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Biomechanical Properties of the Skin in Cutis Laxa

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To the Editor

Cutis laxa (CL) is a heterogeneous group of disorders characterized by loose, redundant, inelastic or prematurely wrinkled skin (Berk *et al.*, 2012; Uitto *et al.*, 2013). Several inherited forms of CL have been identified (Urban and Davis, 2013), with 9 causative genes known to date (*ALDH18A1, ATP6V0A2, ATP7A, EFEMP2/FBLN4, ELN, FBLN5, LTBP4, PYCR1, RIN2*). A shared feature of all types of inherited CL is a reduced or abnormal deposition of elastic fibers in the skin and other tissues (Berk *et al.*, 2012). The consequences of this disorder for the biomechanics of the skin has received little attention (Grahame and Beighton, 1971). Such studies are essential for a fundamental understanding of the contribution of elastic fibers to the mechanical properties of the skin, and for an improved, objective diagnosis of cutis laxa.

In the present study, 118 participating controls and 17 CL patients were included with written informed consent. The same control cohort was used in a concurrent study on the mechanical properties of the skin in Williams-Beuren syndrome (Kozel *et al.*, 2014). The IRB committees at Washington University School of Medicine and the University of Pittsburgh approved the studies. Age and sex were not significantly different between cases

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and controls (Table 1). The CL group comprised individuals diagnosed with cutis laxa based on physical examination and medical history. Eight individuals of the CL group were positive for mutations in known CL genes with *LTBP4* mutations in 2, *ELN* mutations in 3 and *ATP6V0A2* mutations in 3 patients (Table S1). In addition, we included 9 patients with unknown mutational status (Table S2): 3 individuals with congenital and 6 subjects with late-onset CL. As skin elasticity measurements did not show consistent differences between CL subgroups, we pooled all types of CL into one case group.

Cases and controls underwent testing using a DermaLab® skin elasticity module, a suction cup device extensively validated in previous studies (Anthonissen *et al.*, 2013; Gandanke *et al.*, 2014; Grove *et al.*, 2006; Pedersen *et al.*, 2003). The device applies vacuum to a patch of skin and measures the pressure difference (ΔP) required to raise the skin to a height of 1.5 mm and the time required for the skin to return to the original position (retraction time, RT). The elastic modulus (E) was calculated from this pressure difference, assuming uniform skin thickness (1 mm). In addition, a viscoelastic modulus (VE) was computed from E and RT as variables (Supplementary Materials and Methods).

Cases had significantly lower E, higher RT, and lower VE (all $p < 0.05$) than controls (Figure S1, Table 1). In controls, RT and VE were significantly correlated with age, but E was not (Table S3). In cases, VE was marginally correlated with age (Table S3). Multivariate logistic regression analysis revealed that age (p=0.005, odds ratio (OR): 1.21, 95% confidence interval (CI): 1.06-1.37), VE (p=0.002, OR: 16.39, 95% CI: 2.85-95.18) and E (p=0.043, OR: 3.55, 95% CI: 1.04-12.15) were significant predictors of disease status. VE was the strongest predictor and one unit reduction in VE increased the odds of CL 16.39-fold.

We analyzed the receiver operating characteristic (ROC) to evaluate the utility of E, RT and VE as predictors. Of the three, VE performed best, with ROC area under curve (AUC) reaching 0.908 when applied to the entire study population (Figure 1a). Restricting the analysis to individuals younger than 47 years (bottom 75 percentile of the control group) yielded some improvement in the AUC (AUC = 0.964, Figure S2).

We next evaluated if an additional variables improved on VE only as a diagnostic measures in the entire study population. Two models were considered. Model 1 incorporated VE, age and E, as suggested by the logistic regression model described above. Model 2 included VE and age only. Model 1 (AUC=0.992) performed significantly (p=0.0026, ANOVA) better than Model 2 (AUC=0.958) in distinguishing cases from controls (Figure 1b).

The performance of a model on the same data that was used to fit that model can give an overly optimistic measure of performance. To test if such overfitting had occurred, cross-validation tests were performed. As the cross-validation, on average, resulted in only a modest decrease in AUC values (Table S4), overfitting was not a major issue in this analysis, and similar sensitivity and specificity values can be expected in future replication studies to our present results.

A diagnostic variable (D) can be calculated from the ROC analysis using the following device-specific formula: $D = -27.570 + 0.187 \times \text{Age} + 2.795 \times \text{VE} + 1.267 \times \text{E}$, where Age

is in years, VE is the viscoelastic modulus and E is the elastic modulus, both in MPa units. If an individual satisfies the inequality of D < 2.538, the probability of the individual having CL is 99.2%. This cutoff value of D distinguishes cases from controls with 100% specificity and 91.5% sensitivity, supporting the use of the DermaLab® device for the objective, specific and sensitive diagnosis of CL in future studies.

