Not a stretch: Variant near the dermal gene elastin is associated with stretch marks

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Introduction

Striae distensae, or stretch marks, are a common skin condition that appear as red or white lines on the skin. These lines represent scars of the dermis, and may begin with lysis of the elastic fibers, eventually ending with linear bundles of collagen lying parallel to the surface of the skin[1,2]. Estimates of the prevalence of stretch marks range from 50-80%[3,4]. Excessive skin distension, as with pregnancy or puberty, prolonged exposure to cortisol, as with Cushing syndrome, and genetics all play a role[5]. A few monogenic diseases, including Marfan syndrome and Ehlers-Danlos syndrome, count stretch marks among their characteristics. These syndromes are caused by mutations in genes that encode dermal proteins (fibrillin-1 and various collagens, respectively). However, to date no genes are known to be associated with the stretch marks that afflict the general population.

Methods

- We conducted a genome-wide association analysis of stretch marks in a cohort of 21,282 23andMe customers of European descent who answered the following question on the 23andMe website: "Do you have stretch marks on your hips, thighs, or backs of your arms? Yes/No/I'm not sure".
  - A total of 8,339 responded "yes" and 12,943 "no". The 11,738 men in the cohort were much less likely to report stretch marks (26% versus 55.4%).

- For replication, we used a disjoint cohort consisting of 3,944 female 23andMe customers of European descent who reported on severity of stretch marks during pregnancy, with responses "None / Mild (just a few) / Moderate (covering about half my belly) / Severe (covering most of my belly)", coded as 0—3.
  - Counts in the replication group were 1,785, 1,172, 703, and 284, respectively.

- We conducted a genome-wide association analysis using approximately 7 million SNPs imputed from about 1 million SNPs genotyped.

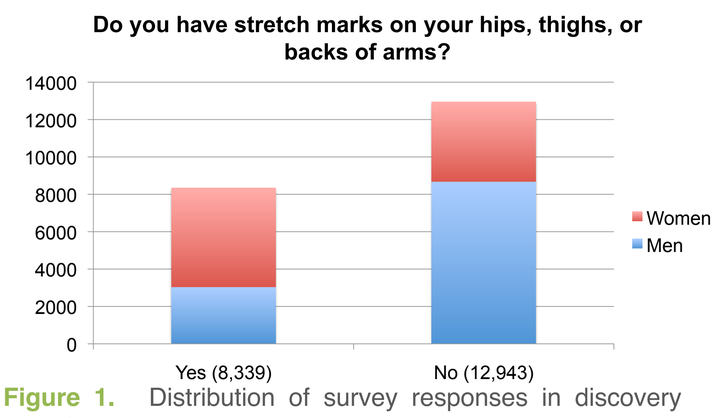

Figure 1. Distribution of survey responses in discovery cohort.

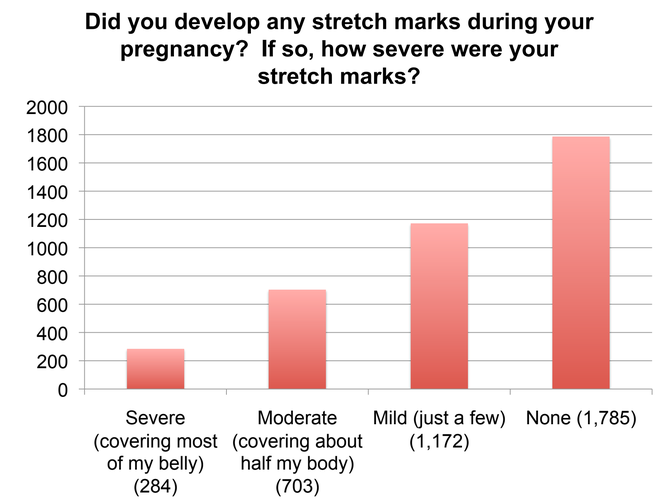

Figure 2. Distribution of survey responses in disjoint replication cohort.

Results

- Two regions were significantly ($p < 5e-8$) associated with stretch marks. The first, rs4078435 lies on chromosome 7, 40 kb upstream of the *ELN* (elastin) gene. It replicates in the pregnancy cohort. Elastin is the major component of elastic fibers, which provide strength and flexibility to connective tissue. Mutations in elastin can lead to autosomal dominant cutis laxa or supravalvular aortic stenosis[6]. Elastin is also one of the genes deleted in Williams syndrome, characterized by symptoms including loose skin, joint problems, and supravalvular aortic stenosis, among others.

- The second association, rs35318931, is a missense variant (serine to phenylalanine) in the *SRPX* (sushi-repeat containing protein, X-linked) gene. It does not replicate in the pregnancy cohort, and it lacks clear biological relevance to stretch marks.

