Idiopathic Bronchiectasis and Connective Tissue Fibrillinopathies: Dural Ectasia as a Marker of a Distinct Bronchiectasis Subgroup

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Background

- Bronchiectasis: airway dilation, increased infections
  - Occurs in cystic fibrosis (CF) & primary ciliary dyskinesia (PCD)
- Idiopathic bronchiectasis (IB): unknown cause
  - Prevalence up to 271.8/100,000 in US
  - Seen in RML, lingula, lower lobes
- Dural ectasia: dural sac dilation → large spinal canal.
  - Detected in lower thoracic & lumbar spine with CT or MRI
- Present in "fibrillinopathies", eg Marfan, Ehlers-Danlos, Loeys-Dietz
  - Not seen in absence of NF1, ankylosing spondylitis, scoliosis, tumor
  - No gender difference in prevalence, severity.
- Spinal canal dimensions published but not validated.

Phenotypic Connection

Bronchiectasis & NTM

- "Lady Windermere":
  - tall, slender; predominantly female
  - often with scoliosis, pectus, & mitral valve prolapse
- Anatomy and impaired structural integrity → distorted tissue organization, impaired mucociliary clearance
- Mutations unknown

Marfan Syndrome (Fibrillinopathies)

- Manifestations in heart, skeleton, eyes, lung
- Lung disease due to weak supporting tissue framework
  - Spontaneous pneumothorax, emphysema, occasional bronchiectasis
- Autosomal dominant with mutations in fibrillin-1, TGFBR1, TGFBR2
  - Fibrillin polymers form organ specific structural matrix, interact with elastin protein

Hypothesis

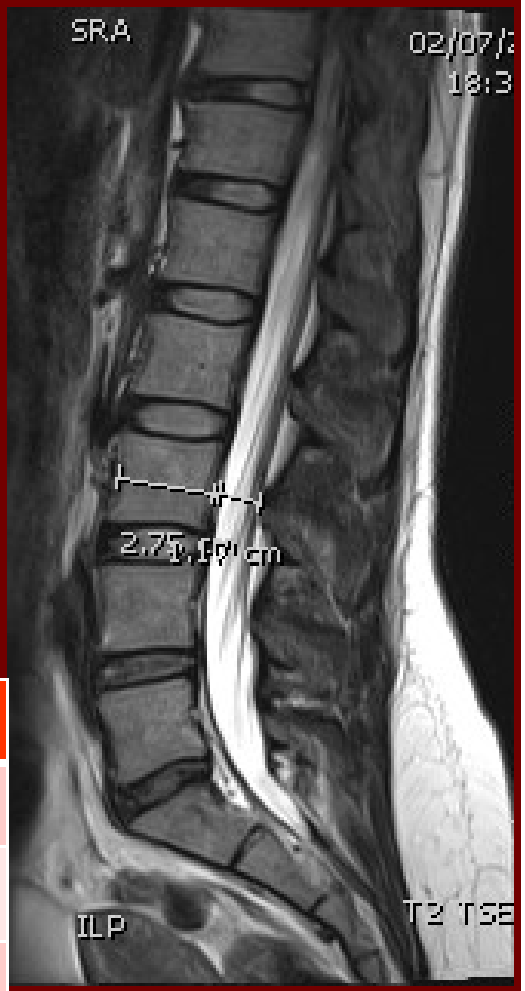
- **Aha moment**: Our stellar chest radiologist notices enlarged dural sac at L1 on chest CTs from IB patients
- IB patients have similar body structure phenotypes (pectus, scoliosis) to Marfan.
- Lung disease in fibrillinopathy patients raises question of shared variation in structural tissue genes.
- Hypothesis: IB patients have an increased prevalence of dural ectasia compared to patients with bronchiectasis with known cause (CF, PCD) & non-bronchiectasis control subjects

Study Design

- Standard non-contrast MR of thoraco-lumbar spine on 1.5T MR scanner.
- Three reviewers blinded to diagnosis
  - DSD measured at L1 to S1 midcorpus level in AP plane
- Other variables collected:
  - Height, weight, arm span
  - Presence & degree of scoliosis, pectus abnormalities, other skeletal abnormalities, mitral valve prolapse

Development of Methods in Control (Non-Bronchiectasis) Subjects

- Undergoing abdominal or lumbar MRI for medical reason (N=45)
- Measure AP dural sac diameter (DSD) perpendicular to long axis of dural sac at midcorpus level from L1 to S1
- Not influenced by age, gender, height
- Reproducible by 3 reviewers



