

## **Increased Airway Wall Thickness in Interstitial Lung Abnormalities and Idiopathic Pulmonary Fibrosis**

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### **Data Supplement**

**Table E1.** Association of Pi10 levels and effect modification by interstitial lung abnormality subtypes

Cohort	ILA Group	Subtype	N	Mean Pi10, mm (SD)	P-value*	P-value for the difference between groups†
COPDGene		No ILA	5375	3.66 (0.13)	-	-
	IPF HRCT imaging patterns‡	Inconsistent with UIP§	5783	3.74 (0.14)	<0.001	<0.001
		Indeterminate for UIP§	5563	3.71 (0.14)	<0.001	
		Probable UIP§	5464	3.67 (0.11)	0.64	
		UIP§	5390	3.72 (0.20)	0.07	
	Presence or absence of fibrosis	Fibrosis	5505	3.70 (0.14)	0.009	0.07
No fibrosis		5944	3.72 (0.14)	<0.001		
ECLIPSE		No ILA	473	3.94 (0.20)	-	-
	Presence or absence of fibrosis	Fibrosis	498	4.00 (0.17)	0.20	0.83
		No Fibrosis	590	3.99 (0.22)	0.04	
Framingham Heart Study		No ILA	1062	3.64 (0.22)	-	-
	IPF HRCT imaging patterns‡	Inconsistent with UIP§	1087	3.72 (0.20)	0.14	0.89
		Indeterminate for UIP§	1120	3.71 (0.26)	0.04	
		Probable UIP§	1082	3.74 (0.31)	0.04	
		UIP§	1064	3.73 (0.29)	0.79	
	Presence or absence of fibrosis	Fibrosis	1088	3.75 (0.29)	0.02	0.35
No fibrosis		1141	3.71 (0.25)	-		

\* P-values are for the comparison between those with and without ILA were ILA is limited to those with a particular subgroup.

† P-values represent a comparison between Pi10 and particular ILA subgroups limited to those with ILA. The p values for the IPF HRCT (Idiopathic pulmonary fibrosis high-resolution chest computed tomography) imaging patterns, and for those with and without fibrosis represent an ANOVA between groups.

‡ IPF HRCT (Idiopathic pulmonary fibrosis high-resolution chest computed tomography) imaging patterns: Represents the 2018 recommendations by the ATS/ERS/JRS/ALAT on the utilization of HRCT imaging to identify four IPF diagnostic categories.(1)

§ UIP: usual interstitial pneumonia.

||The presence or absence of fibrosis: Includes those with ILA with and without interstitial lung abnormalities limited to those with pulmonary parenchymal architectural distortion highly suggestive of a fibrotic lung disease.(2)

**Supplemental table E2a:** Association of interstitial lung abnormalities and individual airway characteristics in COPDGene.

