

ALLERGY, GENETICS

# AN UPDATE ON THE ASTHMA EXOME

12.05.2023

Here is a quick update on some genes of my [recent asthma exome paper](#) coming now from the 1 M exome paper published yesterday as a [preprint](#).

Variant	rsID	Source	Consequence	Annotations	AAF	Type
2:102338927:C...	rs757810551	Exome	p.Asn54LysfsTer18	frameshift (4)	0.000004	Indel (deletion)
2:102340688:C:A		Exome	p.Ser157Ter (3)	stop_gained (3)	0.000007	SNP
2:102343291:T:A	rs1418752113	Exome	p.Cys282Ter (3)	stop_gained (3)	0.000029	SNP
2:102343310:AT...	rs1223668698	Exome	p.Ile289LysfsTer4	frameshift (3)	0.000036	Indel (deletion)
2:102343343:C:T		Exome	p.Gln300Ter (3)	stop_gained (3)	0.000007	SNP
2:102343354:T:A	rs1481578726	Exome	p.Cys303Ter (3)	stop_gained (3)	0.000011	SNP
2:102349150:G...		Exome	p.Glu398Ter (2)	frameshift (2)	0.000007	Indel (insertion)
2:102351549:A...	rs78111634	Exome	p.Val434TrpfsTer1E	frameshift (1)	0.000018	Indel (deletion)
2:102351565:C:T	rs764765442	Exome	p.Arg439Ter (1)	stop_gained (1)	0.000087	SNP
2:102351811:AG:A		Exome	p.Arg521SerfsTer3	frameshift (1)	0.000011	Indel (deletion)
2:102351910:C:T		Exome	p.Gln554Ter (1)	stop_gained (1)	0.000004	SNP

loss of function variants IL1RL1. <https://rgc-mcps.regeneron.com/gene/IL1RL1>, 12 May 2023

Also [ClinVar](#) shows that the IL33 receptor is not “essential” making [anti IL33 receptor antibodies](#) like etokimab, itepekimab, tozorakimab a safe therapy although not being effective in any LOF mutation carrier.

The most interesting thing in the preprint is in supplemental table 2 with the s-het values for 16,704 genes. From that table I have selected my favorite target IL33 receptor together with TLR1, ALOX15, GSDMA, IL13 and IKZF3 (BTNL2 could not be found in the list).

Gene	mean	sd	shet_lower	shet_upper	shet_cons_n	N_total	mutation_rate	MAF	CDI_length	pKD	ex_lcf	loaf	loaf_underpower	annotations	
IL33	0.84743714660254	0.013483299918555	0.026244102824195	0.087022794644109	FALSE	14	1648159.33333333	3.9764194e-07	0.49433437596071e-06	441	FALSE	0.68818	1.085	TRLE	ClinVarHGMD
IL1RL1	0.818021988443879	0.007923368030277	0.714609619324771	0.021761142673262	FALSE	86	1648120.8	3.691362e-07	0.4200870340306e-06	1671	FALSE	0.2142	1.173	FALSE	ClinVarHGMD
TLR1	0.20732960361115726	0.227961543880399e-05	0.0112319624987813	0.0214322891782073	FALSE	652	1648287.20829206	0.2253304e-07	0.00238653721679108	2281	TRUE	1.4112	1.881	FALSE	ClinVarHGMD
ALOX15	0.20385014327638213	8.77811483632715e-05	0.026878970956618	0.02823345724515637	FALSE	7090	1648329.23843682	1.8115459e-06	0.002637120732381785	1989	TRUE	NA	NA	NA	ClinVarHGMD
GSDMA	0.20439695022181552	0.02818048834235837	0.0276347176257818	0.06442623031962988	FALSE	651	1648198.75	1.612243e-06	0.00238498292773617	1338	TRUE	1.0187	1.422	FALSE	ClinVarHGMD
IKZF3	0.1265851524021	0.0284181188882073	0.0817791938827628	0.22229538860353	TRUE	15	1648277.88888889	1.22256721e-08	0.1384574232181e-06	1533	FALSE	0.09412	294	FALSE	ClinVarHGMD,cosmic

asthma exome <https://rgc-mcps.regeneron.com/gene/IL1RL1>, 12 May 2023

IKZF3 would be dangerous to be touched ([see my 2008 commentary](#)) while in the [2022 ex-](#)

[ome paper](#) I also found only protective variants in the 5'-UTR but not any LOF variant - probably as IKZF3 is the only essential gene in the list.

So what's next? I am still thinking how to reduce my exome set to the causal variants as half of the mutations are probably LD artefacts. And well, it would be super interesting to examine now two extreme inbred populations for their mutation spectrum, loosing either asthma variants by healthy (Amish) or diseased founders (Tristan da Cunha). Unfortunately there is little hope that this will happen - current science is built more on competition than collaboration.