Missing Heritability *circa* 2009

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Missing Heritability Ten Years On
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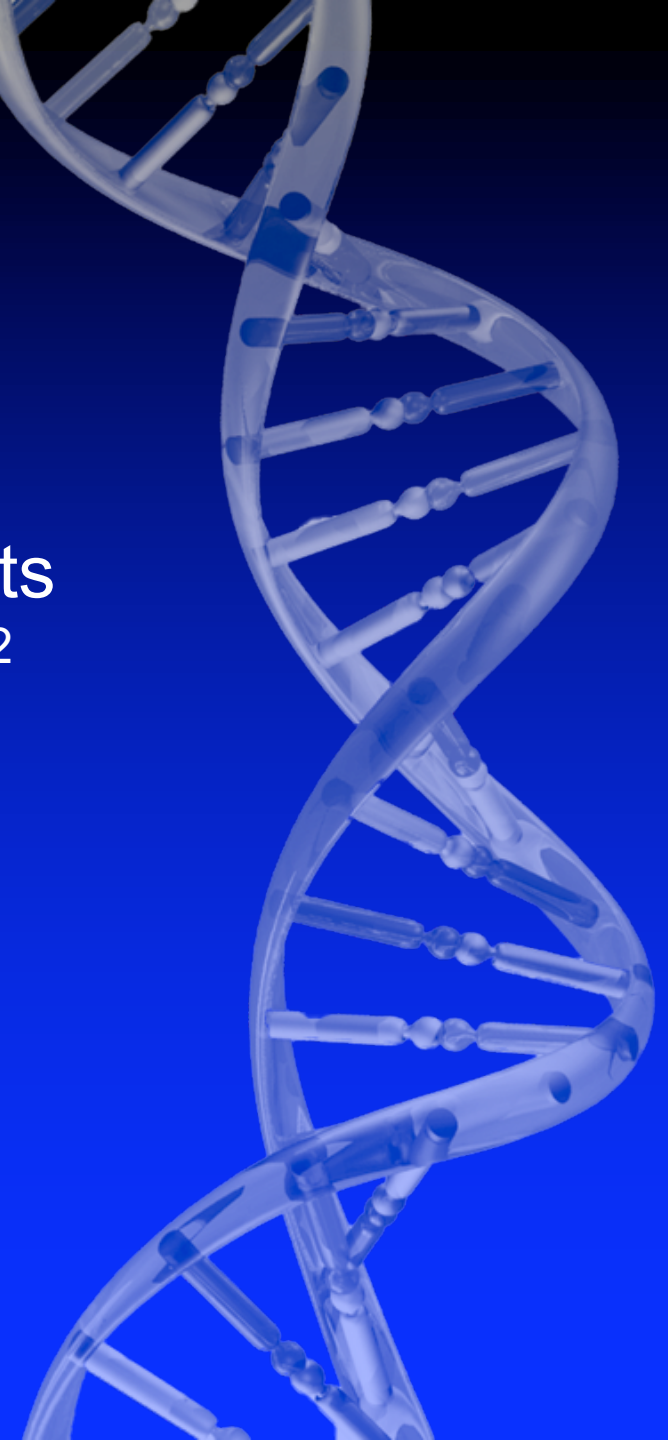
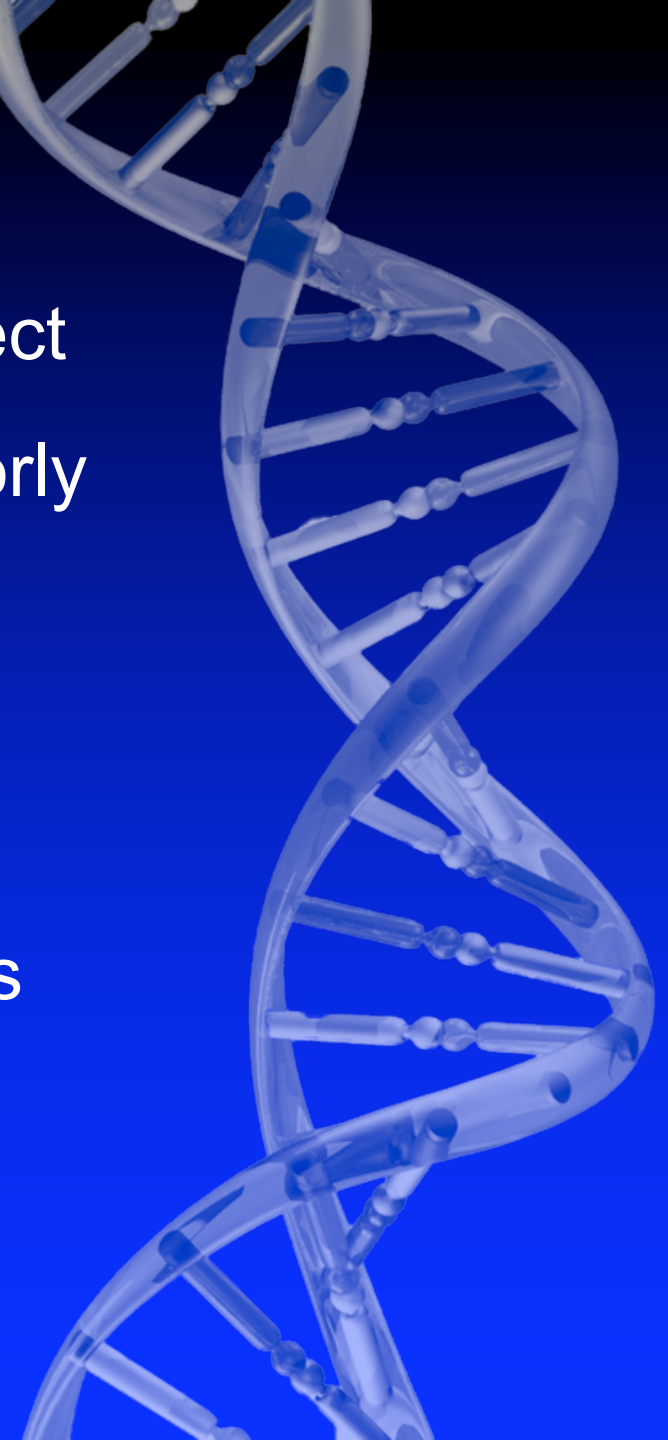
Way Back Then…

- GWAS (barely 4 years old!) had identified hundreds of associated variants
- Most GWAS variants conferred small increments in risk and explained only small proportion of h^2
- 40 loci for height explained 5% of phenotypic variance, but estimated h^2 about 80%
- Where was all this heritability?



