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## Pulmonary Function and Emphysema in Williams-Beuren Syndrome

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### Abstract

Williams-Beuren Syndrome (WBS) is caused by a submicroscopic deletion on chromosome 7q11.23 that encompasses the entire elastin (*ELN*) gene. Elastin, a key component of elastic fibers within the lung, is progressively destroyed in emphysema. Defects in the elastin gene have been associated with increased susceptibility towards developing chronic obstructive pulmonary disease (COPD) and emphysema in both humans and mice. We postulate that hemizygosity at the elastin gene locus may increase susceptibility towards the development of COPD and emphysema in subjects with WBS. We describe an adult subject with WBS who was a lifelong non-smoker and was found to have moderate emphysema. We also examined the pulmonary function of a separate cohort of adolescents and young adults with WBS. Although no significant spirometric abnormalities were identified, a significant proportion of subjects reported respiratory symptoms. Thus while significant obstructive disease does not appear to be common in relatively young adults with WBS, subclinical emphysema and lung disease may exist which possibly could worsen with advancing age. Further investigation may elucidate the pathogenesis of non-smoking related emphysema.

### Keywords

Elastin; emphysema; pulmonary function tests; Williams Syndrome

### Introduction

Williams-Beuren Syndrome (OMIM 194050) is a contiguous gene deletion disorder typically characterized by mild-to-moderate mental retardation, characteristic facial dysmorphism, and vascular abnormalities including supravalvular aortic stenosis (SVAS) [Ewart 1993]. The disorder is estimated to have a prevalence of 1 in 7500 [Stromme 2002]. The causative defect is a submicroscopic deletion at chromosome 7q11.23 approximately 1.5-1.8 Mb in size that includes the entire elastin (*ELN*) gene in 97-98% of cases [Del Campo 2006; Lowery 1995]. Though the deletion is usually the result of a de novo mutation [Urban 1996], transmission from parent to child in an autosomal dominant fashion has been documented [Morris 1993; Sadler 1993].

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Elastin is a key component of elastic fibers within the lung. Emphysema, a subtype of chronic obstructive pulmonary disease (COPD), is characterized by progressive destruction and loss of elastic fibers [Shifren and Mecham 2006]. Imbalances between proteases and anti-proteases increase susceptibility towards developing COPD; the best described imbalance remains severe deficiency of  $\alpha$ -1 antitrypsin, an antiprotease which acts against neutrophil elastase. Defects within the elastin gene may also contribute to COPD susceptibility - a functional mutation in the elastin gene has been found in two unrelated subjects with early-onset COPD [Cho 2009; Kelleher 2005]. Mutations in the elastin gene have also been described in cases of autosomal dominant cutis laxa (OMIM 123700) associated with severe, premature emphysema [Rodriguez-Revenga 2004; Urban 2005]. Mice deficient in elastin (*Eln*<sup>-/-</sup>) exhibit impaired terminal airway development which morphologically resembles emphysema [Wendel 2000].

Despite biological plausibility, respiratory impairment is not typically described in conjunction with Williams-Beuren Syndrome (WBS). To date, there has been no published report of pulmonary function testing in subjects with WBS; we hypothesized that WBS subjects would have increased risk for COPD due to hemizyosity at the *ELN* locus. In the following communication, we describe pulmonary function data from adolescents and young adults with WBS in conjunction with a separate adult patient who was a lifelong non-smoker and was found to have emphysema.

## Methods

### Study population at the Williams-Beuren Syndrome music camp

The protocol was approved by the Partners Healthcare institutional review board. The parents of teenagers and young adults attending a summer music camp for children with WBS at Belvoir Terrace in Lenox, MA in 2003 were sent a letter requesting their participation in the study. Sixteen camp participants enrolled in the study. Informed consent for participation and for review of the subjects' medical records was obtained from the subjects and their parents or guardians. All camp participants reported a clinical diagnosis of WBS. Eleven subjects were personal patients of one of the authors (B.R.P.) and previously had *ELN* deletions confirmed by FISH analysis as part of their clinical care. We attempted to re-contact the five remaining subjects in whom the *ELN* gene deletions had not been confirmed; three additional subjects had *ELN* deletions confirmed by FISH analysis under the care of their private physicians.

### Spirometry testing, questionnaire, and medical history

Spirometry testing was performed using a Collins Survey Tach spirometer. At least three maneuvers were attempted for each subject. Acceptability criteria for spirometry measurements included 1) back extrapolated volume <0.15L, 2) effort free from cough in the first second, 3) difference between two largest volumes for forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) achieved <200 mL [Miller 2005]. Spirometry results are expressed in terms of percent predicted values normalized for race, age, gender, and height [Hankinson 1999]. A questionnaire on basic medical history, smoking behavior, exposure to secondhand smoke, and respiratory symptoms was completed by the subject and his or her parent or guardian.

### Reference population

Population based control subjects were drawn from a cohort from East Boston and Watertown, MA which has previously been described [Silverman 1998]. The analysis was restricted to subjects who had never smoked and were under the age of 40.