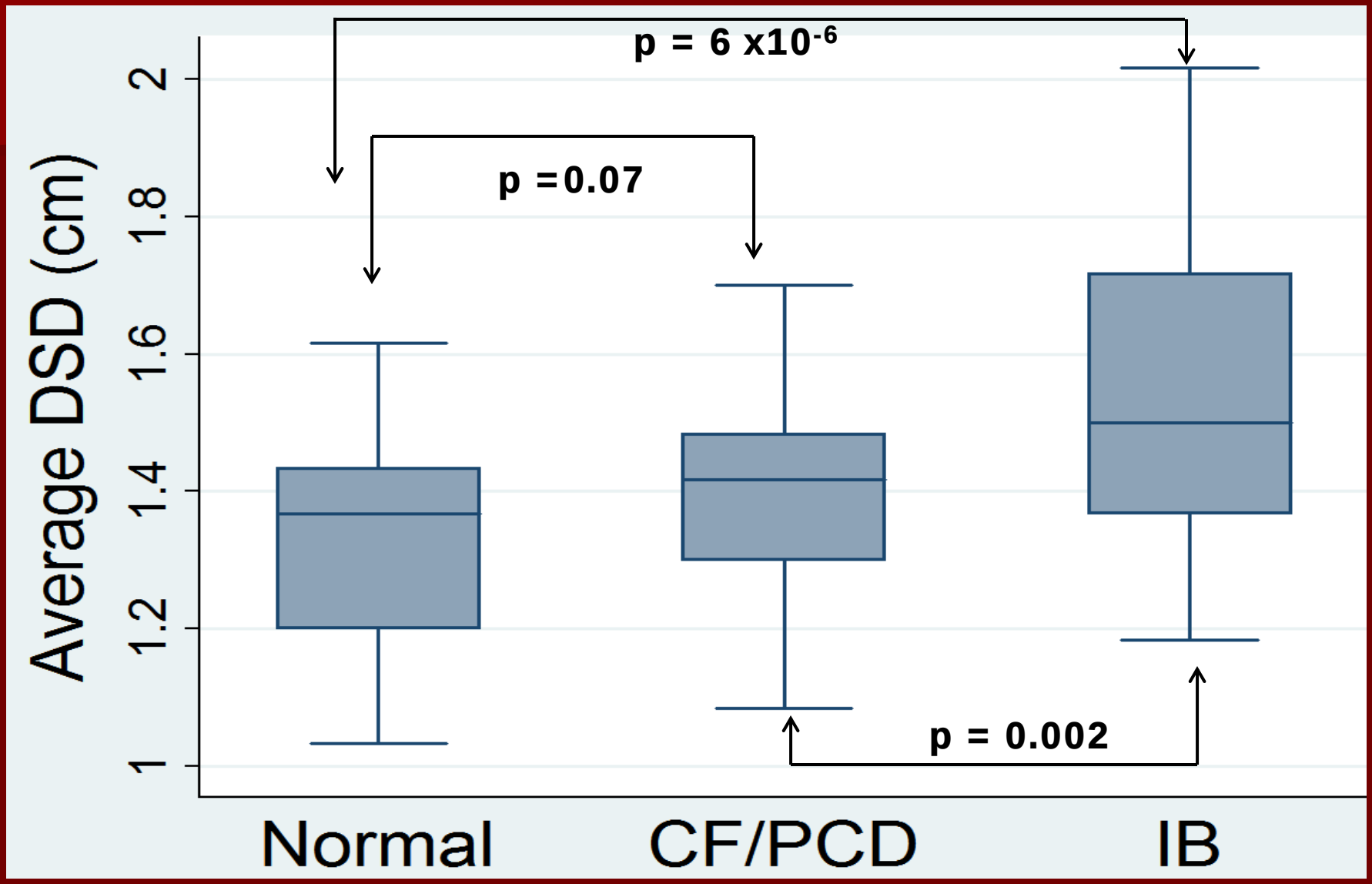
	Males	Females
Number	19	26
Average Age (range)	45 (19-83)	43.7 (18-81)
Average Height [cm] (range)	178.1 (162.6 – 188.0)	161.3 (147.3 – 172.7)

Bronchiectasis Study Subjects

- IB and disease controls (PCD, CF) identified from our GDMCC participants, UNC CF & Pulmonary Center, & Bronchiectasis Research Registry.
- Exclusion: < age 18, severe scoliosis, spine surgery, vertebral body injury, contraindication to MRI.

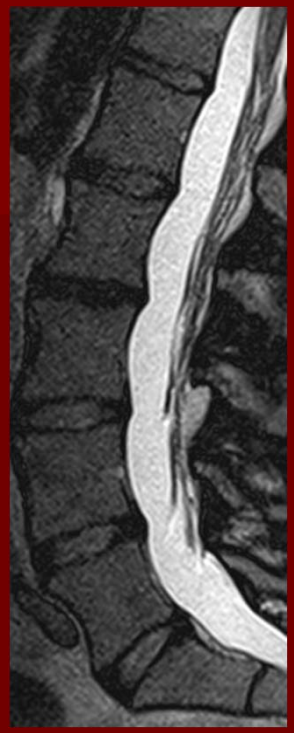
	Non-bronchiectasis Control	Idiopathic Bronchiectais	Primary Ciliary Dyskinesia	Cystic Fibrosis
Number	45	28	28	13
Gender	F=26, M=19	F=24, M=4	F=23, M=5	F=8, M=5
Age (range)	44 (18 – 83)	54.6 (21 – 82)	34.7 (18 – 53)	31.8 (19 – 48)
Height [cm] (range)	164.5 (147.3 – 188)	163.7 (149.5 – 187.6)	167.6 (150 – 183.4)	162.9 (149 – 180)

Dural Sac Diameter Measurements

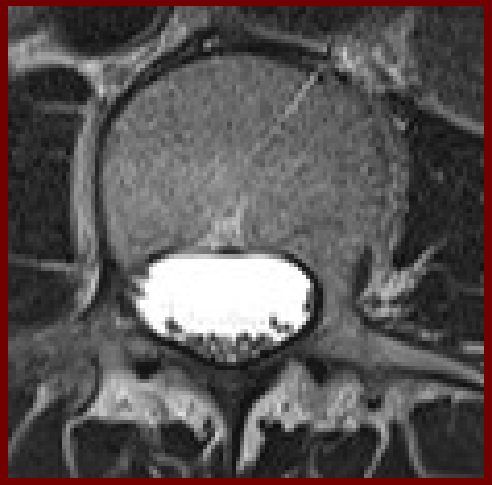


Non-bronchiectasis

Idiopathic bronchiectasis



Marfan



IB Subjects Phenotypes Ranked by DSD

- Compared prevalence of pectus abnormality or scoliosis in patients with DSD above the non-bronchiectasis mean to those below the mean (p=0.05)

Non-Bronchiectasis Mean 1.335

Age at Time of Scan	Gender	Race	Ethnicity	Average DSD	Pectus Abnormality	Scoliosis
72	F	C	Non-H	**2.01667**	No	Yes
63	F	C	Non-H	**2**	Yes	No
68	F	C	Non-H	**1.91667**	Yes	Yes
58	F	C	Non-H	**1.88333**	Yes	No
41	F	C	Non-H	**1.85**	No	Yes
82	F	C	Non-H	**1.8**	No	No
81	M	C	Non-H	**1.71667**	No	No
56	F	C	Non-H	**1.71667**	No	No
29	M	C	Non-H	**1.66667**	No	No
72	F	C	Non-H	**1.58333**	Yes	No
69	M	AA	Non-H	**1.56667**	No	Yes
58	F	C	Non-H	**1.55**	Yes	No
43	F	C	Non-H	**1.51667**	Yes	No
62	F	C	Non-H	**1.5**	No	Yes
55	F	C	UNK	**1.5**	No	No
64	F	C	Non-H	**1.48333**	No	No
68	F	C	Non-H	**1.46667**	No	Yes
59	F	C	Non-H	**1.41667**	No	No
46	F	C	Non-H	**1.4**	No	No
63	M	C	Non-H	**1.38333**	No	No
41	F	C	Non-H	**1.38333**	No	No
23	F	NA	Non-H	**1.36667**	No	Yes
21	F	NA	Non-H	**1.35**	No	No
64	F	C	Non-H	**1.31667**	No	No
31	F	C	Non-H	**1.31667**	No	No
59	F	C	Non-H	**1.31667**	No	No
18	F	NA	Non-H	**1.23333**	No	No
63	F	C	Non-H	**1.18333**	No	No

Further Analysis and Direction

- Test for associations between dural ectasia & other pertinent clinical phenotypes
- Extend principle to see if differences in dural ectasia in IB can be detected in lower thoracic spine on chest CTs.
- Pilot study of genetic variation: 30 candidate genes (exome sequence data) in 24 IB & 24 PCD patients
- Link genetic variation in patients with IB & dural ectasia, as well as other clinical phenotypes such as scoliosis, pectus, mitral valve prolapse, joint hypermobility

Thanks to . . .