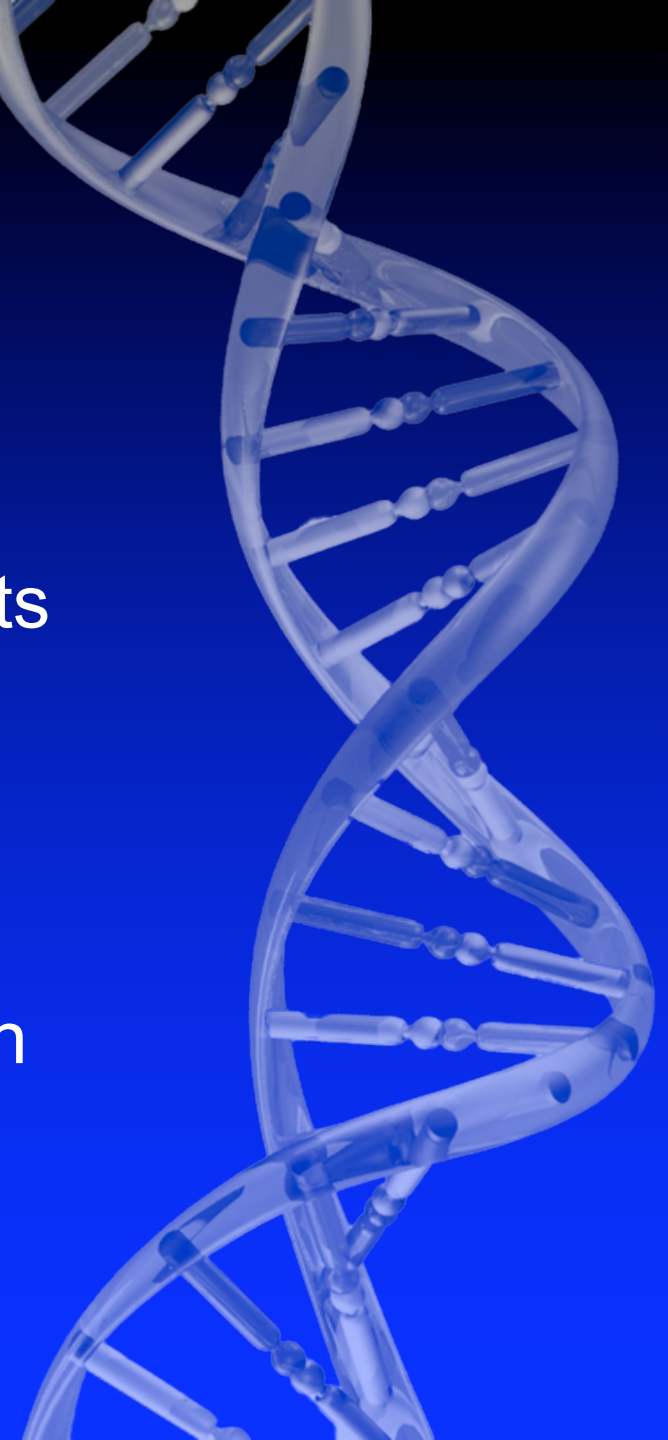
Proposed Explanations

- Much larger numbers of variants of smaller effect
- Rarer variants (possibly with larger effects) poorly detected by available arrays
- Structural variants poorly captured by arrays
- Gene-gene interactions
- Gene-environment correlations and interactions
- Inadequate accounting for shared environment
- Over-estimation of h^2



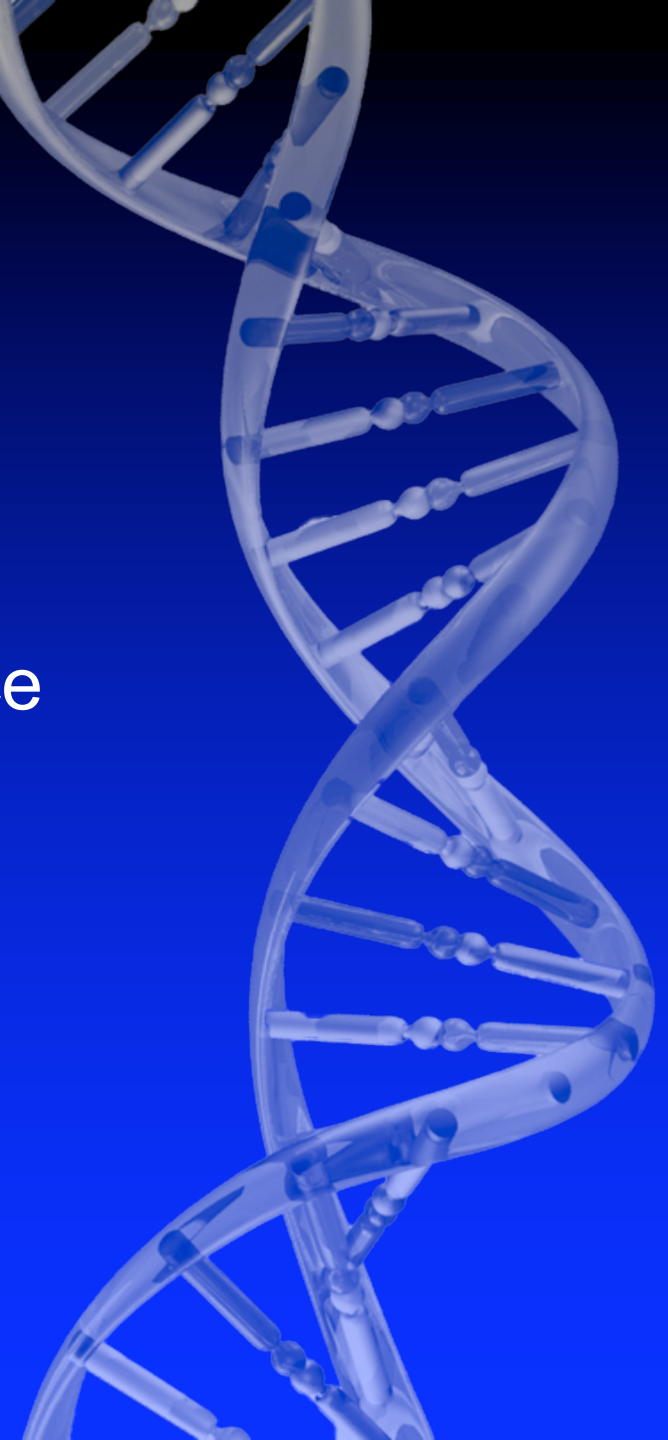
Bold Predictions

- Expanded diversity should:
  - Identify more rare and high impact variants
  - Narrow association regions
- Isolated populations may identify unique variants
- High impact rare variants will be found underlying or co-located with common variants
- Low frequency variants could have substantial effect sizes without clear Mendelian segregation
- Numerous rare variants in a gene will have disparate effects on phenotype



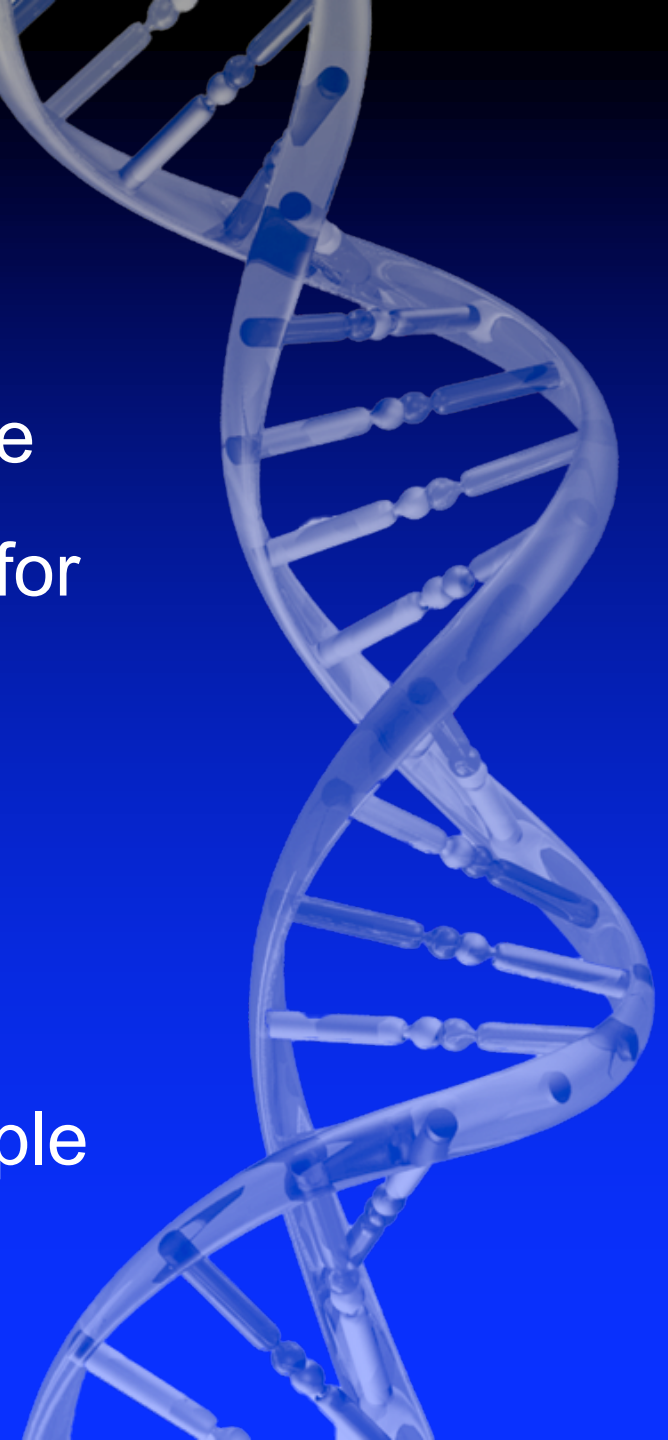
Bold Predictions

- Heritability estimates in unrelated individuals could be more accurate than family-based
- Well-phenotyped groups; large, accessible families; and iterative phenotyping will help
- Improved CNV detection algorithms will produce rapid progress
- Other fruitful sources or approaches:
  - Copy-neutral SVs (inversions and translocations)
  - Chromosomal-region-specific matching
  - Exhaustive characterization of key trait(s)



