Significant pattern mining for GWAS data

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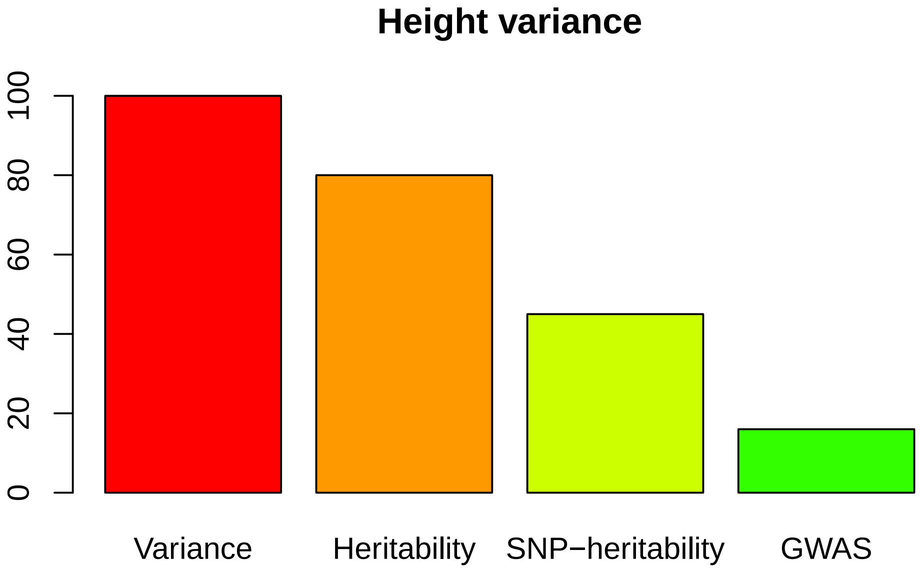
Missing heritability problem on GWAS



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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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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Discovered combinations are statistically unlikely due to multiple testing correction

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Statistical problem

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

Finding combinations of features

Machine learning approaches

Random Forests, Suport Vector Machines, Multifactor Dimensionality Reduction

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Variable rankings

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Too much false positives

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Machine learning approaches

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Very costly to futher explore hypothesis

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Fisher's exact test

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	Case	Control	Total
Has S_i			13
Hasn't S_i			357
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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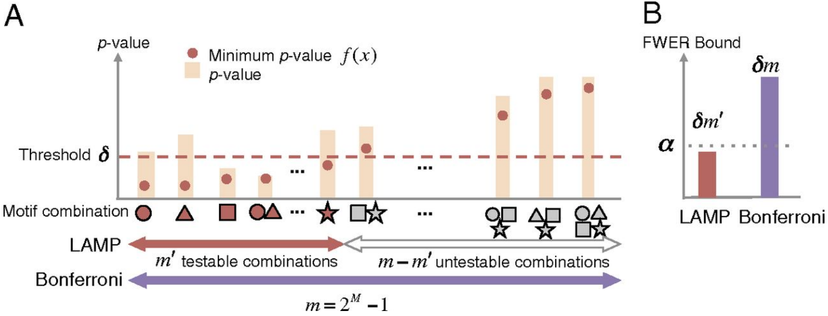
Upper bound of Family Wise Error Ratio (FWER)



[Terada et al. 2013]

LAMPLINK

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

- Find all significant combinations
- Remove combinations with SNPs in linkage desequilibrium