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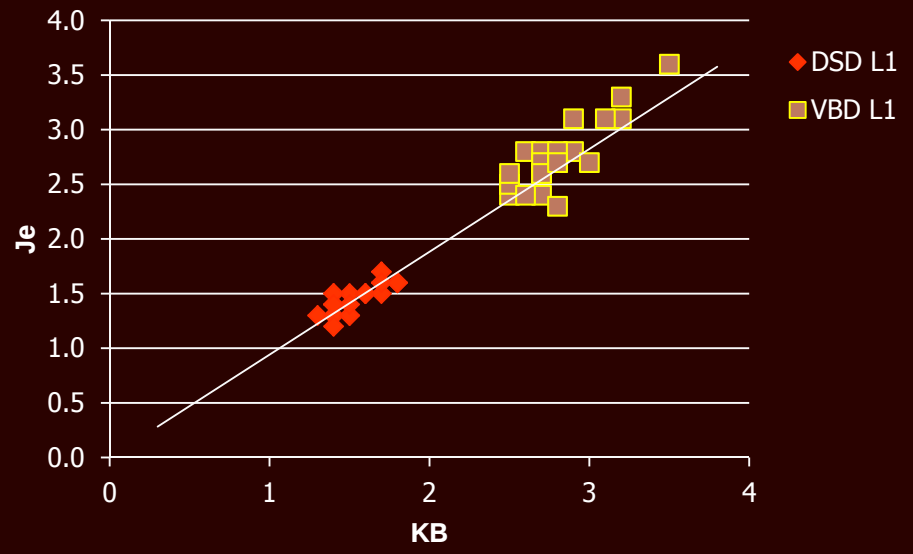
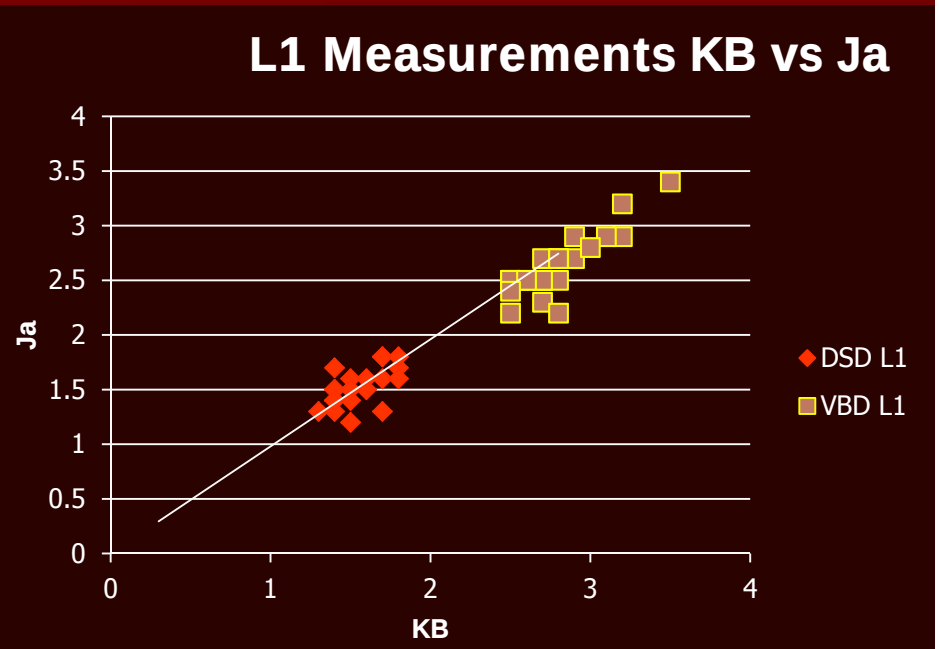
Dural Sac Ratio

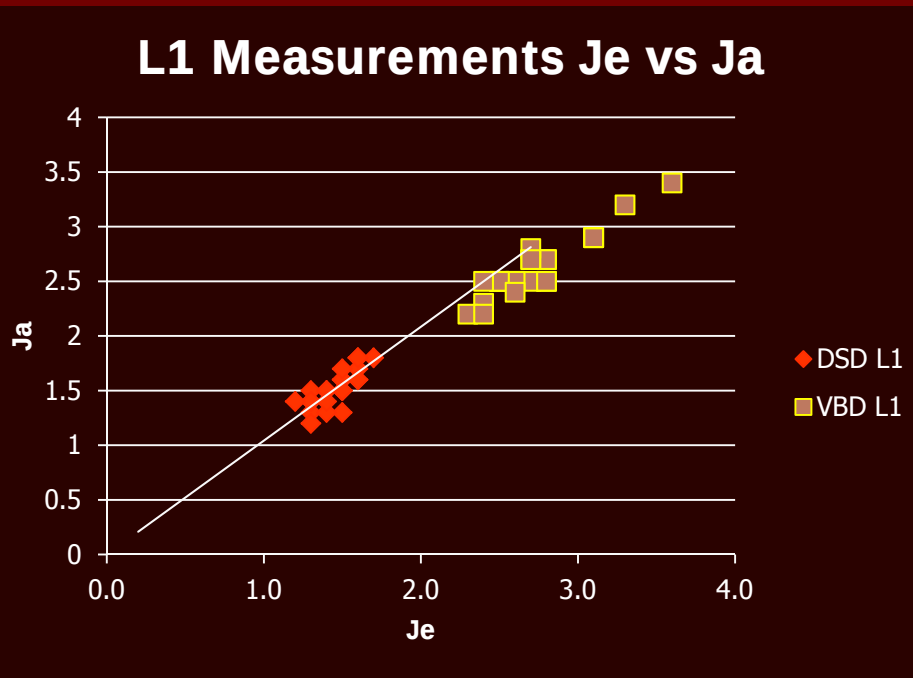
	Male	Female	P-value
L1	0.52 (0.09)	0.59 (0.08)	**0.012**
L2	0.47 (0.09)	0.54 (0.07)	**0.005**
L3	0.41 (0.06)	0.51 (0.07)	**4.5×10^{-5}**
L4	0.42 (0.07)	0.49 (0.07)	**0.002**
L5	0.42 (0.07)	0.48 (0.08)	**0.02**
S1	0.44 (0.09)	0.49 (0.1)	**0.12**
Ave	0.45 (0.06)	0.52 (0.06)	**0.0004**