Things Remaining to be Determined

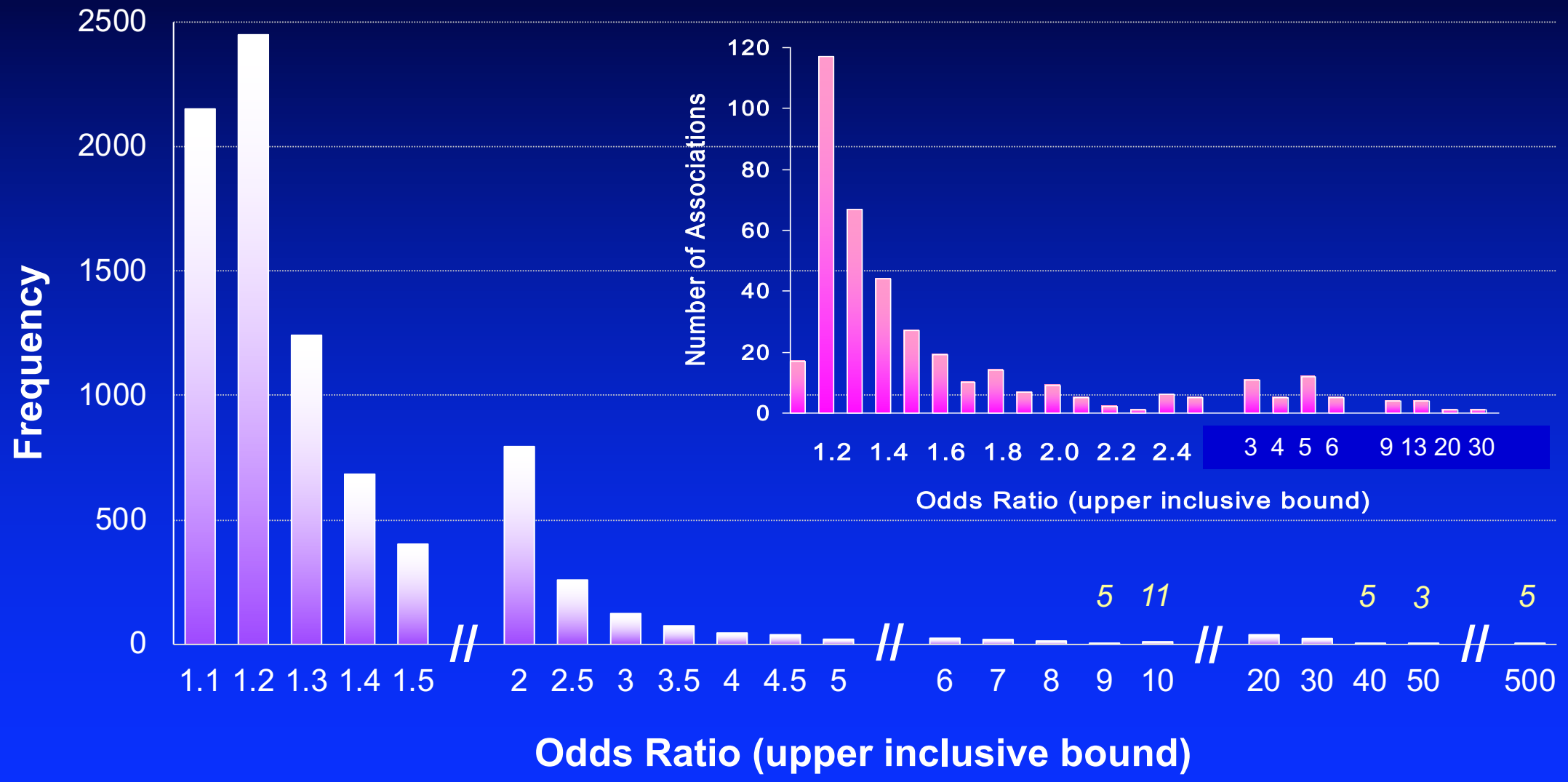
- Best approaches for:
  - Combining functional and statistical evidence
  - Using common SNPs to predict and control for differences in rare SNPs
  - Pooling: classes of variants, optimal MAF
- Has the common disease-common variant hypothesis stood the test of time?
- Is much of the information still provided by people at the extremes of trait distributions?



Heritability Estimates Then and Now

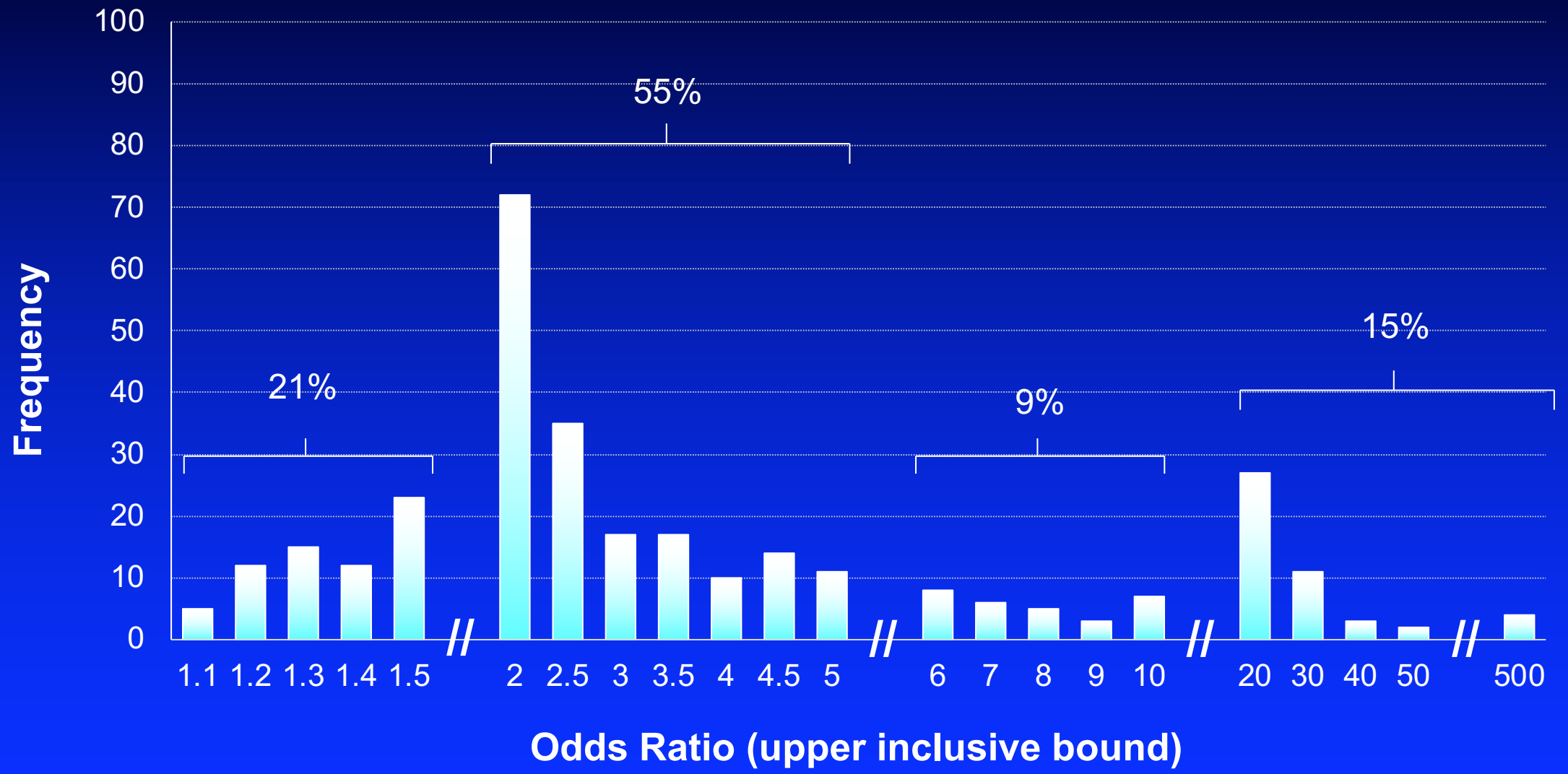
Trait	Source	N Alleles	% h2	Measure
AMD	Maller 2006	5	50	Sibling recurrence risk
	Fritsche 2016	52	55	Disease variability
Crohn's	Barrett 2008	32	20	Liability
	Liu 2017	203	13	Liability
SLE	SLEGEN 2008	6	15	Sibling recurrence risk
	Bentham 2017	43 (Europ)	15	Disease variability
	Molineros 2017	78 (Asian)	28	Variance in liability
T2DM	Zeggini 2008	18	6	Sibling recurrence risk
	Mahajan 2018	243	18	Disease liability
HDL-C	Kathiresan 2008	7	5.2	Residual phenotypic variance
	Surakka 2015	62	12.8	Variance
Height	Visscher 2008	40	5	Phenotypic variance
	Nolte 2017	635	15.5	Phenotypic variance

