ALLERGY, GENETICS

HOW ATOPIC DERMATITIS IS LINKED TO VITAMIN D AND HOW IL33 SPLICE VARIANTS ASSOCIATE TO EOSINOPHIL NUMBERS

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We had a major discussion right before our 2010 paper where I argued that rare variants should have been included into our asthma/allergy/dermatitis GWAS. Ten years after there is now a nice paper using massive exome sequencing that finally includes them.

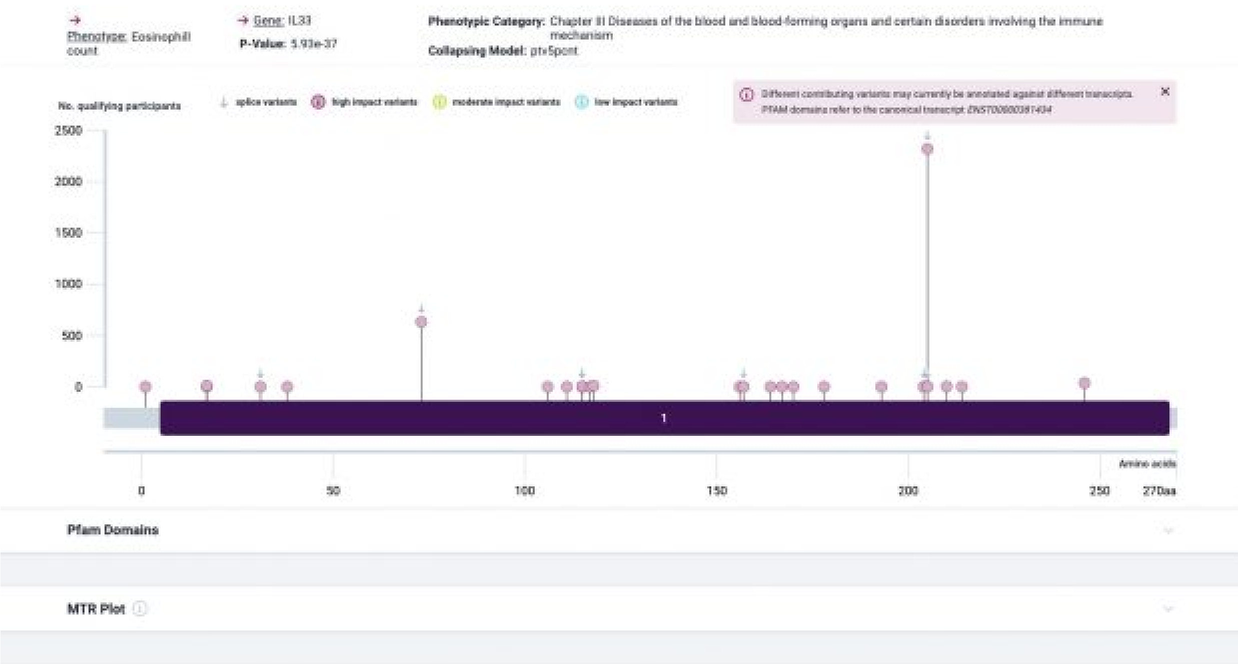
It seems that the respiratory tract isn't so much influenced by rare gene variants but that there is a strong effect in the immune system.

And there is another interesting fact.

> …Surveying the contribution of rare variants to the genetic architecture of human disease through exome sequencing of 177,882 UK Biobank participants …if we look at the …. European population who are carriers of a filaggrin (FLG) PTV, we find those carriers have significantly higher risk for well-known associations, such as dermatitis … and asthma … Concomitant increases in vitamin D levels suggest … increased sensitivity to ultraviolet B radiation.