<b>Model*</b>	<b>Airway</b>	<b>ILA Effect Measure (95%CI)</b>	<b>P-value</b>
Change in wall area (mm <sup>2</sup> )	Right Main Bronchus	0.98 (-0.39, 2.35)	0.16
Adjusted change in wall area (mm <sup>2</sup> ) <sup>†</sup>	Right Main Bronchus	2.25 (1.10, 3.39)	<0.001
Change in lumen area (mm <sup>2</sup> )	Right Main Bronchus	-0.01 (-1.85, 1.82)	0.99
Adjusted change in lumen area (mm <sup>2</sup> )	Right Main Bronchus	2.23 (0.75, 3.71)	0.003
Change in wall area percent <sup>‡</sup> (%)	Right Main Bronchus	0.17 (0.05, 0.29)	0.006
Adjusted change in wall area percent <sup>‡</sup> (%)	Right Main Bronchus	0.11 (-0.01, 0.23)	0.08
Change in wall area (mm <sup>2</sup> )	RUL Bronchus	-0.01 (-0.98, 0.95)	0.98
Adjusted change in wall area (mm <sup>2</sup> )	RUL Bronchus	0.62 (-0.30, 1.55)	0.19
Change in lumen area (mm <sup>2</sup> )	RUL Bronchus	-0.53 (-2.16, 1.09)	0.52
Adjusted change in lumen area (mm <sup>2</sup> )	RUL Bronchus	0.57 (-1.04, 2.18)	0.49
Change in wall area percent (%)	RUL Bronchus	0.14 (-0.05, 0.32)	0.15
Adjusted change in wall area percent (%)	RUL Bronchus	-0.01 (-0.19, 0.17)	0.90
Change in wall area (mm <sup>2</sup> )	RUL Apical Segment	0.42 (0.03, 0.8)	0.03
Adjusted change in wall area (mm <sup>2</sup> )	RUL Apical Segment	0.68 (0.31, 1.04)	0.0003
Change in lumen area (mm <sup>2</sup> )	RUL Apical Segment	0.22 (-0.21, 0.66)	0.32
Adjusted change in lumen area (mm <sup>2</sup> )	RUL Apical Segment	0.62 (0.19, 1.04)	0.005
Change in wall area percent (%)	RUL Apical Segment	0.19 (0.02, 0.36)	0.03
Adjusted change in wall area percent (%)	RUL Apical Segment	-0.03 (-0.19, 0.13)	0.73
Change in wall area (mm <sup>2</sup> )	Right Intermediate Bronchus	0.61 (-0.06, 1.28)	0.08
Adjusted change in wall area (mm <sup>2</sup> )	Right Intermediate Bronchus	1.09 (0.58, 1.60)	<0.001
Change in lumen area (mm <sup>2</sup> )	Right Intermediate Bronchus	0.65 (-0.40, 1.69)	0.23
Adjusted change in lumen area (mm <sup>2</sup> )	Right Intermediate Bronchus	1.54 (0.73, 2.34)	<0.001
Change in wall area percent (%)	Right Intermediate Bronchus	0.05 (-0.8, 0.17)	0.45
Adjusted change in wall area percent (%)	Right Intermediate Bronchus	-0.2 (-0.14, 0.10)	0.73
Change in wall area (mm <sup>2</sup> )	RML Lateral Segment	0.57 (0.27, 0.86)	<0.001
Adjusted change in wall area (mm <sup>2</sup> )	RML Lateral Segment	0.71 (0.44, 0.99)	<0.001
Change in lumen area (mm <sup>2</sup> )	RML Lateral Segment	0.19 (-0.07, 0.46)	0.15

Adjusted change in lumen area (mm <sup>2</sup> )	RML Lateral Segment	0.38 (0.13, 0.63)	0.003
Change in wall area percent (%)	RML Lateral Segment		
Adjusted change in wall area percent (%)	RML Lateral Segment	0.07 (-0.06, 0.02)	0.3
Change in wall area (mm <sup>2</sup> )	RLL Bronchus	-0.002 (-0.41, 0.41)	0.99
Adjusted change in wall area (mm <sup>2</sup> )	RLL Bronchus	0.41 (0.05, 0.77)	0.03
Change in lumen area (mm <sup>2</sup> )	RLL Bronchus	-0.30 (-0.88, 0.28)	0.31
Adjusted change in lumen area (mm <sup>2</sup> )	RLL Bronchus	0.3 (-0.25, 0.85)	0.28
Change in wall area percent (%)	RLL Bronchus	0.15 (-0.04, 0.33)	0.11
Adjusted change in wall area percent (%)	RLL Bronchus	-0.02 (-0.19, 0.15)	0.82
Change in wall area (mm <sup>2</sup> )	RLL Posterior Basal Segment	0.49 (0.16, 0.81)	0.004
Adjusted change in wall area (mm <sup>2</sup> )	RLL Posterior Basal Segment	0.68 (0.37, 0.98)	<0.001
Change in lumen area (mm <sup>2</sup> )	RLL Posterior Basal Segment	0.14 (-0.25, 0.53)	0.49
Adjusted change in lumen area (mm <sup>2</sup> )	RLL Posterior Basal Segment	0.47 (0.09, 0.84)	0.02
Change in wall area percent (%)	RLL Posterior Basal Segment	0.20 (0.04, 0.36)	0.02
Adjusted change in wall area percent (%)	RLL Posterior Basal Segment	0.0003 (-0.15, 0.15)	0.99
Change in wall area (mm <sup>2</sup> )	Left Main Bronchus	0.46 (-0.43, 1.36)	0.31
Adjusted change in wall area (mm <sup>2</sup> )	Left Main Bronchus	1.42 (0.68, 2.16)	<0.001
Change in lumen area (mm <sup>2</sup> )	Left Main Bronchus	0.12 (-1.20, 1.44)	0.86
Adjusted change in lumen area (mm <sup>2</sup> )	Left Main Bronchus	1.85 (0.84, 2.86)	<0.001
Change in wall area percent (%)	Left Main Bronchus	0.11 (-0.02, 0.25)	0.11
Adjusted change in wall area percent (%)	Left Main Bronchus	0.007 (-0.12, 0.14)	0.91
Change in wall area (mm <sup>2</sup> )	LUL Bronchus	-0.79 (-1.61, 0.02)	0.06
Adjusted change in wall area (mm <sup>2</sup> )	LUL Bronchus	0.26 (-0.50, 1.02)	0.50
Change in lumen area (mm <sup>2</sup> )	LUL Bronchus	-1.37 (-2.62, -0.13)	0.03
Adjusted change in lumen area (mm <sup>2</sup> )	LUL Bronchus	0.23 (-0.95, 1.42)	0.70
Change in wall area percent (%)	LUL Bronchus	0.23 (0.05, 0.41)	0.01
Adjusted change in wall area percent (%)	LUL Bronchus	0.07 (-0.10, 0.24)	0.41
Change in wall area (mm <sup>2</sup> )	LUL Apicoposterior Segment	0.32 (0.01, 0.63)	0.04
Adjusted change in wall area (mm <sup>2</sup> )	LUL Apicoposterior Segment	0.57 (0.28, 0.86)	<0.001
Change in lumen area (mm <sup>2</sup> )	LUL Apicoposterior Segment	0.10 (-0.15, 0.35)	0.42