Histogram of Odds Ratios, All MAFs



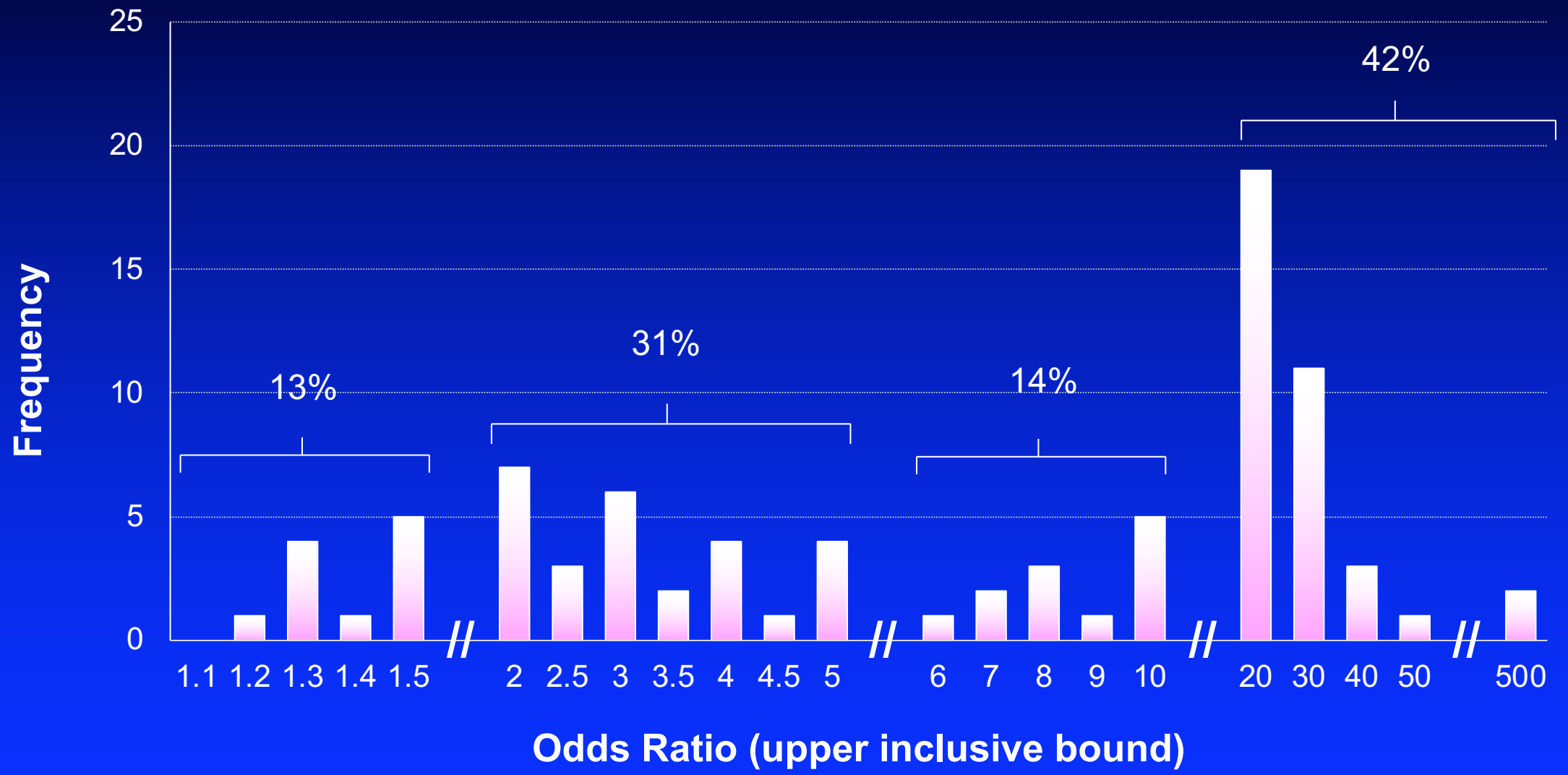
NHGRI-EBI Catalog, 8,439 discrete trait OR, 4/26/18

Histogram of Odds Ratios, MAF ≤ 0.05



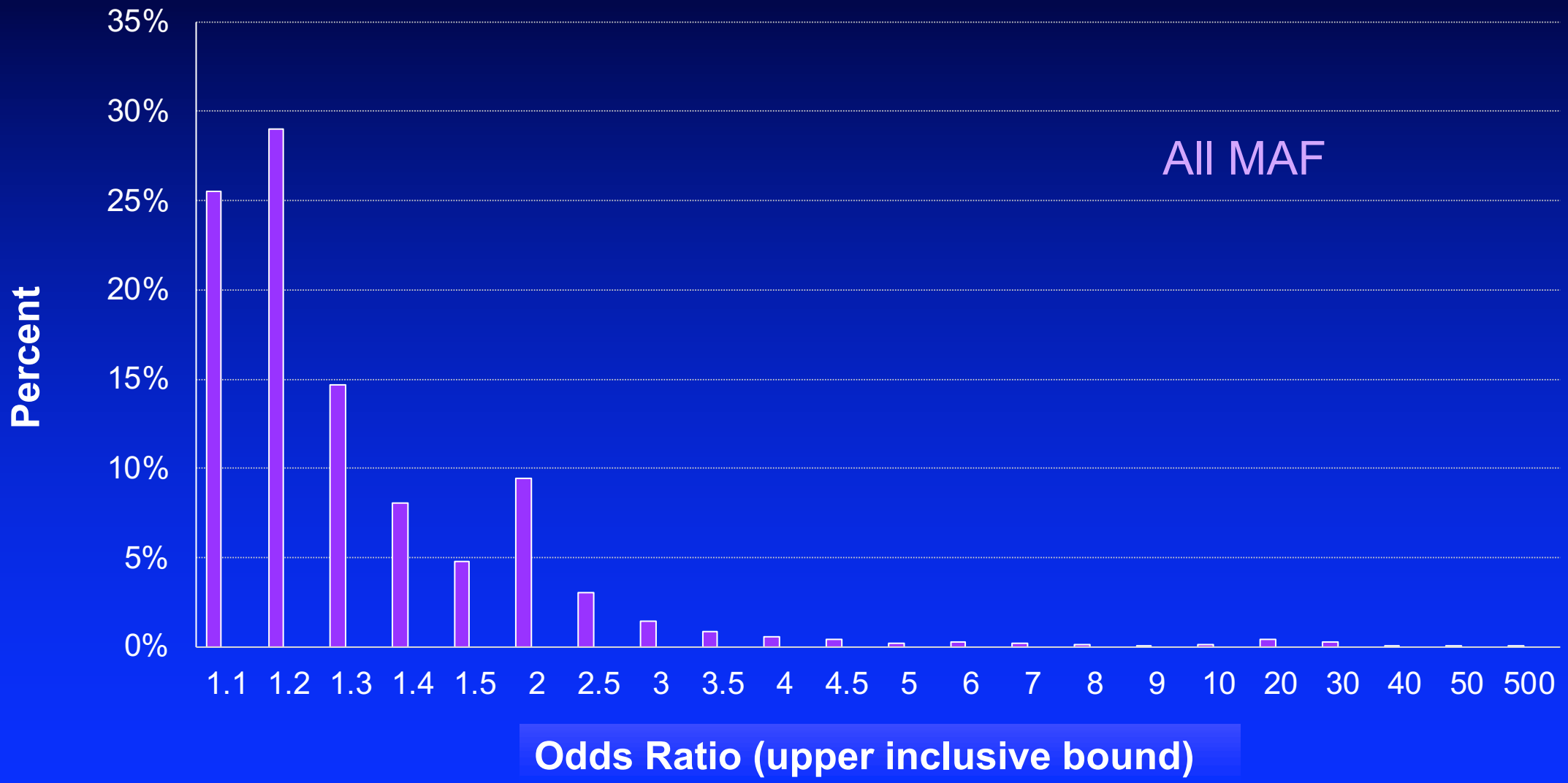
NHGRI-EBI Catalog, 323 discrete trait OR for MAF < 0.05, 4/26/18

