

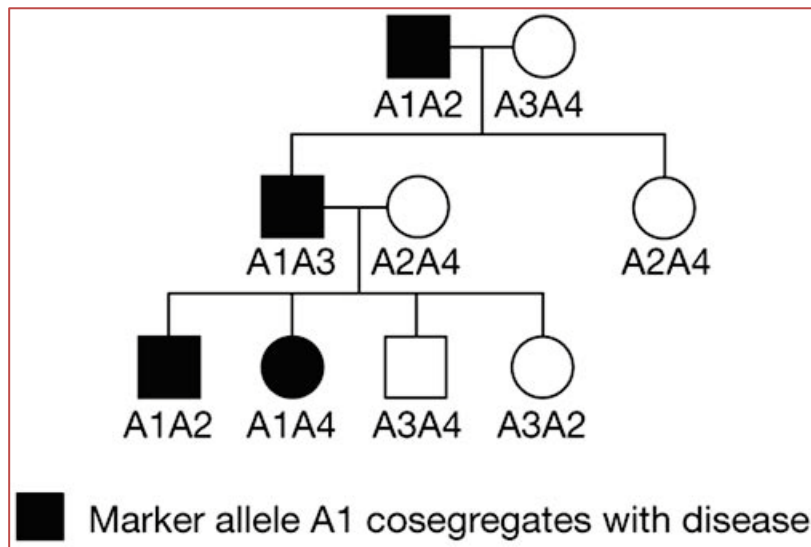


Asthma Genetics

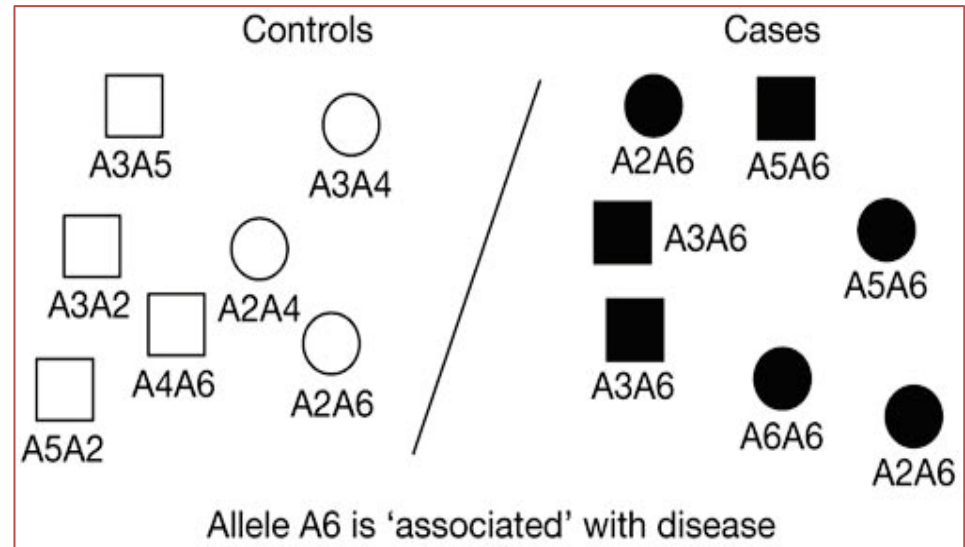
Donata Vercelli, MD
Functional Genomics Laboratory, Arizona Respiratory Center
Arizona Center for the Biology of Complex Diseases (ABCD)
Department of Cellular and Molecular Medicine
The Bio5 Institute
University of Arizona
Tucson, AZ, USA