LAMPLINK

LAMP in a lung cancer dataset

GWAS data of lung cancer progression

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

LAMPLINK

LAMP in a lung cancer dataset

COMBID	Raw_P	Adjusted_P	COMB	arity
COMB7	0.00000000	0.00001538	rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	5
COMB10	0.00000000	0.00002144	rs2271545:16095316:C:T,rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G	4
COMB39	0.00000000	0.00004028	rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs9788969,rs139996291:17192744:G:A	6
COMB42	0.00000000	0.00008586	rs2271545:16095316:C:T,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs139996291:17192744:G:A	4
COMB47	0.00000000	0.00009664	rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs9788969,rs139996291:17192744:G:A	5
COMB62	0.00000000	0.00011584	rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	4
COMB85	0.00000000	0.00013264	rs2271545:16095316:C:T,rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs139996291:17192744:G:A	5
COMB159	0.00000000	0.00025099	rs2937667:117246037:C:A,rs10985542:124887090:G:A,12:48798429:T:C,rs139996291:17192744:G:A	4
COMB192	0.00000000	0.00050371	rs35684:10326686:A:G,rs2937667:117246037:C:A,rs1565656:188922545:A:G,rs139996291:17192744:G:A	4
COMB274	0.00000000	0.00058472	rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs4545589,rs9788969	5
COMB278	0.00000000	0.00058472	rs438228:161484124:A:C,rs35684:10326686:A:G,rs6822954:35695840:A:G,rs1565656:188922545:A:G,rs4545589	5
COMB287	0.00000000	0.00067780	rs1565656:188922545:A:G,rs7111257:9930813:A:G,rs4545589,rs139996291:17192744:G:A	4
COMB328	0.00000000	0.00078732	rs2271545:16095316:C:T,rs438228:161484124:A:C,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs9788969	5
COMB368	0.00000000	0.00078732	rs35684:10326686:A:G,rs2937667:117246037:C:A,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	5
COMB374	0.00000000	0.00078732	rs35684:10326686:A:G,rs2937667:117246037:C:A,rs1565656:188922545:A:G,rs71317450:27405120:A:T,rs139996291:17192744:G:A	5
COMB376	0.00000000	0.00078732	rs35684:10326686:A:G,rs6822954:35695840:A:G,rs1565656:188922545:A:G,rs4545589	4
COMB423	0.00000000	0.00079983	rs2271545:16095316:C:T,rs35684:10326686:A:G,rs1565656:188922545:A:G,rs9788969,rs139996291:17192744:G:A	5
COMB425	0.00000000	0.00079983	rs35684:10326686:A:G,rs6822954:35695840:A:G,rs11740157:10041128:A:G,12:51088287:AATACATAC:A	4
COMB447	0.00000000	0.00117950	rs438228:161484124:A:C,rs1565656:188922545:A:G,rs4545589,rs139996291:17192744:G:A	4
COMB610	0.00000000	0.00151520	rs2937667:117246037:C:A,rs10985542:124887090:G:A,12:48798429:T:C,rs9788969,rs139996291:17192744:G:A	5

Table 4: Statistically significant variant combinations

LAMPLINK

LAMP in a lung cancer dataset

CHR	SNP	A1	A2	TEST	AFF	UNAFF	P	OR	COMB
22	rs139996291:17192744:G:A	A	G	DOM	34/7	74/62	0.00094253	4.06950	106
4	rs1565656:188922545:A:G	G	A	DOM	33/8	74/62	0.00327766	3.45608	92
3	rs35684:10326686:A:G	G	A	DOM	30/11	56/80	0.00035202	3.89610	88
16	rs9788969	C	T	DOM	34/7	72/64	0.00051405	4.31746	56
1	rs438228:161484124:A:C	C	A	DOM	32/9	77/59	0.01679720	2.72439	49
1	rs2271545:16095316:C:T	C	T	DOM	32/9	64/72	0.00058287	4.00000	41
11	rs4545589	G	A	DOM	28/13	57/79	0.00409010	2.98516	41
12	12:51088287:AATACATAC:A	AATACATAC	A	DOM	33/8	79/57	0.00967982	2.97627	36
3	rs2937667:117246037:C:A	C	A	DOM	32/9	77/59	0.01679720	2.72439	32
5	rs11740157:10041128:A:G	G	A	DOM	27/14	42/94	0.00009612	4.31633	31
4	rs6822954:35695840:A:G	G	A	DOM	33/8	68/68	0.00055543	4.12500	15
9	rs10985542:124887090:G:A	G	A	DOM	26/15	49/87	0.00224055	3.07755	13
12	12:48798429:T:C	T	C	DOM	21/20	33/103	0.00174931	3.27727	12
21	rs71317450:27405120:A:T	T	A	DOM	30/11	82/54	0.14438900	1.79601	9
12	12:48792747:A:G	A	G	DOM	21/20	33/103	0.00174931	3.27727	7
5	rs11744968:10054699:T:C	C	T	DOM	23/18	36/100	0.00064061	3.54938	5
11	rs7111257:9930813:A:G	A	G	DOM	29/12	56/80	0.00120037	3.45238	5
16	rs59689196:78692994:A:C	C	A	DOM	18/23	27/109	0.00366244	3.15942	5
4	rs28657552:161256788:G:A	A	G	DOM	31/10	69/67	0.00661204	3.01014	3
13	rs41286971:41026812:G:A	A	G	DOM	30/11	74/62	0.04572730	2.28501	3
17	rs8065393:12974799:T:C	C	T	DOM	32/9	65/71	0.00063784	3.88376	3
11	rs61400460:8176765:TA:T	T	TA	DOM	18/23	11/125	0.00000071	8.89328	2
21	rs2242720	G	A	DOM	30/11	59/77	0.00118010	3.55932	2
11	rs9943610:86367530:C:T	C	T	DOM	24/17	47/89	0.01033820	2.67334	1
13	rs1464811:108513537:A:G	G	A	DOM	25/16	50/86	0.00706479	2.68750	1

Table 5: Variants statistically significant in any combination

Summary

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

Significant pattern mining can help finding statistically significative combinations of SNPs

Teh methodology is valid for other types of biomedical data