Histogram of Odds Ratios, MAF ≤ 0.01



NHGRI-EBI Catalog, 86 discrete trait OR for MAF < 0.01, 4/26/18

Histogram of Odds Ratios, by MAF



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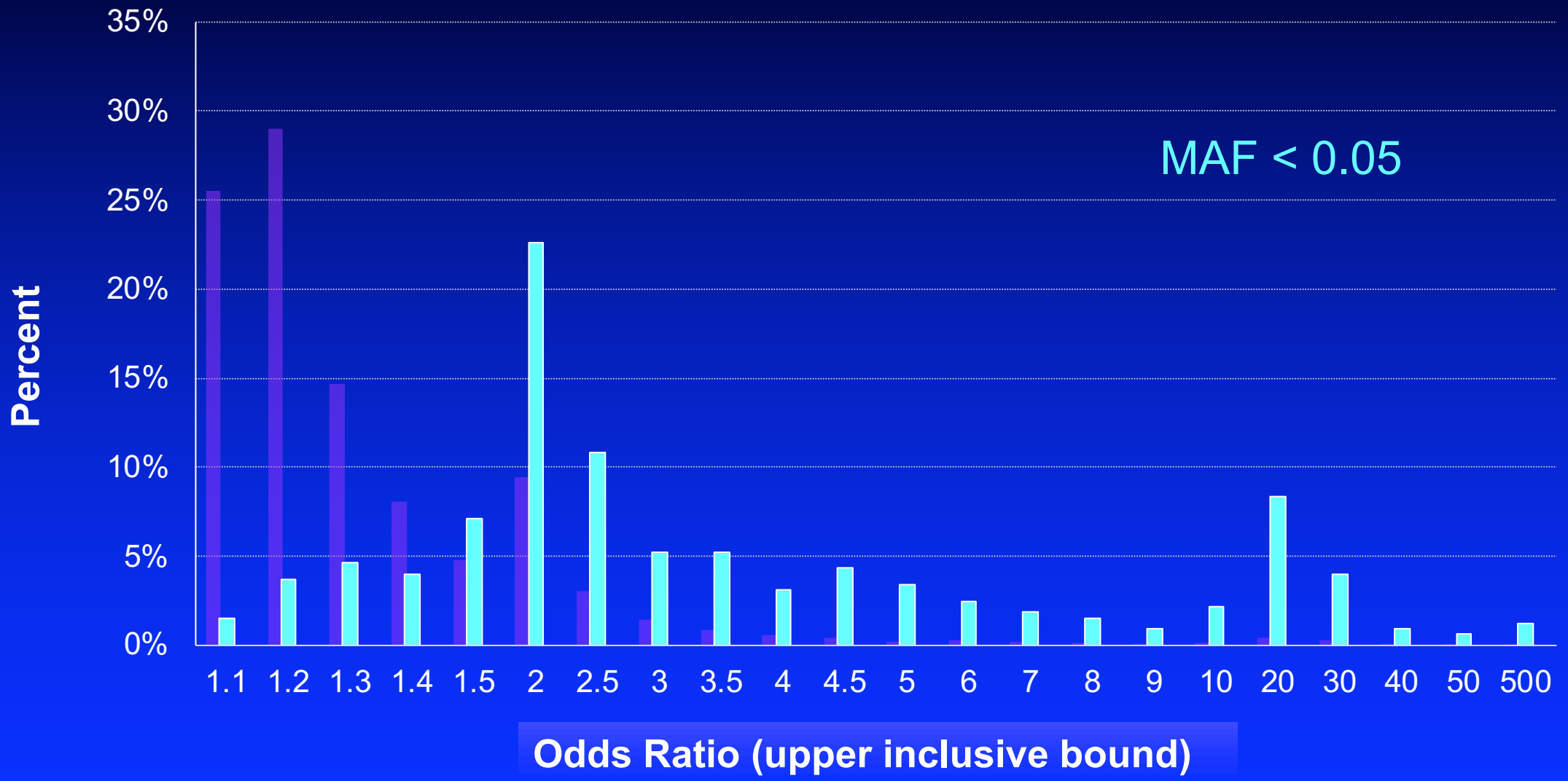

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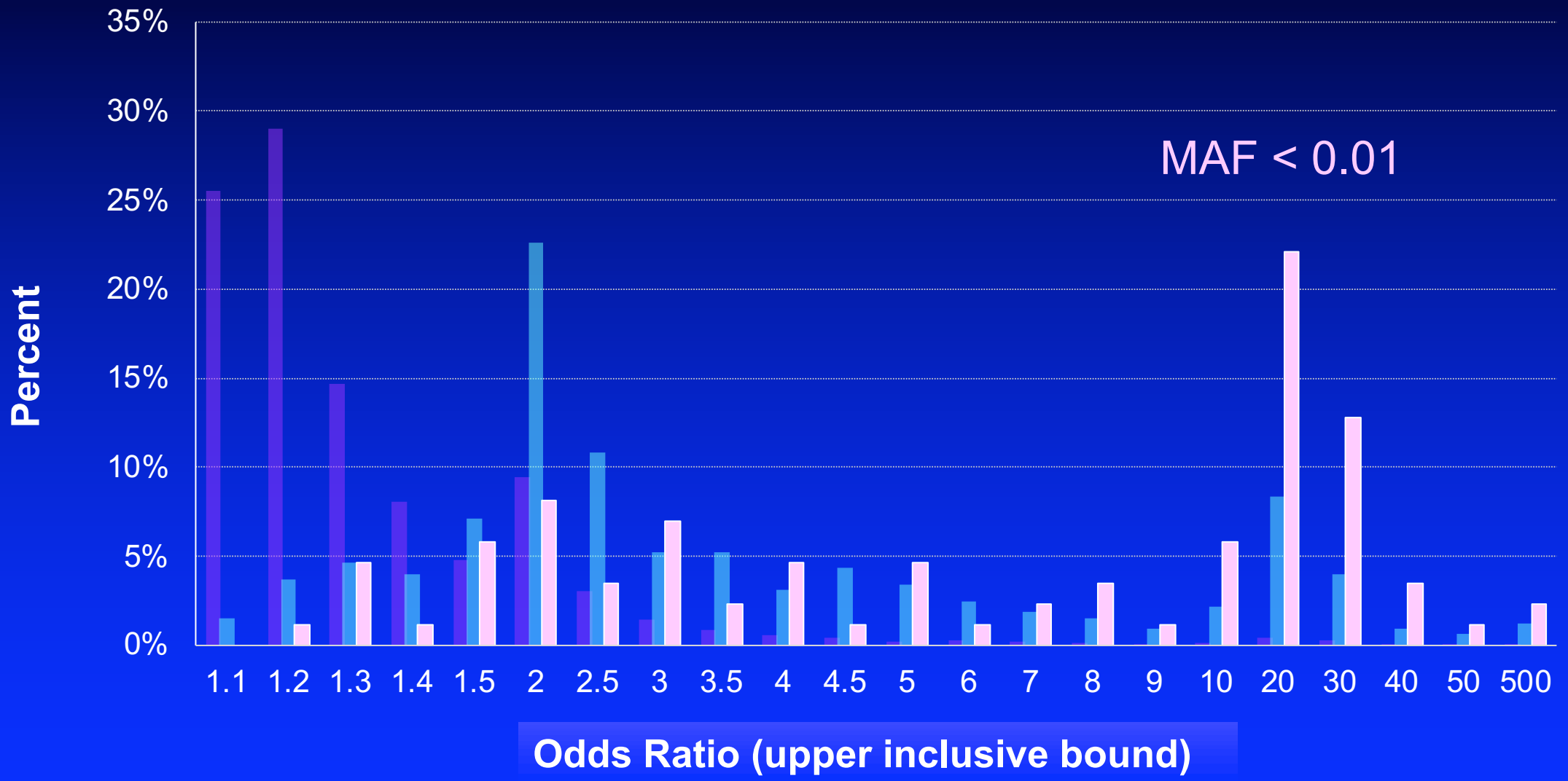