Classical genetic population studies

Genotype \leftrightarrow Phenotype

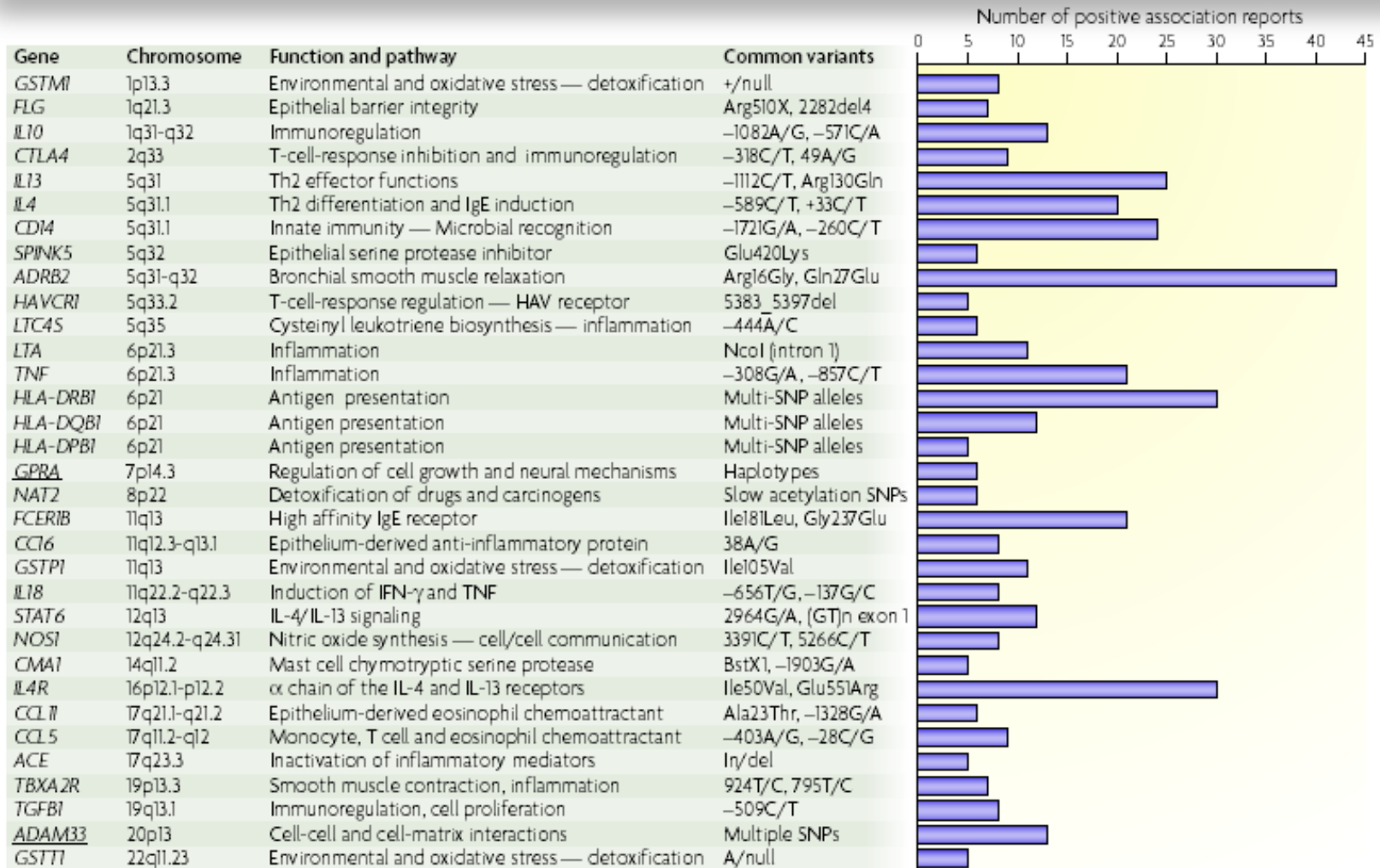


Linkage studies



Candidate gene association studies

An example: Asthma genetics



Genetics of Asthma and Asthma-related Traits - 2011

Study	Disease	Sample	Region	Gene	Risk allele frequency in controls	OR
Ferreira 2011	Asthma	12,475 European cases, 19,967 European controls	1q21.3	<i>IL6R</i>	0.37	1.09
			11q13.5	<i>LRRC32</i>	0.34	1.09
			10q21.1	<i>PRKG1</i>	0.11	1.13
			13q21.31	<i>PCDH20</i>	0.51	1.08
Hirota 2011	Asthma	1,532 Japanese cases, 3,304 Japanese controls	6p21.32	<i>NOTCH4</i>	0.50	1.21
			5q22.1	<i>TSLP</i>	0.35	1.17
			6p21.32	<i>PBX2</i>	0.58	1.17
			10p14	<i>LOC338591</i>	0.433	1.16
			6p21.32	<i>C6orf10</i>	0.62	1.17
			6p21.32	<i>HLA-DQB1</i>	0.63	1.17
			12q13.2	<i>IKZF4</i>	0.18	1.19
			6p21.32	<i>HLA-DRA</i>	0.61	1.15
			4q31.21	<i>LOC729675</i>	0.27	1.16
			6p21.32	<i>HLA-DQA2</i>	0.79	1.18
			6p21.32	<i>BTNL2</i>	0.25	1.16
			12q13.2	<i>CDK2</i>	0.23	1.15
			6p21.32	<i>HLA-DOA</i>	0.26	1.13
			4q31.21	<i>GAB1</i>	0.25	1.12

Genetics of Asthma and Asthma-related Traits - 2011

Study	Disease	Sample	Region	Gene	Risk allele frequency in controls	OR
Torgerson 2011	Asthma	2,088 European American cases, 1,612 Afr. American and Afr. Caribbean cases, 1,688 Latino cases	17q12 2q12.1 5q22.1 9p24.1 1q23.1 11q23.2 1q21.3	<i>GSDMB</i> <i>IL1RL1</i> <i>TSLP</i> <i>IL33</i> <i>PYHIN1</i> <i>C11orf71</i> <i>CRCT1</i>		
Noguchi 2011	Asthma	938 Japanese pediatric cases, 2,376 controls	8q24.11 6p21.32	<i>SLC30A8</i> <i>HLA, DPB1</i>	0.31 0.14	1.34 1.4