Average DSD by Gender

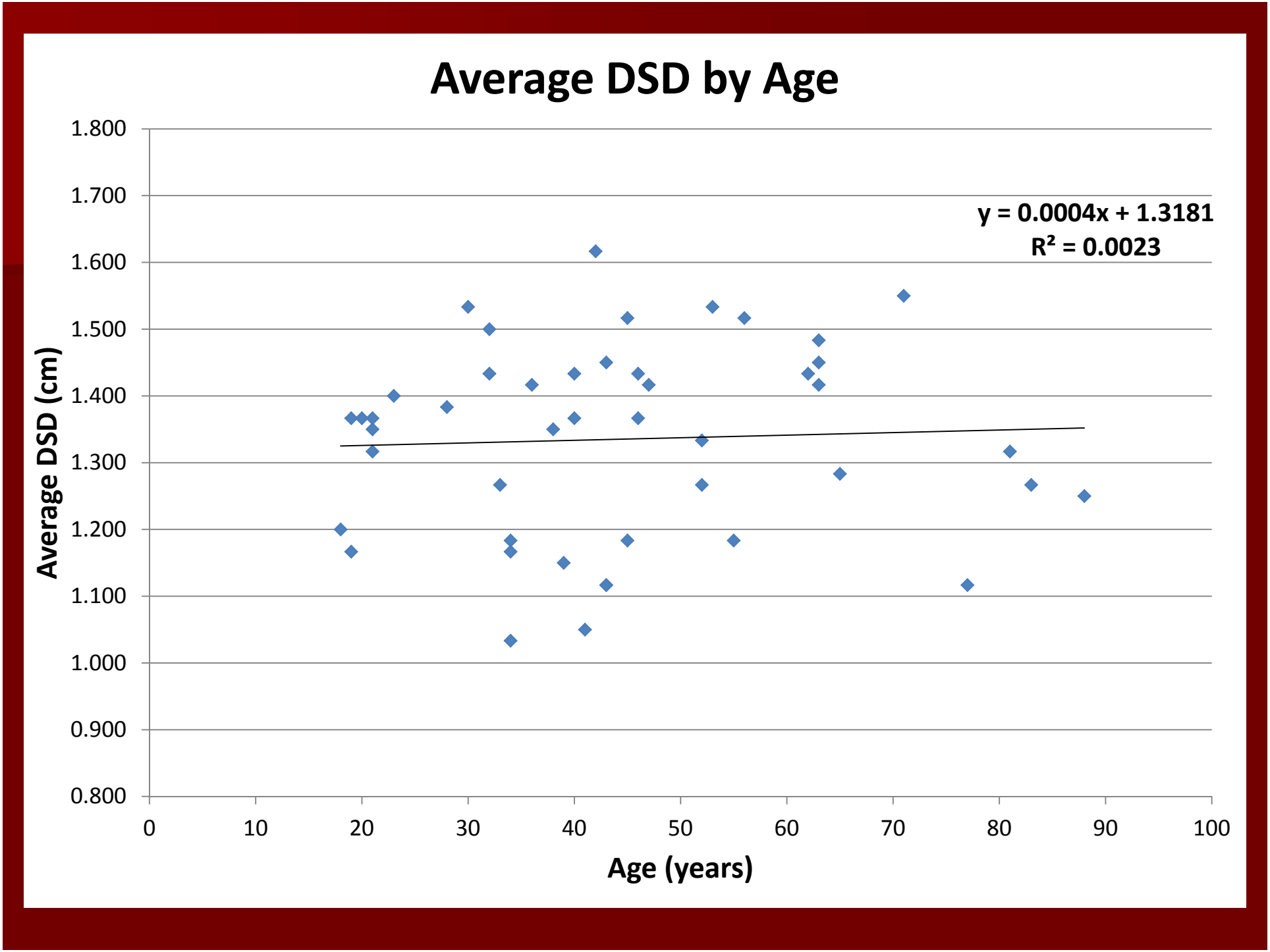
	Male	Female	P-value
L1	1.5 (0.12)	1.5 (0.16)	**0.8**
L2	1.4 (0.16)	1.4 (0.16)	**0.5**
L3	1.3 (0.15)	1.4 (0.17)	**0.2**
L4	1.4 (0.16)	1.4 (0.19)	**0.5**
L5	1.3 (0.15)	1.3 (0.22)	**1**
S1	1.1 (0.21)	1.0 (0.20)	**0.3**
Ave	1.33 (0.13)	1.34 (0.15)	**0.782**