The skin was visually loose in individuals with cutis laxa and decreased VE values (Figure S3). Although there were insufficient number of individuals within each type of inherited cutis laxa to allow for subgroup analysis, individuals with autosomal dominant cutis laxa (ADCL) caused by *ELN* mutations showed the greatest degree of variation in VE (Figure 1b) compared to individuals with other mutations, consistent with previous reports of variable expression of the skin phenotype in ADCL patients (Szabo *et al.*, 2006).

Our studies show significant reduction of the elastic (E) and viscoelastic moduli (VE) and significant increase of the retraction time (RT) of the skin of CL patients irrespective of the etiology of the disease. Individuals with acquired or late onset CL had similar reductions in VE compared to controls as individuals with *ELN*, *LTBP4* or *ATP6V0A2* mutations, suggesting that the disruption of elastic fibers leads to similar biomechanical alterations independent of the precise molecular disease mechanisms. VE showed significant inverse correlation with age in both CL and control individuals, but in controls the decline started from a higher level and was thus steeper. Therefore, VE appears to be a good measure of biomechanical aging of the skin, and our observations suggest that CL results in similar changes in skin mechanics to aging. VE also offers the best specificity and sensitivity in distinguishing cases from controls among the individual variables measured in our study.

To date, only one study investigated the mechanics of the skin in CL (Grahame and Beighton, 1971). As this early report had few cases and controls (6 each), and only measured E but not retraction, it did not find significant difference between cases and controls. In contrast, the present report demonstrates the utility of biomechanical measurements in CL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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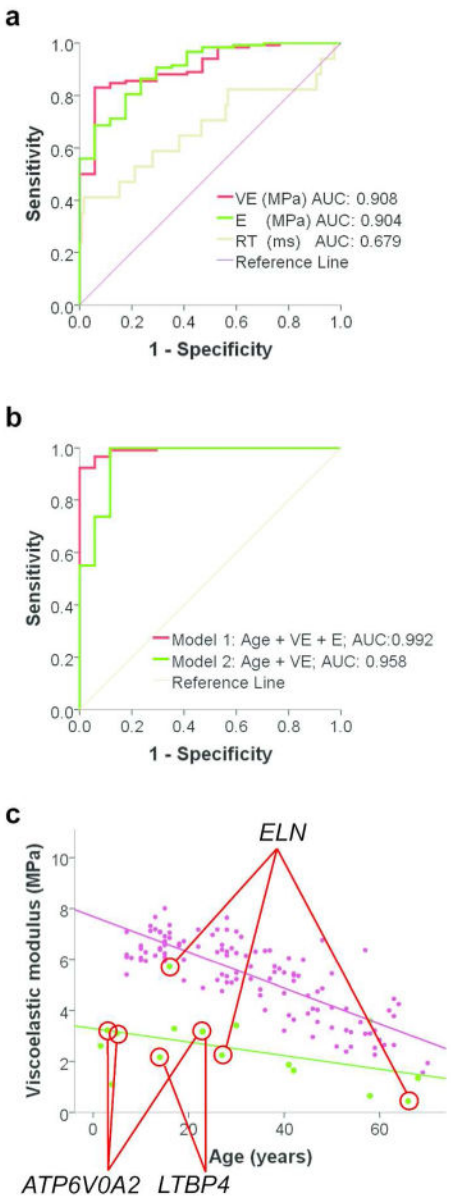

Figure 1. ROC analysis of biomechanical variables and viscoelastic modulus in relation to the causative gene mutation

(a) Viscoelastic modulus is more effective than elastic modulus or retraction time in differentiating cases from controls as indicated by receiver operating characteristic (ROC) curves. (b) Composite variables under Model 1 (Age + VE + E) perform better than Model 2 (Age + VE). (c) VE values of individuals with known gene mutations are identified by red tie-lines. Controls are represented by magenta dots and CL cases by green dots. Linear regression lines are shown in each group (cases: green, controls: magenta). Note that one individual with *ATP6V0A2*-related CL had similar age and VE data to another participant with *LTBP4*-related CL, resulting in overlapping data points.

Table 1
Demography and elasticity parameters in the participants

	Controls (n=118)	Patients (n=17)	*p*-value
Age	33.22 ± 1.58	29.21 ± 5.47	0.490*
Gender (male %)	37.3%	35.3%	0.874**
E (MPa)	11.61 ± 0.15	7.85 ± 0.60	< 0.0001*
Retraction time (ms)	622.82 ± 21.20	1152.82 ± 211.21	0.024*
VE (MPa)	5.35 ± 0.14	2.51 ± 0.32	< 0.0001*

Abbreviations: E, elastic modulus; VE, viscoelastic modulus.

Continuous variables: mean ± standard error mean

* independent t-test;

** Chi-square test