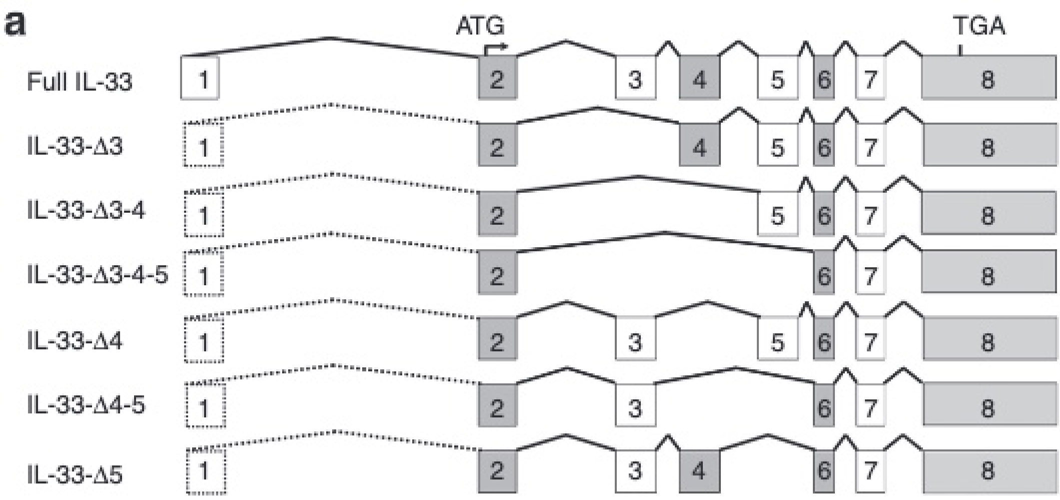
So far, I have only assumed an asthma/allergy priming effect of oral vitamin D in the new-born gut. This paper now argues for an increased vitamin D sensitivity also in the skin of FLG dermatitis patients which is interesting given the largely contradictory data of serum vitamin D and atopic dermatitis. Maybe dermatologists should focus their research more on skin and local vitamin D turnover?

The most prominent IL33 variant carried by over 2,300 people is splice acceptor 9-6250473-G-C followed by 600+ individuals with splice donor 9-6250600-G-T.



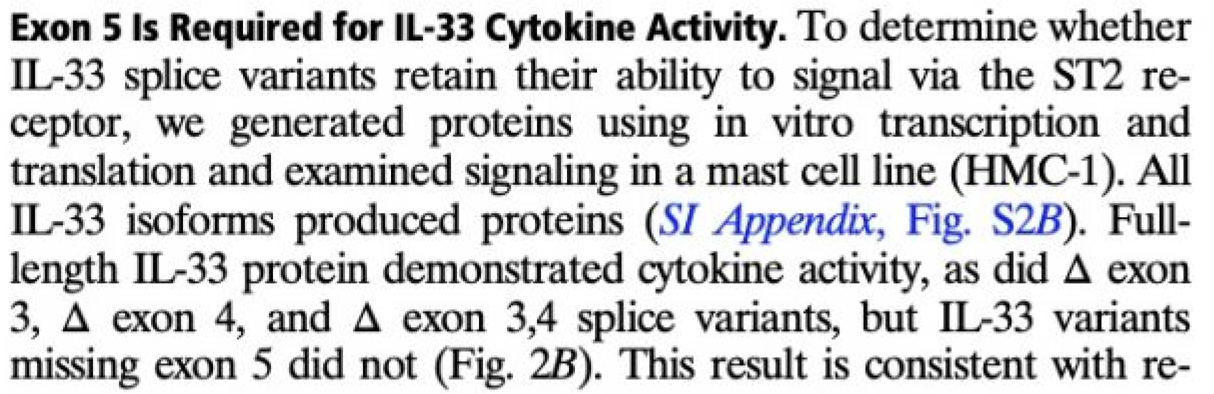
1 Variant	2 Variant type	3 Consequence type	4 Transcript	5 cDNA change	6 Amino acid change	7 Exon rank	8 No. with AB...	9 No. with BB genotype	10 MAC
9-6241697-G-A	snv	start_lost	ENST00000381434	c.3G>A	p.Met1?	'1/7'	0	1	
9-6241743-TG-T	indel	frameshift_variant	ENST00000381434	c.51delG	p.Trp17fs	'1/7'	4	0	
9-6241744-G-A	snv	stop_gained	ENST00000381434	c.50G>A	p.Trp17*	'1/7'	12	0	
9-6250473-G-C	snv	splice_acceptor_variant	ENST00000381434	c.92-1G>C	NA	'1/6'	1	0	

There are not too many carriers of this variant by the sheer amount of 177,882 participants. We nevertheless know already something about the seven IL33 splice variants since 2012.



Novel Splice Variants of IL-33: Differential Expression in Normal and Transformed Cells Journal of Investigative Dermatology (2012) 132, 2661–2664; doi:10.1038/jid.2012.180

with updates [in 2016]


Exon 5 Is Required for IL-33 Cytokine Activity. To determine whether IL-33 splice variants retain their ability to signal via the ST2 receptor, we generated proteins using in vitro transcription and translation and examined signaling in a mast cell line (HMC-1). All IL-33 isoforms produced proteins (*SI Appendix*, Fig. S2*B*). Full-length IL-33 protein demonstrated cytokine activity, as did Δ exon 3, Δ exon 4, and Δ exon 3,4 splice variants, but IL-33 variants missing exon 5 did not (Fig. 2*B*). This result is consistent with re-

Gordon, Alternative splicing of interleukin-33 and type 2 inflammation in asthma, PNAS 2016

as well as in [2017]