Ferreira 2010	Asthma	986 European cases, 1846 controls	17q12	<i>ORMDL3</i>	0.43	1.33
Moffatt 2010	Asthma	10,365 cases, 16,110 controls	6p21.32 9p24.1 2q12.1 15q22.33 17q21.1 22q12.3	<i>HLA-DQ</i> <i>IL33</i> <i>IL18R1</i> <i>SMAD3</i> <i>GSDMA</i> <i>IL2RB</i>	0.58 0.16 0.62 0.49 0.45 0.56	1.18 1.2 1.15 1.12 1.17 1.12
December 2011						

Genetics of Asthma and Asthma-related Traits - 2011

Study	Disease	Sample	Region	Gene	Risk allele frequency in controls	OR
Li 2010	Asthma	607 cases, 3,294 white controls	5q31.1 15q21.2 20p13	<i>RAD50</i> <i>SCG3</i> <i>KIAA1271</i>	0.21 NR NR	1.64 NR NR
Sleiman 2009	Asthma	793 European child cases, 1,988 European child controls	1q31.3	<i>DENND1B</i> , <i>CRB1</i>	0.85	1.43
Himes 2009	Asthma	422 cases, 1,533 controls	5q12.1	<i>PDE4D</i>	0.29	1.18
Moffatt 2007	Asthma	994 cases, 1,243 controls	17q12	<i>ORMDL3</i>	0.52	1.45
Hancock 2009	Asthma (childhood onset)	492 Mexican trios	9q21.31	<i>TLE4</i> , <i>CHCHD9</i>	0.78	1.64
Weidinger 2008	Serum IgE levels	1,530 individuals	1q23.2 5q31.1	<i>FCER1A</i> <i>RAD50</i>	0.26 0.23	19.2 % decrease 13.9 % increase

Problems in Complex Disease Biology

- Phenotypic heterogeneity
- Sample size
- Relative effects of common and rare variants
- Structural variation (copy number variants)
- Gene-gene and gene-environment interactions
- Developmental processes
- Epigenetic factors

“There is something we just don’t fundamentally understand, so different from what we are thinking about that we are not thinking about it yet” (L. Kruglyak)