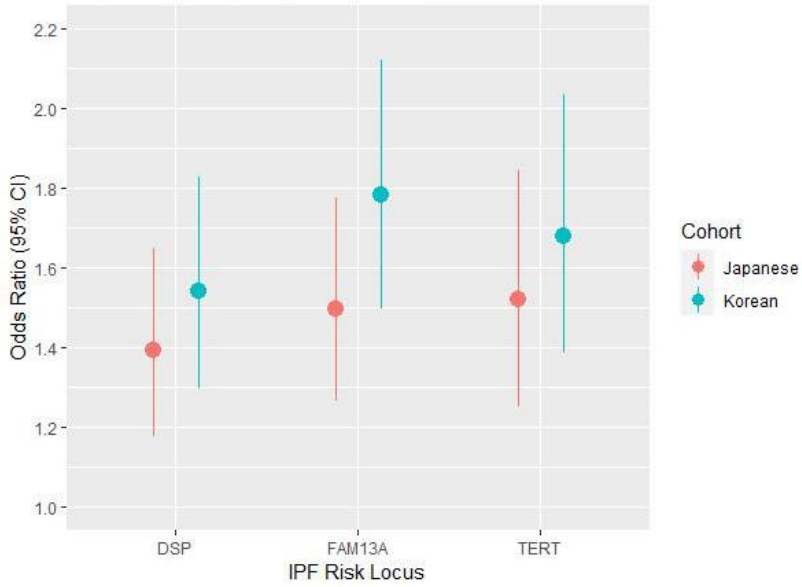
with internally genotyped Korean controls



Effects of significant SNPs

Gene	SNP	Position	Genotyped	P-value	OR, Meta	OR, Japan	OR, Korea
FAM13A	rs7690839	4:89819324	Imputed	3.2×10^{-15}	1.64	1.50 (1.26-1.77)	1.78 (1.50-2.12)
TERT	rs7734992	5:1280128	Imputed	1.9×10^{-11}	1.59	1.52 (1.25-1.85)	1.68 (1.39-2.04)
DSP	rs2076295	6:7563232	Genotyped	5.7×10^{-10}	1.47	1.39 (1.18-1.65)	1.54 (1.30-1.83)
MUC5B	rs35705950†	11:1241221	Taqman	3.5×10^{-8}		20.22 (6.95-58.9)	

† Sample size reduced, N=1,601



- Overlapping confidence intervals suggest similar effects among Japanese and Koreans
- Estimated effect sizes of SNPs appear generally higher for Korean cohort
- Differences may be due to case-control ratio, age, diagnosis/etiology

IPF risk variants identified in European populations

compared to Asian GWAS meta-analysis

			Japanese/Korean, GWAS Meta-analysis				European, Resequencing *	
Gene	**SNP**	**Position**	**Genotyped**	**P-value**	**OR**	**MAF in cases**	**OR**	**MAF in cases**
FAM13A	rs2609260†	4:89836819	Imputed	6.40×10^{-13}	1.56	0.52	1.35	0.23
TERT	rs4449583†	5:1284135	Imputed	4.364×10^{-09}	0.67	0.27	0.68	0.26
DSP	rs2076295	6:7563232	Genotyped	5.73×10^{-10}	1.47	0.60	1.27	0.54
MUC5B	rs35705950‡	11:1241221	Taqman	3.47×10^{-8}	20.22	0.03	5.45	0.35

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† Top SNP in Asian meta-analysis different from SNP in resequencing study (Moore et al., 2019)

‡ Sample size reduced, N=1,601

Conclusions & Next Steps

- IPF risk variants identified within Japanese/Korean and European populations are similar
- Variant effect sizes and allele frequencies among IPF patients are different

- Publication of manuscript is in progress
- *Please continue to share DNA from you patients from different genetic backgrounds so we can build on this research*

Thank you

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Global IPF Collaborators

Future Projects

- Determine the effect of ancestry (Hispanic and African/African American) on rare and common IPF gene variants
- Explore the relationship between the validated genetic variants and clinical/radiographic/pathologic phenotypes (≈1200 HRCT scans)
- Expand to RA-ILD and CHP