## Case study

An adult patient with the diagnosis of WBS followed by two of the authors (B.R.P. and E.K.S.) was incidentally noted to have evidence of emphysema on chest computed tomography (CT). Non-contrast images were obtained using a Siemens Dual Source CT Scanner and were analyzed using 3D Slicer v2.8 ([www.slicer.org](http://www.slicer.org)). The diagnosis of WBS was confirmed by FISH analysis when the subject was in his 20's. The patient and his mother/guardian provided consent to the review of his de-identified medical records and images for the purposes of this case study.

## Results

Basic demographic information, respiratory symptoms, and spirometry results are summarized in Table 1. Of the 16 subjects who consented to the study, twelve were able to perform spirometry meeting reproducibility criteria for FEV<sub>1</sub> measurements [Miller 2005]. While FEV<sub>1</sub> measurements were of reasonable quality, most subjects were not able to sustain expiration 6 seconds or to reach a plateau on their volume-time curve – therefore analyses of FVC and FEV<sub>1</sub>/FVC ratio were not performed. All FEV<sub>1</sub> measurements obtained were within the normal range. Despite a normal FEV<sub>1</sub>, a surprisingly high proportion of subjects were reported by their parents/guardians to have respiratory complaints such as wheezing and coughing. None of the participants had a previous diagnosis of COPD, emphysema, or chronic bronchitis by history (data not shown).

## Case report

An adult patient with the diagnosis of WBS since childhood was incidentally noted to have moderate paraseptal emphysema on computed tomography during evaluation of unrelated symptoms (Figure 1). Quantitative analysis of the high resolution CT images revealed the 15th percentile value of the histogram to be -966.1 Hounsfield units (HU). Mean lung density was -892 HU and the lung volume by CT imaging was 5.01 liters. The percentage of emphysema in the upper, middle, and lower thirds of the lung was 25.8%, 26.4%, and 23% respectively at -950 HU – these values are substantially elevated when compared to a cohort of asymptomatic young adults (0.35%)[Irion 2009] and are suggestive of additional emphysema beyond the grossly evident paraseptal collections. The patient was 31 years old at time of diagnosis of emphysema, had been a lifelong non-smoker, and was subsequently found to have a normal alpha-1 antitrypsin level. Post-bronchodilator FEV<sub>1</sub> was 3.15 liters (106% predicted), FVC was 4.01 liters (106% predicted), and FEV<sub>1</sub>/FVC ratio was 79 (92% predicted). Total lung capacity and DLCO were 117% and 100% of predicted, respectively, while inspiratory capacity was 2.94 liters (108% predicted) and residual volume was 1.43 liters (129% predicted). There was no significant spirometric response to inhaled bronchodilators. Clinically, he denied any respiratory complaints, was on no medications, worked full time as a clerk and denied any history of occupational exposures to respiratory irritants. Family history was negative for COPD or any other respiratory disease.

## Discussion

Respiratory disease in WBS has not been previously reported. Our study suggests that significant obstructive lung disease, as assessed by spirometry, is not typically seen in adolescents and young adults with WBS. However, this does not preclude the possibility of significant subclinical pulmonary disease, as illustrated by the finding of substantial emphysema in a non-smoking WBS patient.

Haploinsufficiency at the elastin locus, a deletion shared by nearly all patients with WBS, may predispose subjects towards premature development of emphysema. Possible

mechanisms for this increased susceptibility may involve increased sensitivity to oxidative and mechanical stress due to differences in elastin gene dosage. This hypothesis is supported by murine models employing mice with a heterozygous deletion of the elastin gene (*Eln* +/-). While mice homozygous for the elastin gene deletion (*Eln* -/-) develop extensive changes in baseline lung architecture, heterozygous mice (*Eln* +/-) exhibit normal lung development and morphology despite having only approximately 45% of the lung elastin levels of wild type mice. However, when compared to wild type (*Eln* +/+) mice, heterozygous mice exhibit an augmented inflammatory response and are more susceptible to developing emphysema when exposed to cigarette smoke [Shifren 2007].

In the absence of a smoking history, other possible factors contributing to emphysema susceptibility may exist. In addition to increased sensitivity towards oxidative stress, reduced elastin levels in *Eln* +/- mouse lungs alter the mechanical properties of the lung [Shifren 2007]. Mechanical stress, in the absence of inflammation or oxidative stress, may contribute to the pathogenesis and propagation of emphysema [Brenner 1998; Suki 2003; West 1971]. Patients with WBS have also been purported to exhibit accelerated signs of aging such as premature cataracts, gray hair, and presbycusis [Cherniske 2004]. “Senile emphysema”, which is distinct from the normal aging lung [Verbeke 1992a; Verbeke 1992b], may be a part of the spectrum of premature aging in these individuals.

The lack of literature on pulmonary function and the development of emphysema in this population may reflect the general paucity of literature on adult WBS patients. Alternatively, because subjects with WBS often have other more salient systemic problems, pulmonary problems may not assume priority and may be underreported. Because many WBS patients have limited exercise capacity due to cognitive, musculoskeletal, or cardiovascular deficits [Giordano 2001], their pulmonary reserve may be adequate to avoid respiratory symptoms in the course of their usual activities. When exertional dyspnea is reported, it may be difficult to discern cardiovascular etiologies from intrinsic pulmonary disease. Increased dyspnea in our WBS cohort is not unexpected and may be due in part to the higher incidence of comorbid cardiovascular disease in this population [Pober 2008].

