

ESP: Asthma Exome Sequencing

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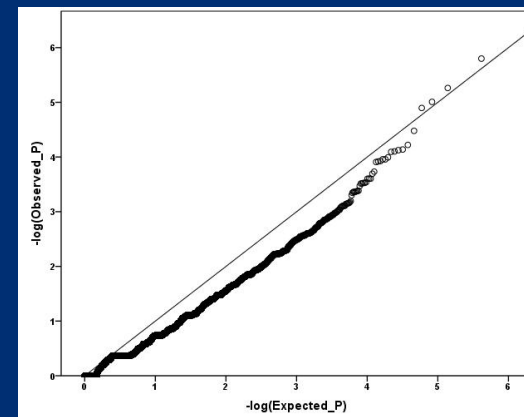
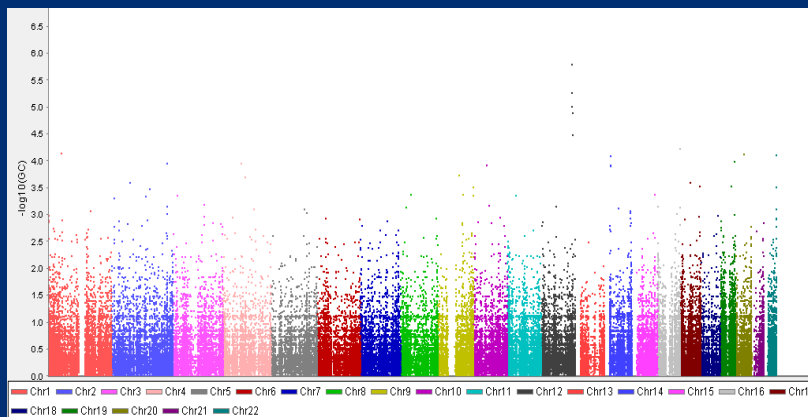


Percent or mean (SD)	Nonsevere n=109	Severe n=82
Sex (% female)	68	61
Age at enrollment, years	32 (11)	31 (16)
Asthma duration, years	21 (11)	21 (14)
Body mass index, kg/m²	32 (9)	31 (12)
Baseline lung function:		
FEV₁ % of predicted	80 (18)	70 (23)
FVC % of predicted	92 (17)	84 (21)
FEV₁/FVC ratio	0.73 (0.1)	0.69 (0.1)
Total serum IgE, IU/mL	417 (749)	703 (1356)
Atopy status, % ≥ 1 positive skin prick test	95	85

Characteristics of 191 SARP African-Americans with exome sequencing by severity status

Single variant analysis results

Gene	Variant	Chr:Position	Variant function	MAF Severe n=82	MAF Nonsevere n=109	Fisher P value	Logistic P value	QD	AB	SB
P2RX7	rs3751144	12:121622239	syn	0.26	0.08	1.59E-06	7.95E-06	21.23	0.49	-35641.9
P2RX7	rs2230911	12:121615131	missense (T357S)	0.26	0.09	5.47E-06	2.10E-05	18.87	0.54	-43025.4
TCTN2	rs73416301	12:124156637	syn	0.20	0.05	3.32E-05	5.09E-05	18.32	0.51	-44832.4
ZNF469	rs74032864	16:88495021	syn	0.07	0.22	6.01E-05	0.0005	27.2	0.55	-6650.77
MYH7	rs2069542	14:23900794	syn	0.59	0.39	8.05E-05	0.0001	24.02	0.52	-133486

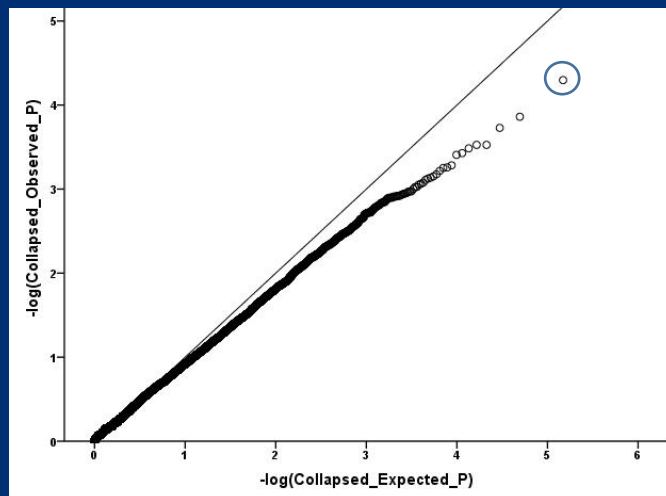


P2RX7 GWAS SNPs have been associated with asthma exacerbations in 3 NHLBI asthma clinical trials (Denlinger, submitted)

Collapsed analysis results

With thanks to Lili Huang
and Rasika Mathias

Gene	Transcript	Location	Number of variants in analysis	Test	P value
SPEG	NM_005876	chr2:220299815..220356901	25	CALPHA	5.05E-05
ADSSL1	NM_199165	chr14:105196232..105213321	8	FRQWGT BURDEN	0.00014 0.00019
SPICE1	NM_144718	chr3:113164170..113187981	8	BURDEN FRQWGT	0.000298 0.000298
IGIP	NM_001007189	chr5:139508113..139508154	2	FRQWGT	0.00033



SPEG: marker for differentiated vascular smooth muscle cells

- 17/20 white SARP severe asthmatics share two missense mutations
- ‘Adjacent’ to linked region from Dutch family studies; 6/19 probands share 3 missense mutations
- Not differentially expressed in lung cells (epithelial or macrophages) from 110 SARP mild to severe asthmatics

- A cluster approach has been used to define asthma heterogeneity
- Exome chip is being run on the SARP population to study:
 - TH2 driven mild to severe asthma clusters
 - Further investigative role of rare variants in all SARP clusters
- SARP3 is now a longitudinal study with collection of additional biomarkers and steroid characterization

