Significant pattern mining on GWAS data

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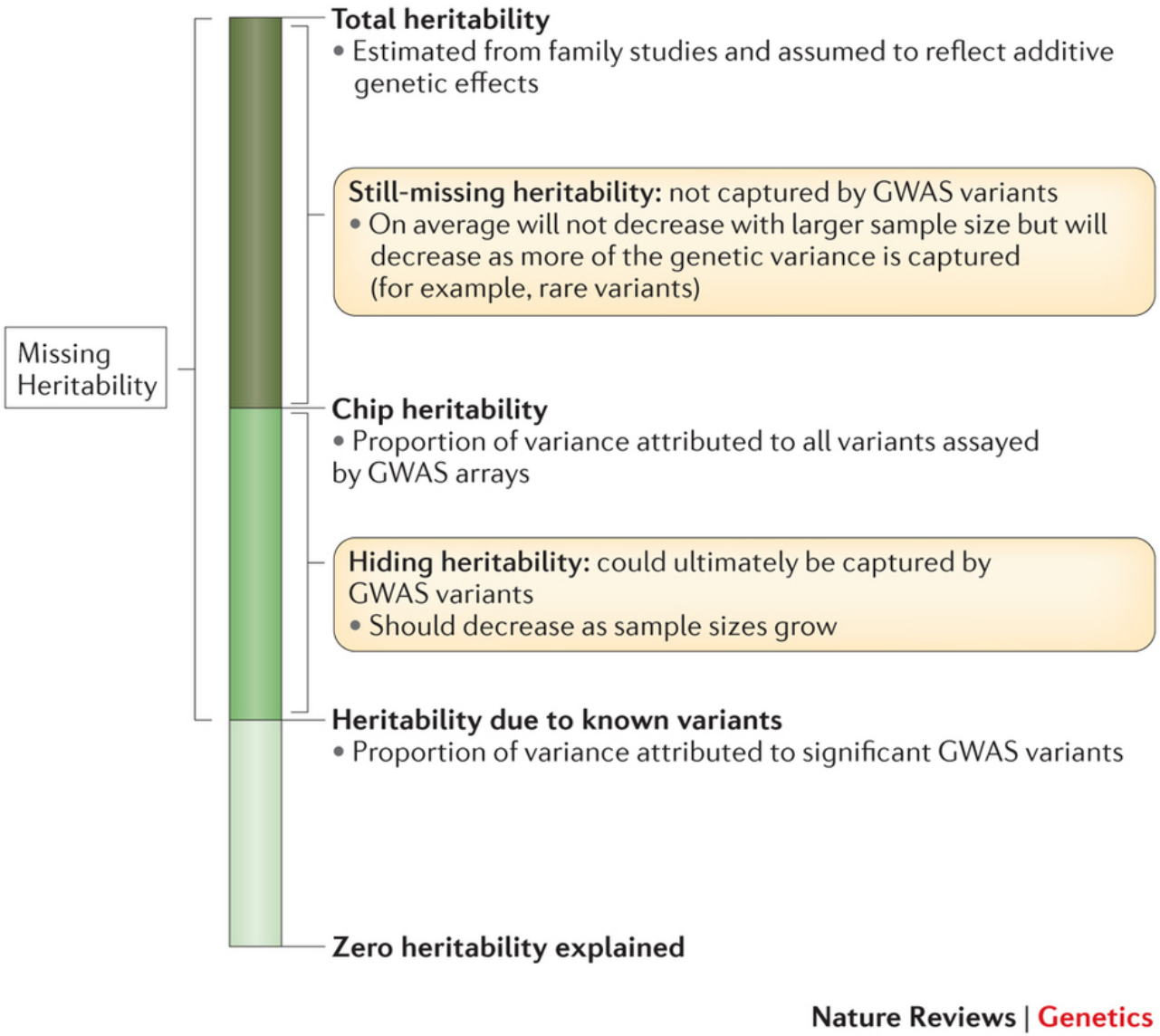
Missing heritability problem on GWAS