Adjusted change in lumen area (mm <sup>2</sup> )	LUL Apicoposterior Segment	0.40 (0.17, 0.64)	<0.001
Change in wall area percent (%)	LUL Apicoposterior Segment	0.15 (0.008, 0.30)	0.04
Adjusted change in wall area percent (%)	LUL Apicoposterior Segment	-0.05 (-0.18, 0.08)	0.47
Change in wall area (mm <sup>2</sup> )	LUL Superior Lingular Segment	0.42 (0.11, 0.73)	0.009
Adjusted change in wall area (mm <sup>2</sup> )	LUL Superior Lingular Segment	0.58 (0.28, 0.88)	<0.001
Change in lumen area (mm <sup>2</sup> )	LUL Superior Lingular Segment	0.08 (-0.19, 0.34)	0.57
Adjusted change in lumen area (mm <sup>2</sup> )	LUL Superior Lingular Segment	0.33 (0.07, 0.58)	0.01
Change in wall area percent (%)	LUL Superior Lingular Segment	0.20 (0.05, 0.34)	0.008
Adjusted change in wall area percent (%)	LUL Superior Lingular Segment	0.006 (-0.13, 0.14)	0.93
Change in wall area (mm <sup>2</sup> )	LLL Bronchus	0.11 (-0.32, 0.54)	0.62
Adjusted change in wall area (mm <sup>2</sup> )	LLL Bronchus	0.73 (0.36, 1.10)	<0.001
Change in lumen area (mm <sup>2</sup> )	LLL Bronchus	-0.39 (-1.01, 0.22)	0.21
Adjusted change in lumen area (mm <sup>2</sup> )	LLL Bronchus	0.69 (0.12, 1.25)	0.02
Change in wall area percent (%)	LLL Bronchus	0.25 (0.07, 0.43)	0.007
Adjusted change in wall area percent (%)	LLL Bronchus	-0.009 (-0.18, 0.16)	0.92
Change in wall area (mm <sup>2</sup> )	LLL Posterior Basal Segment	0.41 (0.07, 0.75)	0.02
Adjusted change in wall area (mm <sup>2</sup> )	LLL Posterior Basal Segment	0.70 (0.39, 1.01)	<0.001
Change in lumen area (mm <sup>2</sup> )	LLL Posterior Basal Segment	0.10 (-0.29, 0.50)	0.61
Adjusted change in lumen area (mm <sup>2</sup> )	LLL Posterior Basal Segment	0.57 (0.20, 0.95)	0.003
Change in wall area percent (%)	LLL Posterior Basal Segment	0.12 (-0.05, 0.29)	0.15
Adjusted change in wall area percent (%)	LLL Posterior Basal Segment	-0.11 (-0.27, 0.04)	0.16

ILA are interstitial lung abnormalities: RUL is right upper lobe; RML is right middle lobe; RLL is right lower lobe; LUL is left upper lobe; LLL is left lower lobe.

\* Models are univariable/multivariable models assessing the effect of ILA (present vs. not present) on changes in individual airway wall area in mm<sup>2</sup>, airway lumen area in mm<sup>2</sup>, and wall area percent.

†All adjusted models adjusted for: Age, Gender, Race, BMI, Pack Years Smoked, Smoking Status, Gold Stage, and Total Lung Capacity Percent Predicted

‡Wall area percent refers to the ratio of wall area to total bronchial area.