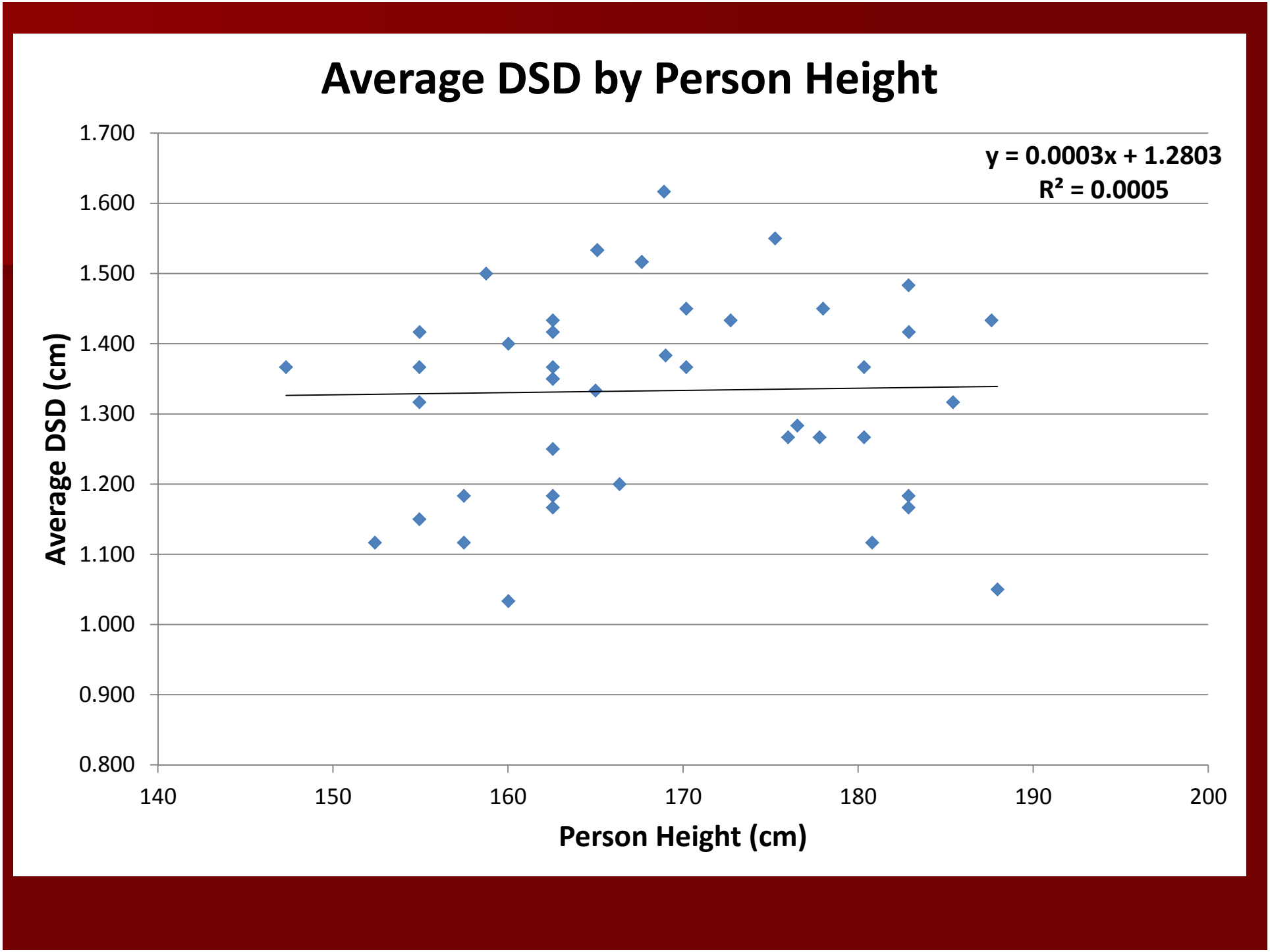






Reproducible measurements by three independent reviewers


Average DSD by Age
y = 0.0004x + 1.3181
R² = 0.0023
Average DSD (cm)
1.800
1.700
1.600
1.500
1.400
1.300
1.200
1.100
1.000
0.900
0.800
0
10
20
30
40
50
60
70
80
90
100
Age (years)


Average DSD by Person Height
y = 0.0003x + 1.2803
R² = 0.0005
Average DSD (cm)
1.700
1.600
1.500
1.400
1.300
1.200
1.100
1.000
0.900
0.800
140
150
160
170
180
190
200
Person Height (cm)