Limitless arity multi-testing procedure (LAMP)

Significant pattern mining techniques can help to find high-order interactions on GWAS data (and other biological data)

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Outline

The complexity of combinatorial variant discovery

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How does LAMP approaches a solution

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The complexity of combinatorial variant discovery

How does LAMP approaches a solution

Results on a lung cancer dataset

Finding combinations of features

Computational problem

Exploring all combinations is computationally prohibitive

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M^2 second order possible interactions

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Statistical problem

Discovered combinations are statistically unlikely due to multiple testing correction

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Statistical problem

Discovered combinations are statistically unlikely due to multiple testing correction

For M binary variables, Bonferroni correction sets significance below $\frac{\alpha}{2^M}$

Finding combinations of features

Machine learning approaches

Random Forests, Support Vector Machines, Multifactor Dimensionality Reduction

Finding combinations of features

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Variable rankings

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Too many false positives

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Machine learning approaches

Random Forests, Support Vector Machines, Multifactor Dimensionality Reduction

Variable rankings

Too many false positives

Very costly to further explore hypothesis

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	Case	Control	Total
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total	184	186	370

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FWER threshold $\delta = \alpha/1000 = 0.05/1000 = 5 * 10^{-5}$

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Multiple testing procedure for listing ALL statistically significant high order interactions

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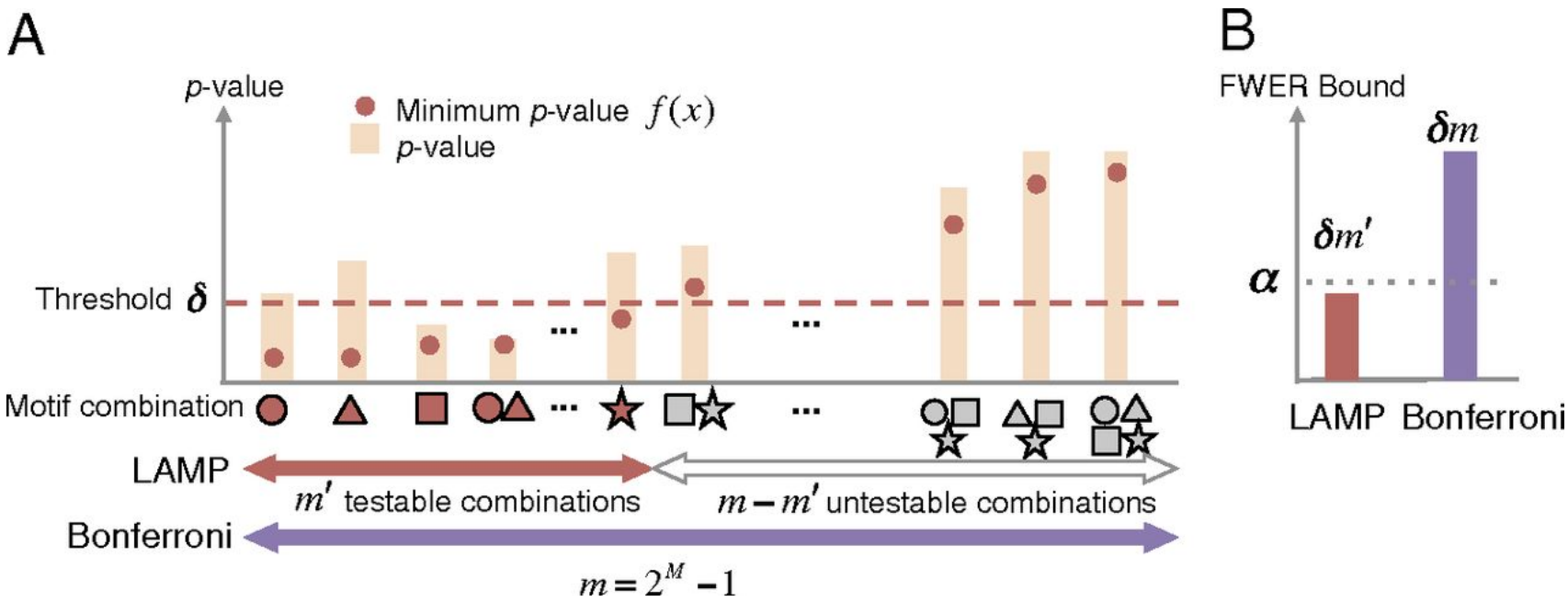
Upper bound of Family Wise Error Ratio (FWER)



