

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](#).

Source	#	EXPORT		RESET TABLE		Search table...									
Variant type	#	Variant	↓↑	rsID	↓↑	Source	↓↑	Consequence	↓↑	Annotations	↓↑	AAF	↓↑	Type	↓↑
Exomes	11/835			11 option(s)	7 option(s)	1 option(s)	11 option(s)	2 option(s)				0.000004		Indel (deletion)	
SNPs	6/2,474	2:102338927:C..	rs757810551	Exome	p.Asn54LysfsTer18	frameshift (4)									
Indels	5/158	2:102340688:CA		Exome	p.Ser157Ter (3)	stop_gained (3)						0.000007		SNP	
Annotations	#	2:102343291:T:A	rs1419752113	Exome	p.Cys282Ter (3)	stop_gained (3)						0.000029		SNP	
LOFs only	11/12	2:102343310:AT...	rs1223688698	Exome	p.Ile289LysfsTer41	frameshift (3)						0.000036		Indel (deletion)	
Intronic	0/2,336	2:102343343:CT		Exome	p.Gln300Ter (3)	stop_gained (3)						0.000007		SNP	
missense	0/169	2:102343354:T:A	rs1481578726	Exome	p.Cys303Ter (3)	stop_gained (3)						0.000011		SNP	
synonymous	0/71	2:102349150:G...		Exome	p.Glu398Ter (2)	frameshift (2)						0.000007		Indel (insertion)	
show more (8)		2:102351549:A..	rs761111634	Exome	p.Val434TrpfsTer15	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:CT		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).

GeneName	mean	sd	shet_lower	shet_upper	shet_cons_n	Nt_total	mutation_rate	NaN	CDS_length	pID	oe_pct	local	local_low	underpower	annotations
IL1RL1	0.0474047146802514	0.0148020969318585	0.0264411626041956	0.0801927546441109	FALSE	14	1849159.338533033	0.8764194e-07	0.49430437258631e-06	441	FALSE	0.888118	1.028	TRUE	ClinVar+GMDB
IL1RL1	0.2130373884420876	0.0779223246634277	0.0148020969318585	0.3203161162013667	FALSE	38	1848122.4	0.861323e-07	0.42008672441320e-06	1815	FALSE	0.8143	1.172	TRUE	ClinVar+GMDB
TLR1	0.20732962061158729	0.22796542868089e-05	0.011231862249678132	0.0214322891780373	FALSE	682	18480317.5802900	0.22953304e-07	0.020385652721679109	2381	TRUE	1.4112	1.481	FALSE	ClinVar+GMDB
ALOX15	0.0328501627382113	0.77851683632316e-05	0.002887887209516218	0.008823193725151637	FALSE	1080	18480302.2384360	1.8115d59e-06	0.005017125132468785	1889	TRUE	NA	NA	NA	ClinVar+GMDB
GSDMA	0.00398950533783162	0.0016048834235937	0.0017604777695719	0.0044292360106294	FALSE	651	1848188.75	1.61233e-06	0.005391998280277367	1234	TRUE	1.2187	1.432	FALSE	ClinVar+GMDB
IKZF3	0.1505851524021	0.036181188882073	0.0817791038821438	0.2229538892503	TRUE	15	1848577.8068067	1.203587216e-06	0.13848243232189e-06	1530	FALSE	0.093412	294	FALSE	ClinVar+GMDB,cancer

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.