

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...			
Exomes	11/835						
Variant type	#						
<input checked="" type="checkbox"/> SNPs	6/2,474						
<input checked="" type="checkbox"/> Indels	5/158						
Annotations	#						
<input checked="" type="checkbox"/> LOF's only	11/12						
Select All / Deselect All							
<input checked="" type="checkbox"/> Intronic	0/2,336						
<input checked="" type="checkbox"/> missense	0/169						
<input checked="" type="checkbox"/> synonymous	0/71						
...show more (8)							
Variant	rsID	Source	Consequence	Annotations	AAF	Type	
11 option(s)	7 option(s)	1 option(s)	11 option(s)	2 option(s)		3 option(s)	
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	rs1419752113	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.Val434TrpfsTer1	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).

	GeneName	mean	sd	shet_lower	shet_upper	shet_conc_n	N total	mutation_rate	MAF	CDL length	pKD	oe_lcl	loef	loef_underpower	annotations	
✓	IL33	0.0474047146602014	0.0134832999118555	0.0280441102834195	0.08032759444109	FALSE	14	1848159.33333333	0.0764194e-07	0.4943343755937e-05	441	FALSE	0.8819	1.085	TRUE	ClinVarHGMD
✓	IL1RL1	0.0180218684439719	0.00792233600342277	0.014609610334771	0.0219411402013367	FALSE	89	1848159.33333333	0.0913439e-07	0.4943343755937e-05	1971	FALSE	0.8142	1.173	FALSE	ClinVarHGMD
✓	TLR1	0.007321650381115726	0.007196143688309e-05	0.00133719624681713	0.00143328947802073	FALSE	652	1848159.33333333	0.2253334e-07	0.00238933721876108	2381	TRUE	1.8112	1.851	FALSE	ClinVarHGMD
✓	ALOX15	0.00355214327538213	8.77851383632715e-05	0.0024878170956618	0.00323345724515637	FALSE	1060	1848159.33333333	1.8115439e-06	0.002437120132288795	1989	TRUE	NA	NA	NA	ClinVarHGMD
✓	GSDMA	0.0040969522785152	0.00218048834235637	0.00276347176257618	0.00442623615962988	FALSE	651	1848159.33333333	1.812234e-06	0.00238933721876108	1338	TRUE	1.8187	1.432	FALSE	ClinVarHGMD
✓	IKZF3	0.1350851524031	0.0384181188882079	0.0817791838821638	0.22226538880553	TRUE	15	1848159.33333333	1.2225672e-06	0.1354573423218e-05	1530	FALSE	0.004102	294	FALSE	ClinVarHGMD, 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.

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