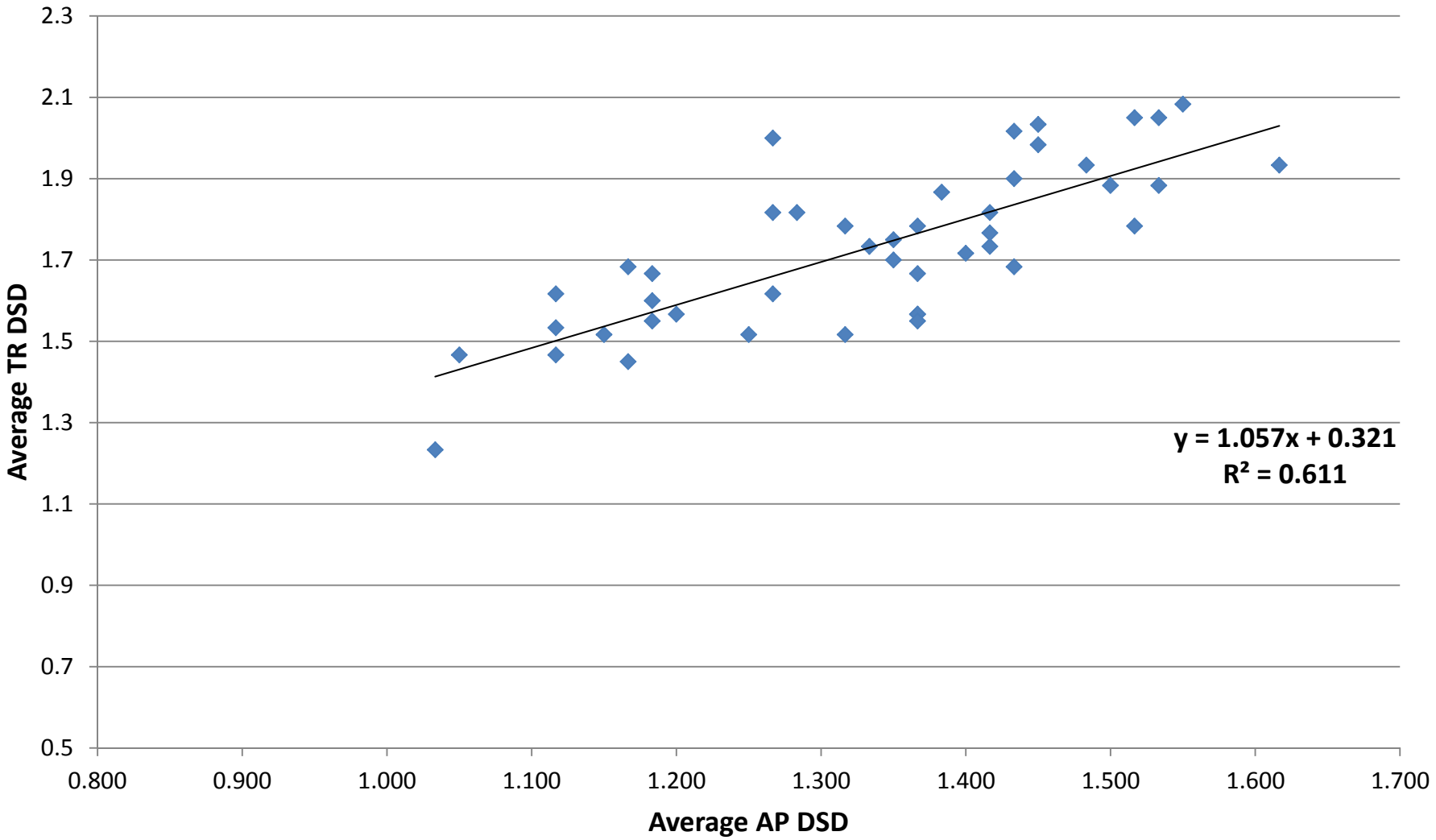
Lung Disease and Marfan's Syndrome

- Manifestations:
  - Spontaneous pneumothorax, generalized emphysema.
  - Cystic lung dz, malformations, incr risk of PNA
  - Bronchiectasis reported
- Due to weakness in pulmonary framework
  - CF, asthma – degraded elastin and collagen
  - Mouse model of COPD and mitral valve disease with elevated TGF-β
  - TGF-β plays role in extracellular matrix formation/homeostasis.

Further Direction for Assessing Dural Ectasia Using Chest CT

- Pilot study comparing MRI quantitation of dural ectasia with estimates of dural ectasia from lower thoracic vertebral levels as seen on routine chest CT
- If successful, could extend quantitation of dural ectasia to 300 IB patients enrolling in our multi-center consortium study.

DSD: AP vs TR


2.3
2.1
1.9
1.7
1.5
1.3
1.1
0.9
0.7
0.5
Average TR DSD
0.800
0.900
1.000
1.100
1.200
1.300
1.400
1.500
1.600
1.700
Average AP DSD
y = 1.057x + 0.321
R² = 0.611

Dural Sac Diameter

	Male	Female	P-value
L1	1.5 (0.12)	1.5 (0.16)	**0.8**
L2	1.4 (0.16)	1.4 (0.16)	**0.5**
L3	1.3 (0.15)	1.4 (0.17)	**0.2**
L4	1.4 (0.16)	1.4 (0.19)	**0.5**
L5	1.3 (0.15)	1.3 (0.22)	**1**
S1	1.1 (0.21)	1.0 (0.20)	**0.3**
Ave	1.33 (0.13)	1.34 (0.15)	**0.782**

Vertebral Body Diameter

	Male	Female	P-value
L1	3.0 (0.35)	2.6 (0.18)	**8.4×10^{-5}**
L2	3.1 (0.40)	2.7 (0.19)	**1.3×10^{-4}**
L3	3.3 (0.28)	2.8 (0.23)	**5.4×10^{-8}**
L4	3.2 (0.27)	2.8 (0.21)	**4.8×10^{-6}**
L5	3.1 (0.30)	2.7 (0.20)	**1.2×10^{-5}**
S1	2.4 (0.24)	2.0 (0.21)	**2.8×10^{-6}**
Ave	3.0 (0.25)	2.61 (0.16)	**1.3×10^{-7}**

Dural Sac Ratio

	Male	Female	P-value
L1	0.52 (0.09)	0.59 (0.08)	**0.012**
L2	0.47 (0.09)	0.54 (0.07)	**0.005**
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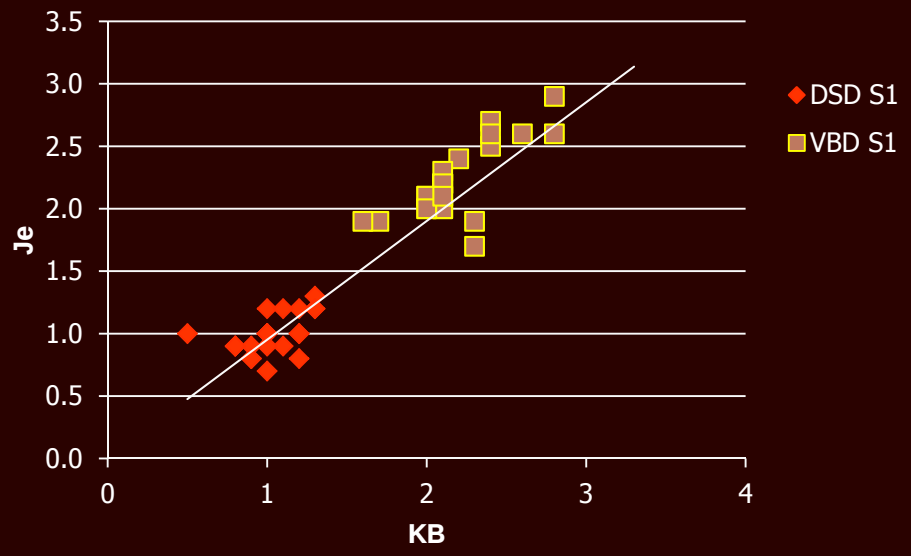
L5	0.42 (0.07)	0.48 (0.08)	**0.02**
S1	0.44 (0.09)	0.49 (0.1)	**0.12**
Ave	0.45 (0.06)	0.52 (0.06)	**0.0004**