Besides dyspnea, a substantial proportion of our WBS patients reported respiratory complaints, such as wheezing and coughing, which have less salient overlap with possible cardiac etiologies. Although the differences between our WBS and reference populations did not reach statistical significance, this likely reflects low power due to our small sample sizes. Given the lack of obstructive pulmonary disease in our WBS patients, investigation into other lung impairments such as diffusion abnormalities or chronic bronchitis may represent an area that warrants further examination.

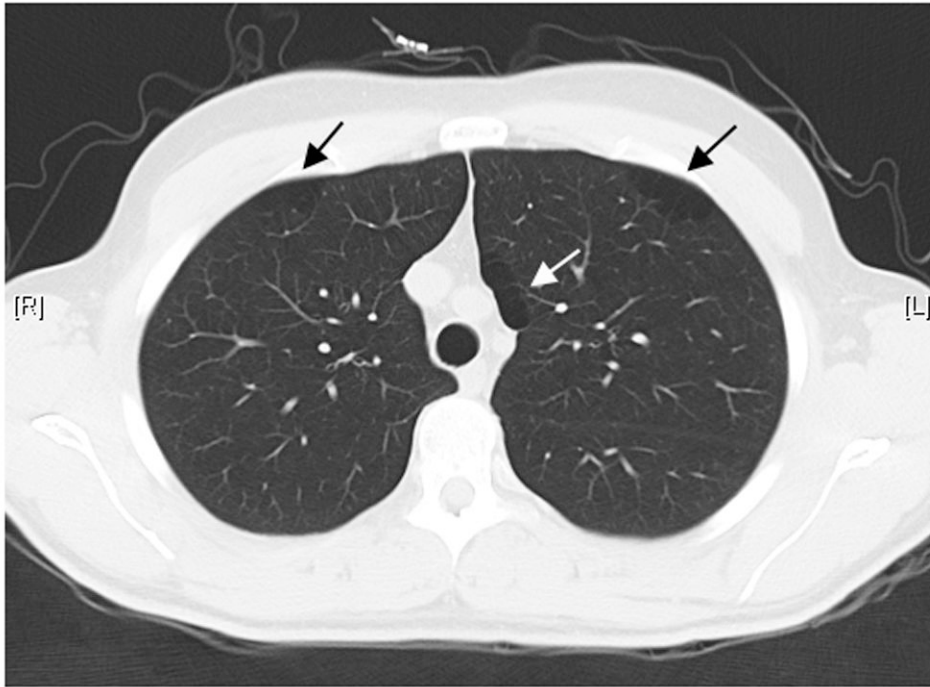
We acknowledge several additional limitations to this largely descriptive study. Our small cohort may be subject to self-selection bias with regards to participation. The diagnosis of WBS was previously confirmed by FISH analysis of the *ELN* gene deletion in the majority of our patients; the remaining minority may be subject to misclassification bias, though we feel this scenario is very unlikely in the setting of their typical WBS features. By using traditional spirometry to assess lung function, only subjects who were physically and mentally able to perform this test were included in the analysis; a possible alternative would be to utilize techniques which require limited subject participation similar to techniques employed for infants and young children. Longitudinal follow up and review of radiographic data in additional WBS subjects in the future would allow for improved detection of subclinical emphysema and lung disease. If emphysema is not a common finding among patients with WBS, more in-depth analysis of our case report subject may yield additional insights on the pathogenesis of non-smoking related emphysema.

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**Figure I.** Paraseptal emphysema in a lifelong non-smoking patient with Williams-Beuren Syndrome.

**Table I**

Characteristics of adolescent and young adults with WBS

	Cases	Controls
N	16	22
Age (range)	20 * (15-27)	27.6 (20-35)
Sex (% male)	56.3	63.6
Race (% white)	93.8	100
BMI (range)	23.1 (16.2-41.6)	25.9 (17.3-40.3)
Smoking (% ever)	0	0
Passive exposure to cigarette smoke	12.5	13.6
FEV <sub>1</sub> % predicted	101.3 (18.4) <sup>§</sup>	92.2 (7.6)
Shortness of breath <sup>‡</sup>	50 *	4.5
Wheezing causing shortness of breath	31.3	18.2
Required medication for wheezing	31.3	18.2
Cough	43.8	22.7

Data presented as mean (SD) or percent unless otherwise indicated

\* p-value &lt;0.05 when compared to controls,

<sup>§</sup>N=12 for FEV<sub>1</sub> analysis<sup>‡</sup>Defined as an affirmative answer to any of the following:

- a. Ever bothered by shortness of breath
- b. Shortness of breath walking up a hill
- c. Shortness of breath walking on the level
- d. Shortness of breath walking < 100 yards
- e. Shortness of breath with dressing or undressing