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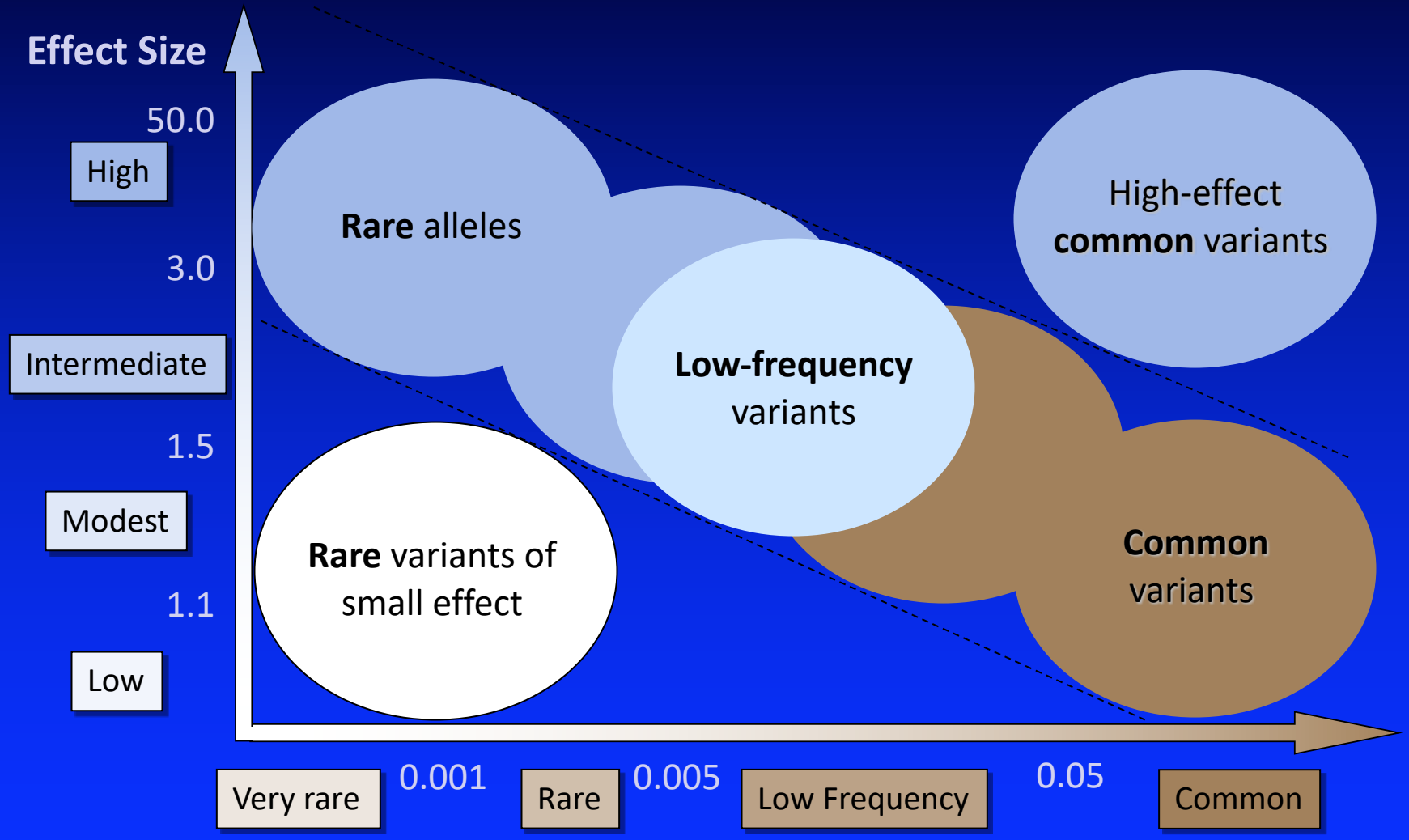
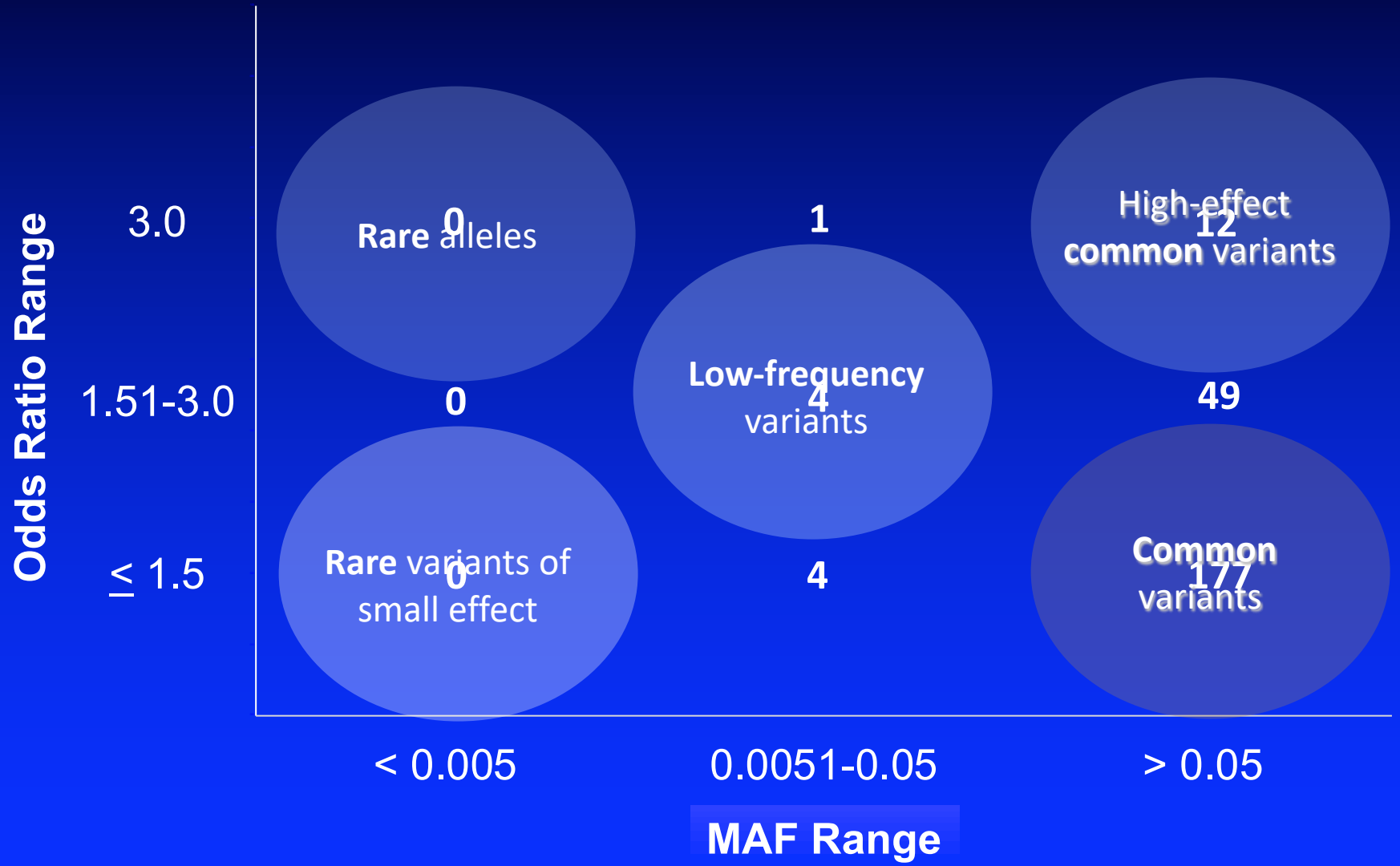