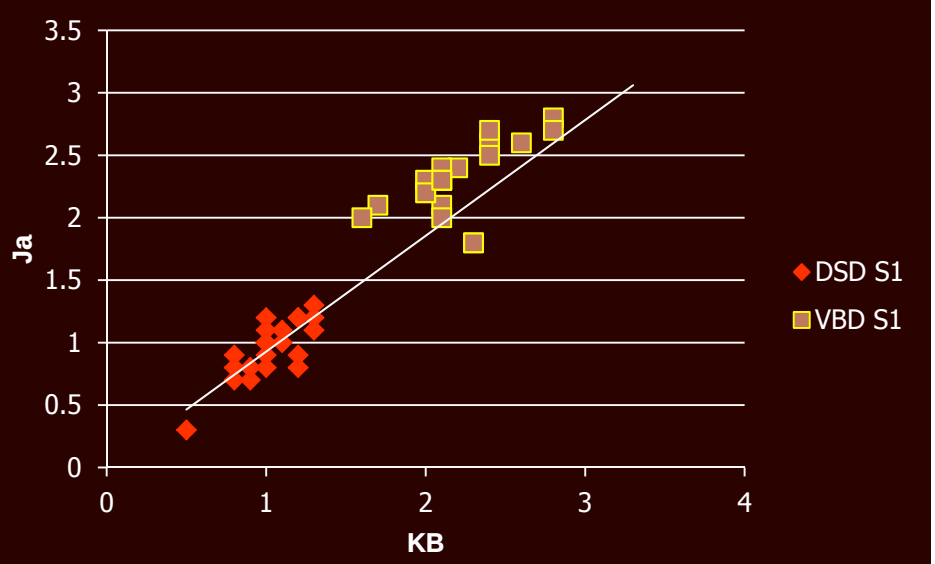
Dural Sac Volume Calculations

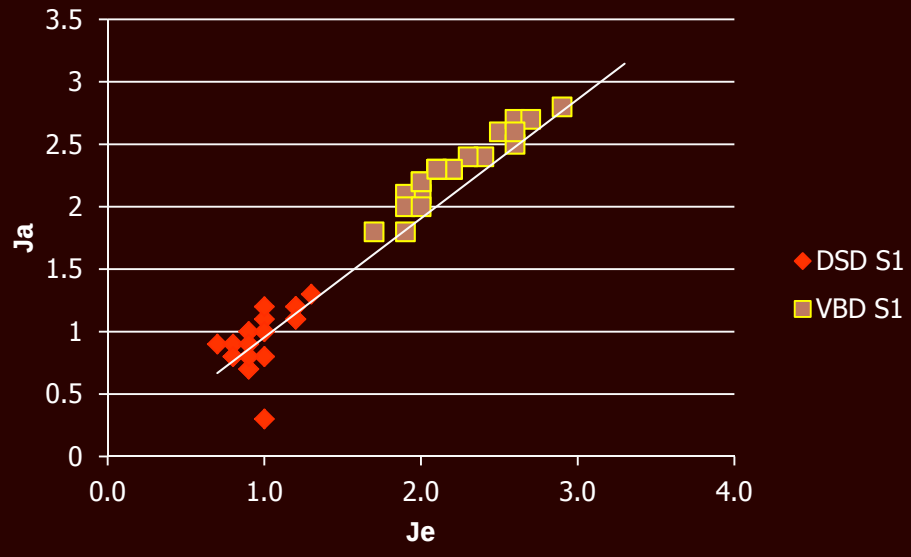
- Assuming an elliptical cylinder as the basic shape of the dural sac, dural sac volumes were calculated using the formula:

  V= Short Radius * Long Radius * Π * Height

- Intervertebral discs were excluded given variability within same individual and between individuals







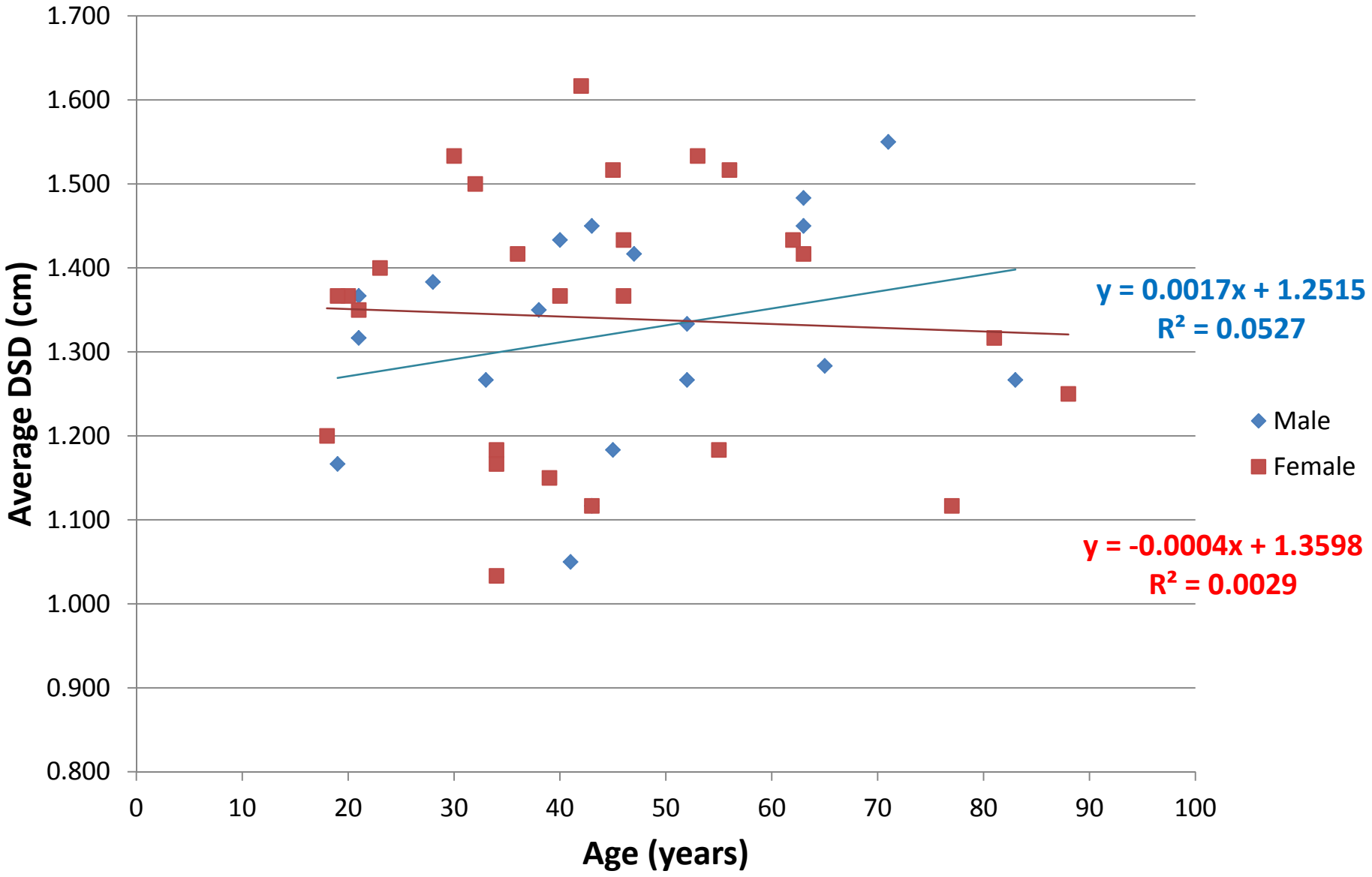
Reproducible measurements by three independent reviewers