[Terada et al. 2013]

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LAMPLINK is implemented as additional features to PLINK

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Model dominant/recessive for the risk class for the minor allele

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Algorithm

Find all significant combinations

Remove combinations with SNPs in linkage disequilibrium ($r^2 < \mathit{threshold}$)

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Progression of non-small cell lung cancer (NSCLC) GWAS data

GWAS threshold	p-value $< 10^{-4}$
SNPs	695
Individuals	178
Statistical test	Fisher's exact test
Adjusted significance level	$5.8 * 10^{-9}$
Correction factor	8619336
Significant combinations	5019
r^2 for LD	0.2
Significant combinations after LD pruning	145
Significant SNPs	25
Maximum arity	7

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Progression of non-small cell lung cancer (NSCLC) GWAS data

Adjusted_P	COMB	arity
0.00001538	rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	5
0.00002144	rs2271545:16095316:C:T,rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G	4
0.00004028	rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs9788969,rs139996291:17192744:G:A	6
0.00008586	rs2271545:16095316:C:T,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs139996291:17192744:G:A	4
0.00009664	rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs9788969,rs139996291:17192744:G:A	5
0.00011584	rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	4
0.00013264	rs2271545:16095316:C:T,rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs139996291:17192744:G:A	5
0.00025099	rs2937667:117246037:C:A,rs10985542:124887090:G:A,12:48798429:T:C,rs139996291:17192744:G:A	4
0.00050371	rs35684:10326686:A:G,rs2937667:117246037:C:A,rs1565656:188922545:A:G,rs139996291:17192744:G:A	4
0.00058472	rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs9788969	5
0.00058472	rs438228:161484124:A:C,rs35684:10326686:A:G,rs6822954:35695840:A:G,rs1565656:188922545:A:G,rs4545589	5
0.00067780	rs1565656:188922545:A:G,rs7111257:9930813:A:G,rs4545589,rs139996291:17192744:G:A	4
0.00078732	rs2271545:16095316:C:T,rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs9788969	5
0.00078732	rs35684:10326686:A:G,rs2937667:117246037:C:A,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	5
0.00078732	rs35684:10326686:A:G,rs2937667:117246037:C:A,rs1565656:188922545:A:G,rs71317450:27405120:A:T,rs139996291:17192744:G:A	5
0.00078732	rs35684:10326686:A:G,rs6822954:35695840:A:G,rs1565656:188922545:A:G,rs4545589	4
0.00079983	rs2271545:16095316:C:T,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs9788969,rs139996291:17192744:G:A	5
0.00079983	rs35684:10326686:A:G,rs6822954:35695840:A:G,rs11740157:10041128:A:G,12:51088287:AATACATAC:A	4
0.00117950	rs438228:161484124:A:C,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	4
0.00151520	rs2937667:117246037:C:A,rs10985542:124887090:G:A,12:48798429:T:C,rs9788969,rs139996291:17192744:G:A	5

Table 4: Top 20 statistically significant variant combinations

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Progression of non-small cell lung cancer (NSCLC) GWAS data