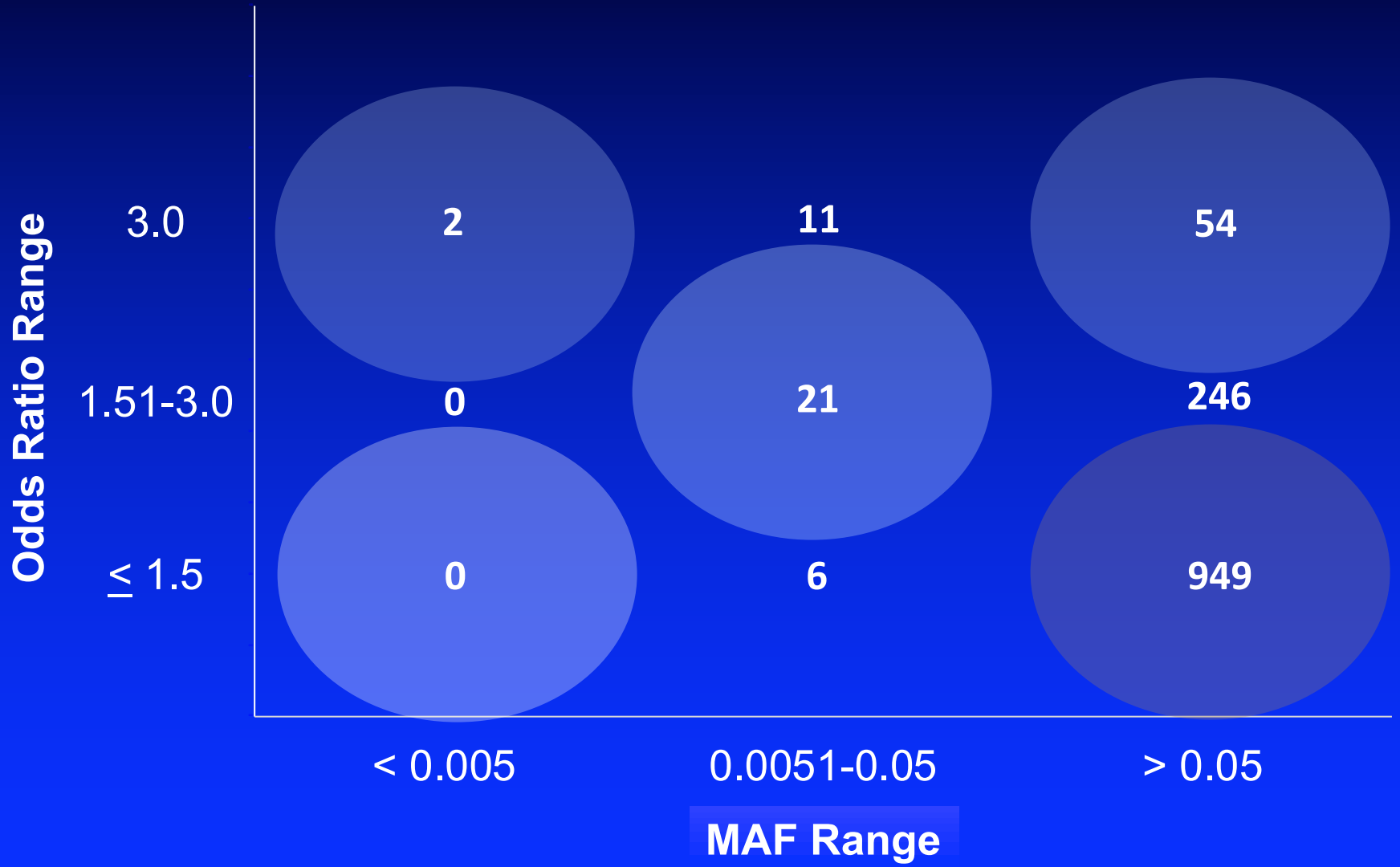
Nature 2009; 461:747-53

Odds Ratios by MAF, through 2008



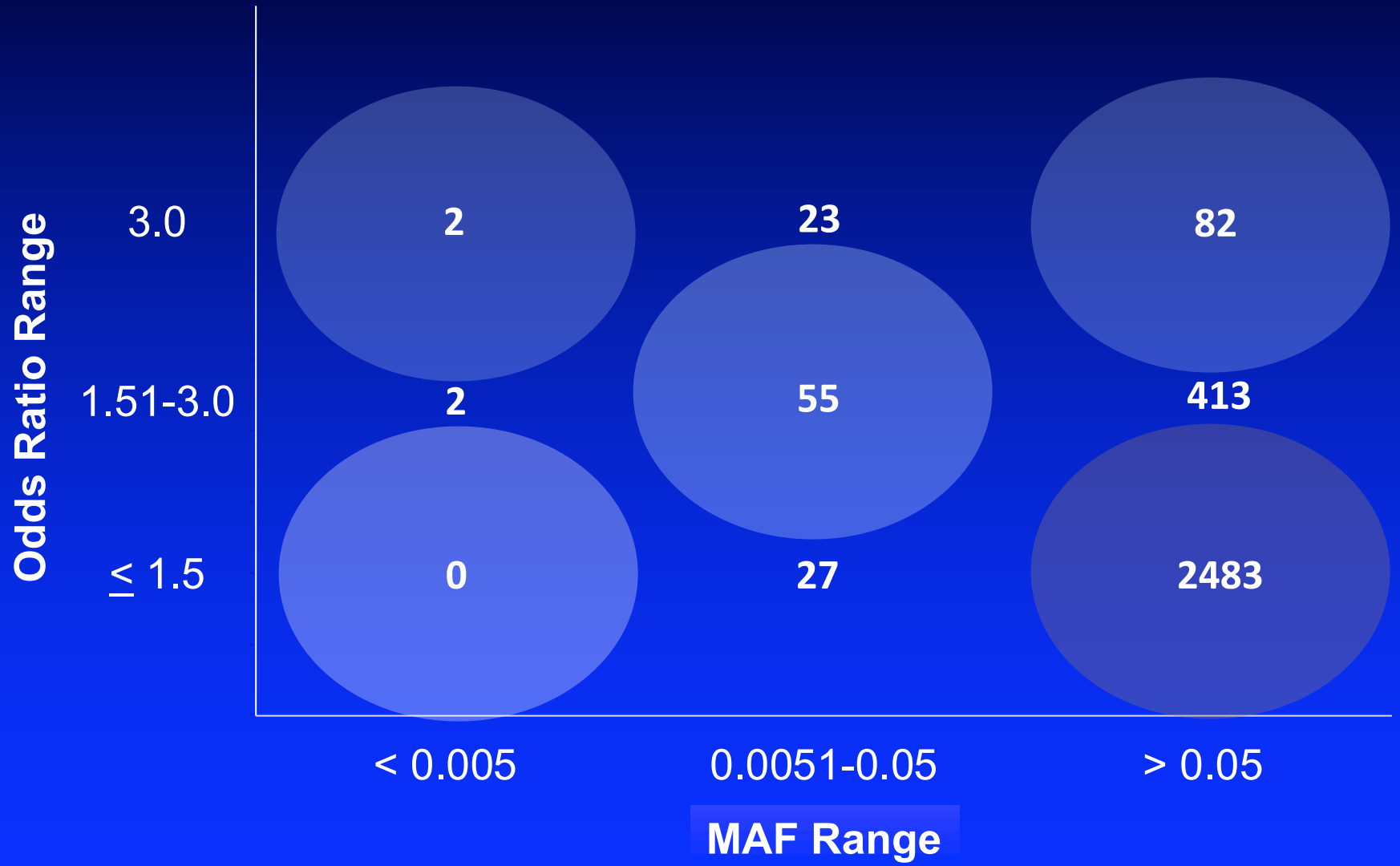
NHGRI-EBI Catalog, 4/26/18

Odds Ratios by MAF, through 2011



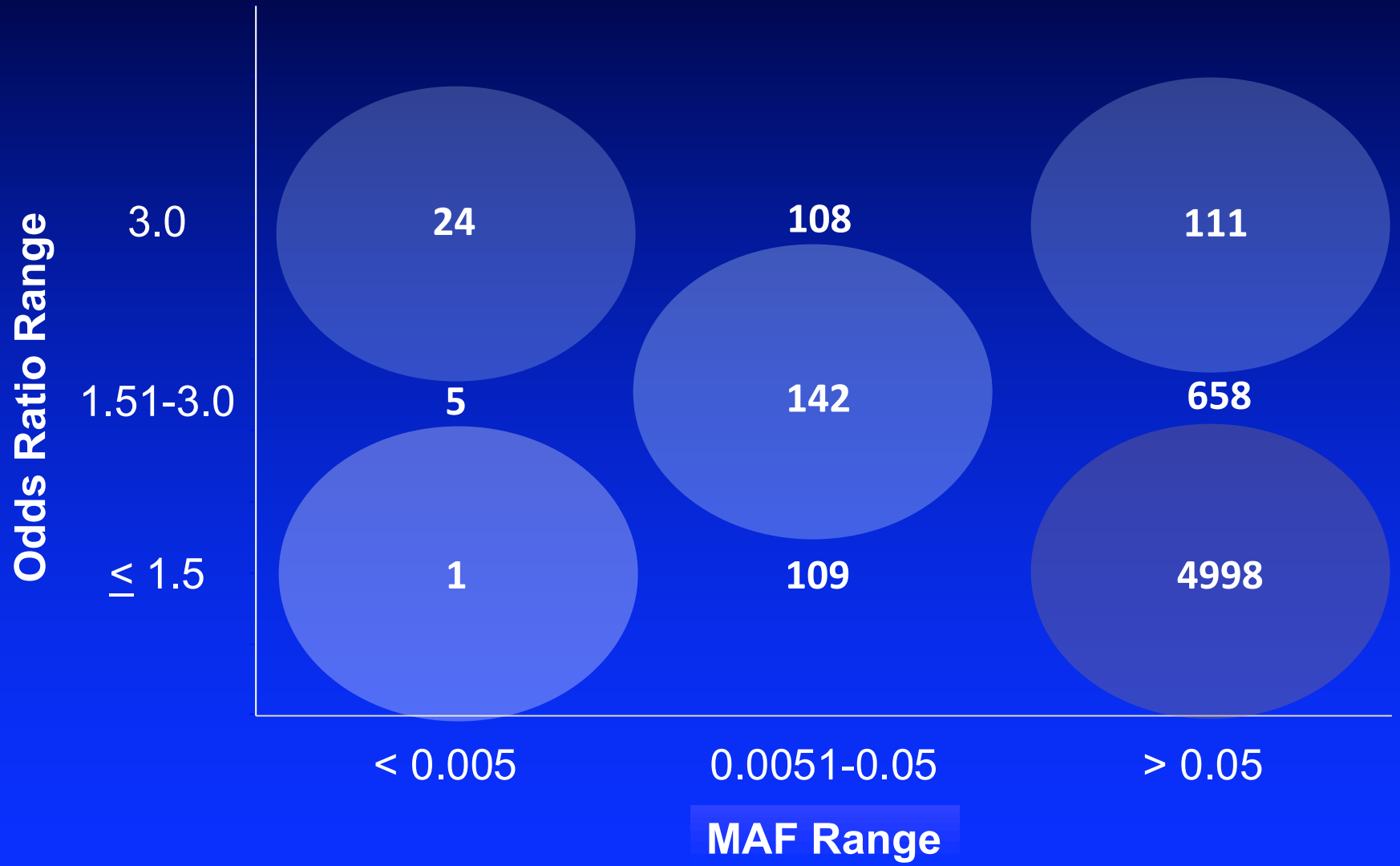
NHGRI-EBI Catalog, 4/26/18

Odds Ratios by MAF, through 2014



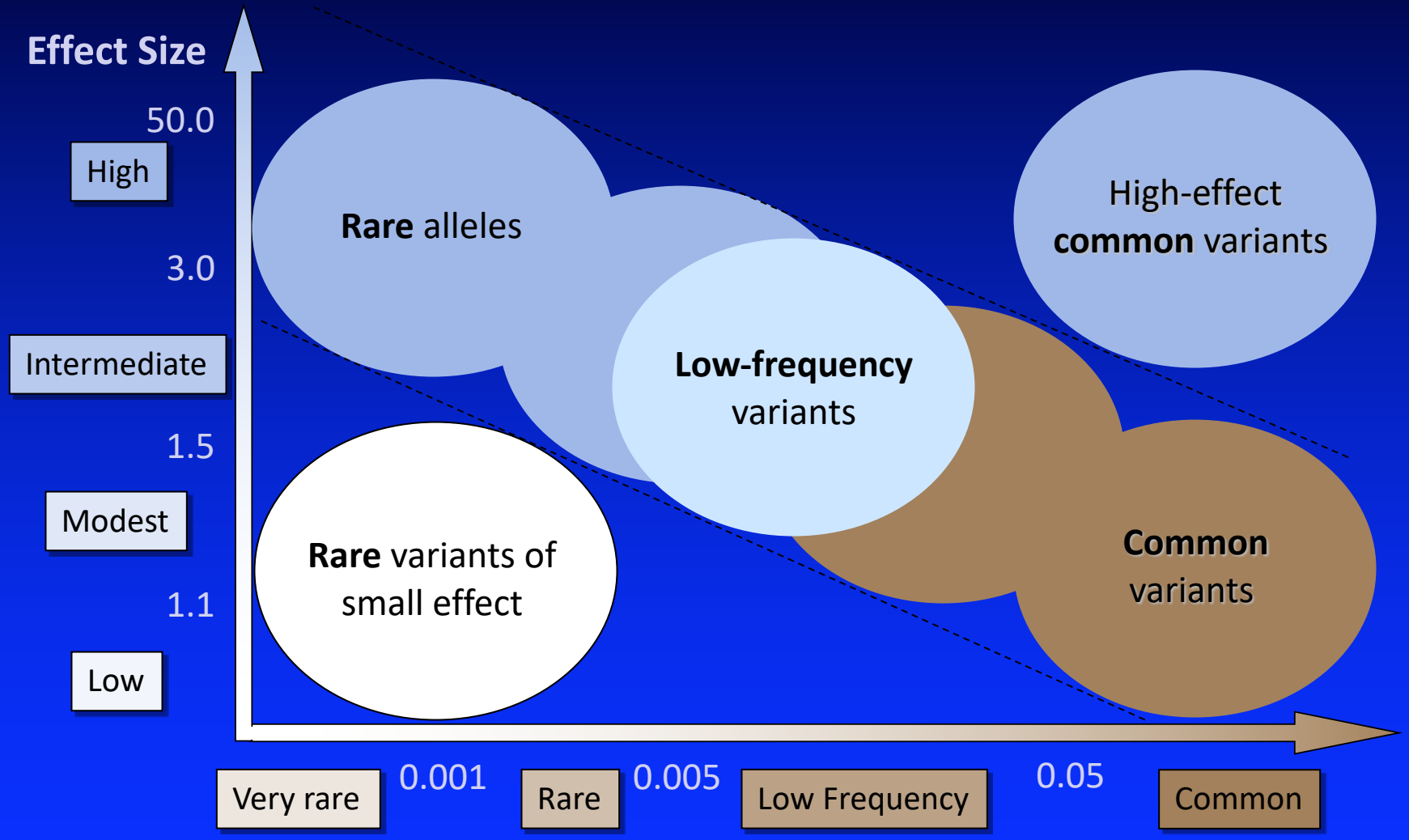
NHGRI-EBI Catalog, 4/26/18

Odds Ratios by MAF, through 2017



NHGRI-EBI Catalog, 4/26/18

Odds Ratios by MAF