**Supplemental table E2b:** Association of interstitial lung abnormalities and individual airway characteristics in Framingham Heart Study.

Model*	Airway	ILA Effect Measure (95%CI)	P-value
Change in wall area (mm <sup>2</sup> )	RUL Generation 3	0.585 (-0.328, 1.500)	0.21
Adjusted change in wall area (mm <sup>2</sup> ) <sup>†</sup>	RUL Generation 3	0.713 (-0.257, 1.683)	0.15
Change in lumen area (mm <sup>2</sup> )	RUL Generation 3	0.843 (-0.632, 2.318)	0.26
Adjusted change in lumen area (mm <sup>2</sup> )	RUL Generation 3	0.851 (-0.703, 2.405)	0.28
Change in wall area percent <sup>‡</sup> (%)	RUL Generation 3	-0.321 (-1.436, 0.795)	0.57
Adjusted change in wall area percent (%)	RUL Generation 3	-0.466 (-1.622, 0.690)	0.43
Change in wall area (mm <sup>2</sup> )	RUL Generation 4	1.273 (0.651, 1.895)	<0.001
Adjusted change in wall area (mm <sup>2</sup> )	RUL Generation 4	1.194 (0.535, 1.852)	<0.001
Change in lumen area (mm <sup>2</sup> )	RUL Generation 4	1.580 (0.647, 2.514)	<0.001
Adjusted change in lumen area (mm <sup>2</sup> )	RUL Generation 4	1.353 (0.368, 2.339)	0.007
Change in wall area percent (%)	RUL Generation 4	-1.250 (-2.509, 0.010)	0.052
Adjusted change in wall area percent (%)	RUL Generation 4	-1.016 (-2.338, 0.305)	0.13
Change in wall area (mm <sup>2</sup> )	RLL Generation 3	0.701 (0.050, 1.351)	0.04
Adjusted change in wall area (mm <sup>2</sup> )	RLL Generation 3	0.673 (0.031, 1.315)	0.04
Change in lumen area (mm <sup>2</sup> )	RLL Generation 3	-0.408 (-1.650, 0.833)	0.52
Adjusted change in lumen area (mm <sup>2</sup> )	RLL Generation 3	-0.081 (-1.332, 1.170)	0.90
Change in wall area percent (%)	RLL Generation 3	1.457 (0.378, 2.537)	0.008
Adjusted change in wall area percent (%)	RLL Generation 3	0.952 (-0.148, 2.052)	0.09
Change in wall area (mm <sup>2</sup> )	RLL Generation 4	0.663 (0.010, 1.316)	0.047
Adjusted change in wall area (mm <sup>2</sup> )	RLL Generation 4	0.676 (0.003, 1.350)	0.049
Change in lumen area (mm <sup>2</sup> )	RLL Generation 4	0.104 (-1.043, 1.252)	0.86
Adjusted change in lumen area (mm <sup>2</sup> )	RLL Generation 4	0.234 (-0.956, 1.423)	0.70
Change in wall area percent (%)	RLL Generation 4	1.059 (-0.157, 2.275)	0.09
Adjusted change in wall area percent (%)	RLL Generation 4	0.772 (-0.496, 2.040)	0.23

ILA are interstitial lung abnormalities; RUL is right upper lobe; RML is right middle lobe; RLL is right lower lobe; LUL is left upper lobe; LLL is left lower lobe.

\* Models are univariable/multivariable models assessing the effect of ILA (present vs. not present) on changes in individual airway wall area in mm<sup>2</sup>, airway lumen area in mm<sup>2</sup>, and wall area percent.

† All adjusted models adjusted for: Age, Gender, Race, BMI, Pack Years Smoked, Smoking Status, and Total Lung Capacity Percent Predicted.

‡ Wall area percent refers to the ratio of wall area to total bronchial area.



## References:

1. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S, Wilson KC, American Thoracic Society ERSJRS, Latin American Thoracic S. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018; 198: e44-e68.
2. Hunninghake GM, Hatabu H, Okajima Y, Gao W, Dupuis J, Latourelle JC, Nishino M, Araki T, Zazueta OE, Kurugol S, Ross JC, San Jose Estepar R, Murphy E, Steele MP, Loyd JE, Schwarz MI, Fingerlin TE, Rosas IO, Washko GR, O'Connor GT, Schwartz DA. MUC5B promoter polymorphism and interstitial lung abnormalities. *N Engl J Med* 2013; 368: 2192-2200.