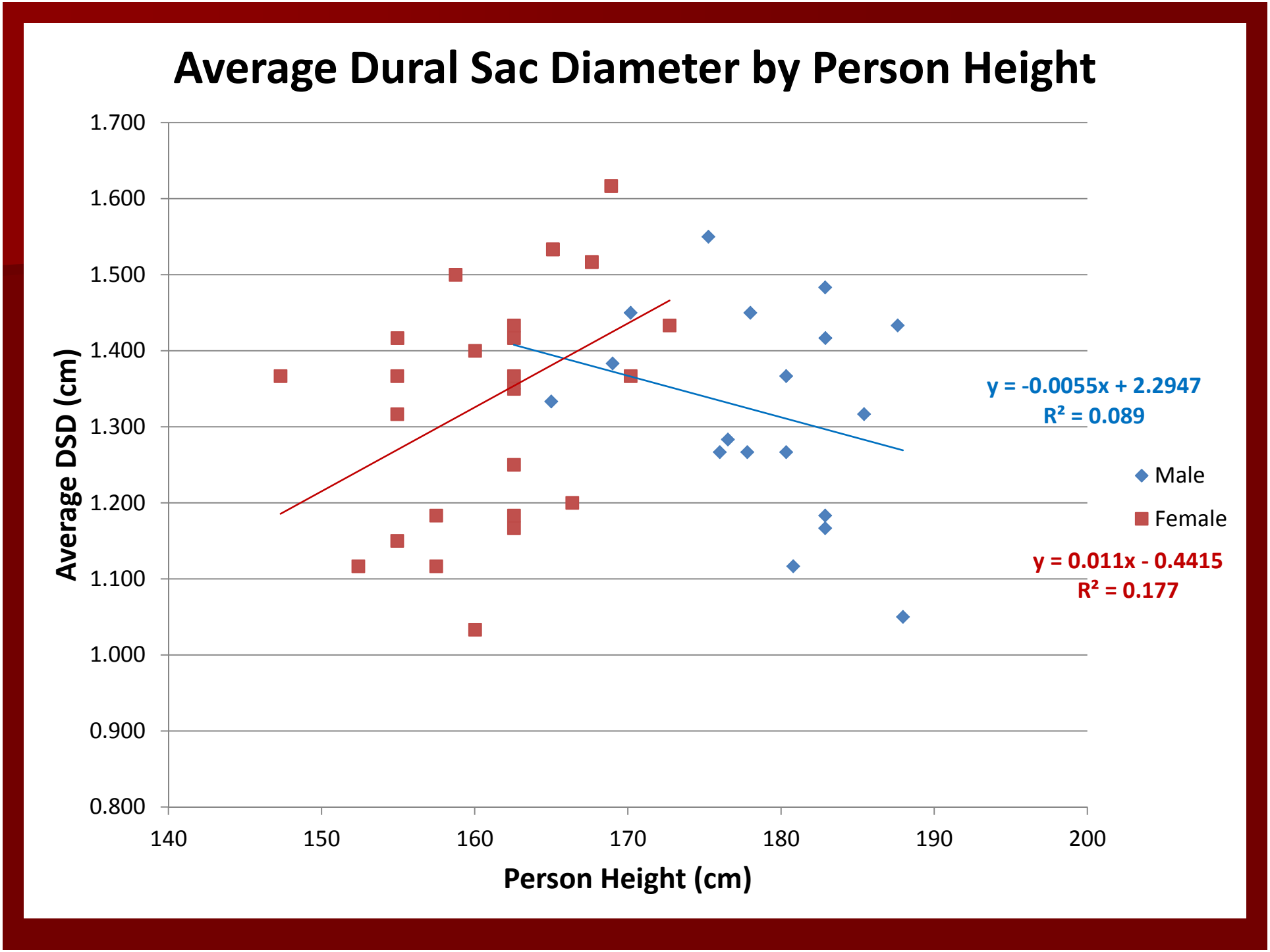
Significance

- Investigation of relationship between idiopathic bronchiectasis and dural ectasia has never been performed.
- A positive correlation between idiopathic bronchiectasis and dural ectasia would help explain the etiology of "idiopathic" bronchiectasis
  - Some of these patients may actually have an underlying connective tissue disorder, which may be amenable to genetic studies
  - It could allow for identification of patients at risk of developing bronchiectasis and allow for closer monitoring.

Demographics of Study Groups

	Non-bronchiectasis Control	Idiopathic bronchiectasis	Primary Ciliary Dyskinesia	Cystic Fibrosis
Number	45	28	28	13
Gender	F=26, M=19	F=24, M=4	F=23, M=5	F=8, M=5
Age	44 (18 – 83)	54.6 (21 – 82)	34.7 (18 – 53)	31.8 (19 – 48)
Height (cm)	164.47 (147.32 - 187.96)	163.7 (149.5 – 187.6)	167.6 (150 – 183.4)	162.9 (149 – 180)


Average Dural Sac Diameter by Age
Average DSD (cm)
1.700
1.600
1.500
1.400
1.300
1.200
1.100
1.000
0.900
0.800
0
10
20
30
40
50
60
70
80
90
100
Age (years)
y = 0.0017x + 1.2515
R² = 0.0527
y = -0.0004x + 1.3598
R² = 0.0029
Male
Female


Average Dural Sac Diameter by Person Height
Average DSD (cm)
1.700
1.600
1.500
1.400
1.300
1.200
1.100
1.000
0.900
0.800
140
150
160
170
180
190
200
Person Height (cm)
y = -0.0055x + 2.2947
R² = 0.089
y = 0.011x - 0.4415
R² = 0.177
Male
Female