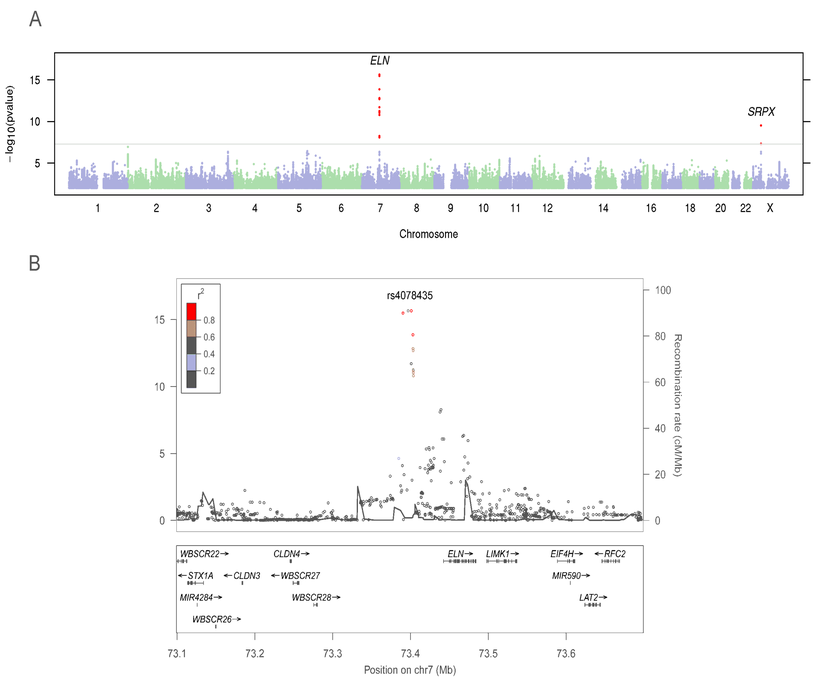

Figure 3. Manhattan plot depicting SNP associations with stretch marks. A. Genome-wide view of associations. SNPs shown in red are genome-wide significant ($p < 5e-8$). Regions are named with the postulated candidate gene. B. Detailed view of local region around rs4076435. Colors depict the squared correlation (r^2) of each SNP with rs4076435, shown in purple. Gray indicates SNPs for which r^2 information was missing.

Table 4. Index SNPs for regions associated with striae distensae at a significance level of p<1e-6.

					Discovery		Replication	
SNP	Region	Gene	MAF	r^2	p	OR (CI)	p	Beta (CI)
rs4078435	7: 73399246	*ELN*	0.476	0.932	2.2E-16	0.84 (0.81—0.88)	0.003	-0.065 (-0.11—-0.02)
rs35318931	X: 38009121	*SRPX*	0.079	0.962	3.1E-10	0.81 (0.76—0.87)	0.25	0.044 (-0.03—0.12)
rs10188334	2: 653874	*TMEM18*	0.16	0.95	1.1E-07	0.86 (0.81—0.91)	0.62	0.015 (-0.04—0.07)
rs59170767	5: 122614522	*PRDM6*	0.027	0.647	3.8E-07	1.46 (1.26—1.69)	0.32	-0.084 (-0.25—0.08)
rs62282671	3: 177929711	*KCNMB2*	0.398	0.945	4.6E-07	0.90 (0.86—0.94)	0.55	-0.014 (-0.06—0.03)
rs11241649	5: 121871189	*LOX*	0.092	1	5.5E-07	0.84 (0.78—0.90)	0.06	0.069 (-0.002—0.14)
rs62390669	5: 127865070	*FBN2*	0.163	0.987	7.8E-07	1.15 (1.09—1.21)	0.95	0.002 (-0.06—0.06)

Regions are with respect to build 37; genes are suspected genes for the association or closest gene; alleles are major/minor in the context of European ancestry; MAF is minor allele frequency; and r^2 is the estimated imputation accuracy. For the discovery set, the odds ratio (OR) plus confidence interval (CI) is with respect to the minor allele and represents the risk of developing stretch marks. For the replication set, the beta plus confidence interval is with respect to the minor allele, with positive numbers representing an increase in the severity of stretch marks.

- Five additional regions show suggestive evidence of association with stretch marks. Of these, rs11241649 and rs62390669 are of particular interest.

- rs11241649 lies 500kb upstream of the *LOX* gene, which encodes lysyl oxidase, an enzyme that initiates the crosslinking of collagen and elastin. This crosslinking adds strength to elastin fibers, as demonstrated by the loose skin phenotype of individuals with lysyl oxidase deficiencies[7].

- rs62390669 is in an intron of *FBN2* (fibrillin-2), which is highly homologous to fibrillin-1 and forms one of the base components of elastic fibers[8]. Mutations in *FBN2* cause congenital contractural arachnodactyly, and individuals with this condition have a Marfan-like appearance[9].

- None of the suggestive associations replicate in the smaller pregnancy cohort.

Discussion

- Given that stretch marks can be symptoms of syndromes caused by mutations in collagen and other dermal genes, it is not surprising that *ELN*, a major dermal gene, is also associated with this common skin condition. Rare mutations in *ELN* are known to be associated with multiple conditions that involve the skin, and loss of elastin can result in loose, creased skin, which shares some similarities with the appearance of stretch marks.

- *SRPX* has not been linked to dermal cells or elastic fibers, so we have less confidence that this is a true association.

- The suggestive associations near *LOX* and *FBN2* provide additional support for the idea that defects in elastic fiber structure and function contribute to the development of stretch marks.

Acknowledgments

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