CHR	BP	SNP	A1	A2	MAF	AFF	UNAFF	P_FISHER	P_GWAS	OR	COMB
22	17192744	rs139996291:17192744:G:A	A	G	0.3649890	34/7	74/62	0.00094253	0.0000210682	4.06950	106
4	188922545	rs1565656:188922545:A:G	G	A	0.3507380	33/8	74/62	0.00327766	0.0000805378	3.45608	92
3	10326686	rs35684:10326686:A:G	G	A	0.2538130	30/11	56/80	0.00035202	0.0000464813	3.89610	88
16	88812250	rs9788969	C	T	0.3649430	34/7	72/64	0.00051405	0.0000467814	4.31746	56
1	161484124	rs438228:161484124:A:C	C	A	0.3755220	32/9	77/59	0.01679720	0.0000519295	2.72439	49
1	16095316	rs2271545:16095316:C:T	C	T	0.3055050	32/9	64/72	0.00058287	0.0000858186	4.00000	41
11	87018161	rs4545589	G	A	0.2931030	28/13	57/79	0.00409010	0.0000384487	2.98516	41
12	51088287	12:51088287:AATACATAC:A	AATACATAC	A	0.3702890	33/8	79/57	0.00967982	0.0000061165	2.97627	36
3	117246037	rs2937667:117246037:C:A	C	A	0.3430310	32/9	77/59	0.01679720	0.0000190999	2.72439	32
5	10041128	rs11740157:10041128:A:G	G	A	0.2049100	27/14	42/94	0.00009612	0.0000475494	4.31633	31
4	35695840	rs6822954:35695840:A:G	G	A	0.3519970	33/8	68/68	0.00055543	0.0000719665	4.12500	15
9	124887090	rs10985542:124887090:G:A	G	A	0.2295800	26/15	49/87	0.00224055	0.0000826039	3.07755	13
12	48798429	12:48798429:T:C	T	C	0.1586230	21/20	33/103	0.00174931	0.0000692089	3.27727	12
21	27405120	rs71317450:27405120:A:T	T	A	0.0950701	30/11	82/54	0.14438900	0.0002445401	1.79601	9
21	27405120	rs71317450:27405120:A:T	T	A	0.3784690	30/11	82/54	0.14438900	0.0002445401	1.79601	9
12	48792747	12:48792747:A:G	A	G	0.1637820	21/20	33/103	0.00174931	0.0000424999	3.27727	7
5	10054699	rs11744968:10054699:T:C	C	T	0.1770790	23/18	36/100	0.00064061	0.0000862621	3.54938	5
11	9930813	rs7111257:9930813:A:G	A	G	0.2614450	29/12	56/80	0.00120037	0.0000422449	3.45238	5
16	78692994	rs59689196:78692994:A:C	C	A	0.1489970	18/23	27/109	0.00366244	0.0000446349	3.15942	5
4	161256788	rs28657552:161256788:G:A	A	G	0.3567330	31/10	69/67	0.00661204	0.0000510835	3.01014	3
13	41026812	rs41286971:41026812:G:A	A	G	0.3478880	30/11	74/62	0.04572730	0.0000474201	2.28501	3
17	12974799	rs8065393:12974799:T:C	C	T	0.3277870	32/9	65/71	0.00063784	0.0000359785	3.88376	3
11	8176765	rs61400460:8176765:TA:T	T	TA	0.0963394	18/23	11/125	0.00000071	0.0000483534	8.89328	2
21	36714156	rs2242720	G	A	0.2729890	30/11	59/77	0.00118010	0.0009028600	3.55932	2
11	86367530	rs9943610:86367530:C:T	C	T	0.2151560	24/17	47/89	0.01033820	0.0000887781	2.67334	1
13	108513537	rs1464811:108513537:A:G	G	A	0.2638090	25/16	50/86	0.00706479	0.0000901488	2.68750	1

Table 5: Variants statistically significant in any combination

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Progression of non-small cell lung cancer (NSCLC) GWAS data

NSCLC literature (mostly asian studies)

ELAC2 and HS3ST3A1 on the 50kb window of rs8065393

No significant pathways enriched

Summary

SNP combined effects may explain a part of the missing heritability but is a computationally and statistically challenging problem

Significant pattern mining can help finding statistically significant combinations of SNPs

The methodology is valid for other types of biomedical data