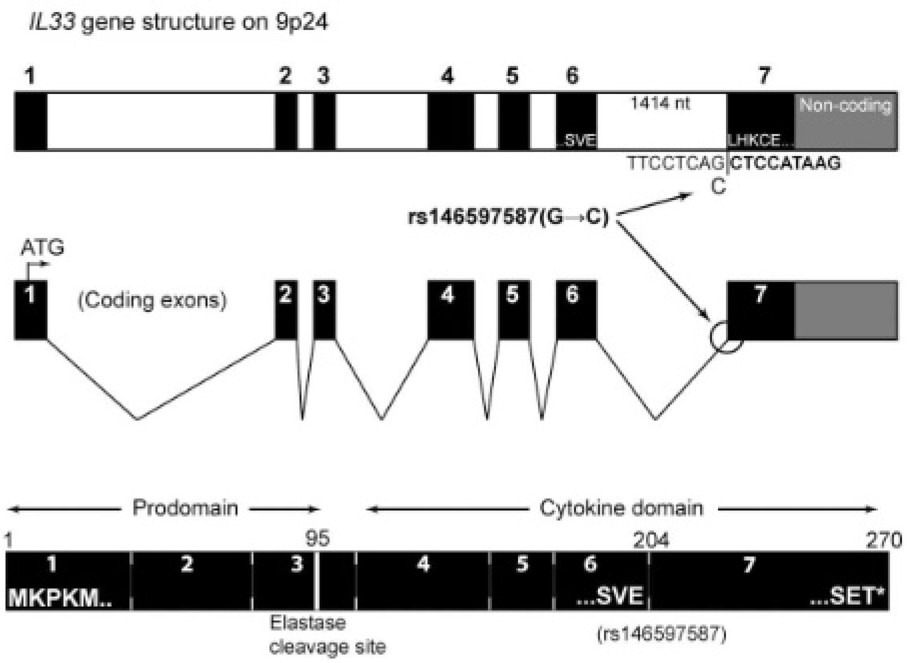
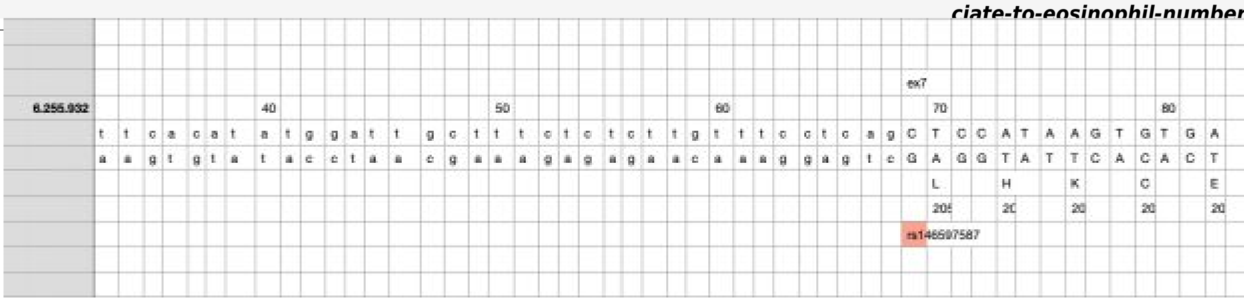


Fig 3A Smith et al. A rare IL33 loss-of-function mutation reduces blood eosinophil counts and protects from asthma, PLoS Genetics 2017 – describes the splice site as NM_001199640:exon7:c.487-1G>C or rs146597587-C

So I did a sequence match to compare the new finding with these older publications.



own sequence match exon7 using data from dbSNP, UCSC GoldenPath and Uniprot – reference is hg19

Indeed, the 2017 paper already described rs146597587 which is probably identical to the splice acceptor 9-6250473-G-C in Astra UK Phewas (genome positions do not match – I used hg19 while I don’t know the Astra reference) . Astra says also c.613-1G>C while rs146597587 is just upfront of my codon 205 (3*205=615) whatever that means.

The Astra UK Phewas at least confirms the Iceland paper above

> rs146597587-C associates with lower eosinophil counts (ß= -0.21 SD, P = 2.5×10-16, N = 103,104), and reduced risk of asthma in Europeans (OR = 0.47; 95%CI: 0.32, 0.70, P = 1.8×10-4, N cases = 6,465, N controls = 302,977). Heterozygotes have about 40% lower total IL33 mRNA expression than non-carriers and allele-specific analysis based on RNA sequencing and phased genotypes shows that only 20% of the total expression is from the mutated chromosome. In half of those transcripts the mutation causes retention of the last intron, predicted to result in a premature stop codon that leads to truncation of 66 amino acids.

So it is basically a rediscovery meaning that we reached saturation.