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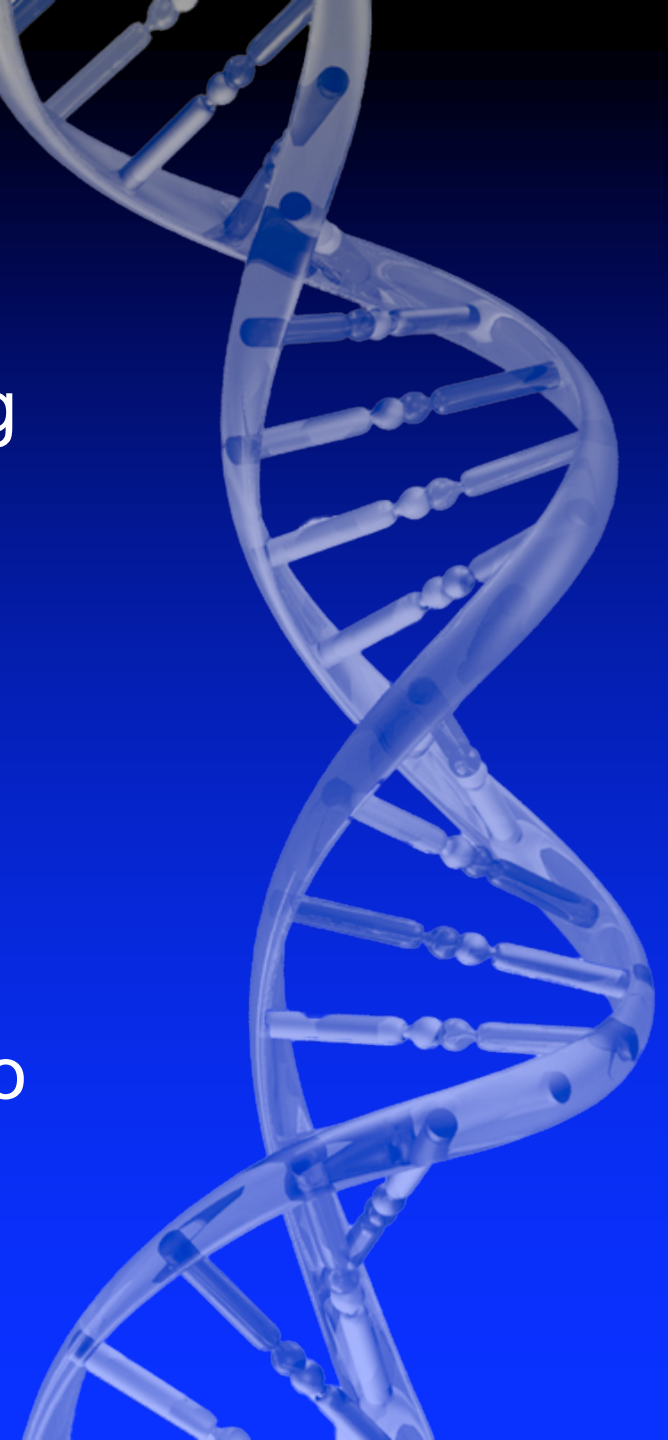
Workshop Objectives

To review scientific progress in the area of missing heritability and answer:

- What have we learned since 2008?
- What has been and/or will be the value of identifying the sources of missing heritability?
- What research can and/or should be pursued to determine these sources?

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