ASHG 2014 meeting highlights: From Bytes to Phenotypes

Mohsen Hosseini

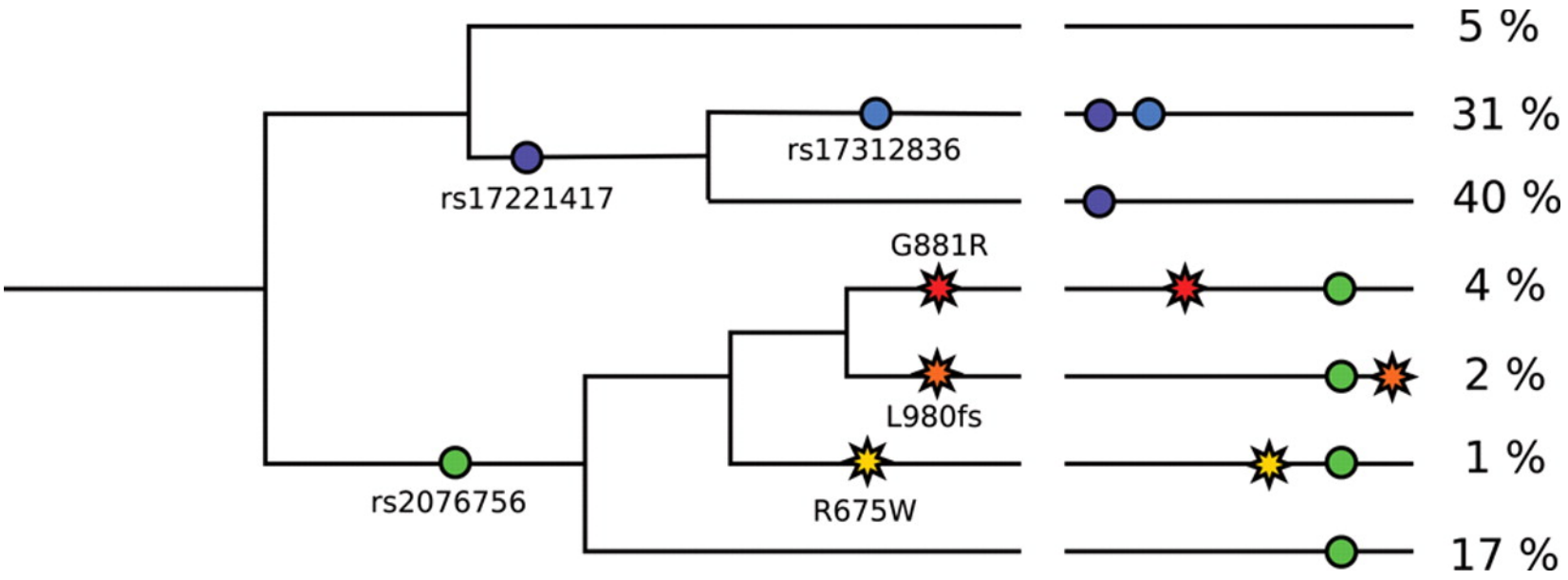
Session's theme

- Phenome
  - The set of all phenotypes in an organism originally used by Davis in 1949.
- PheWAS
  - Analyzing many phenotypes compared to a single genetic variant, originally described in the context of electronic medical records (EMR)
  - Using ICD-9 codes
  - Exploring other ways to do PheWAS

1. Investigation of Synthetic Association (SA) in GWAS using PheWAS and Exome Sequencing

- Causality of GWAS findings is unknown
- SA Hypothesis: one (or more) rare causal alleles on a haplotype containing common neutral allele explain the GWAS findings

Simplified view of genetic variation at the NOD2 locus, a well-documented example of a synthetic association.



Simplified view of genetic variation at the NOD2 locus, a well-documented example of a synthetic association. The left-hand side shows a genealogical tree representing six SNPs in this region after discarding rare recombinant events. The right-hand side shows the resulting haplotypes and their population frequencies (48), with coloured circles representing common GWAS SNPs, and starbursts representing previously identified low-frequency coding variants responsible for association between NOD2 and CD. While none of the GWAS SNPs is strongly correlated with any individual causal allele, the three coding variants create a synthetic association because they cluster by chance on the side of the tree marked by the green GWAS SNP (rs2076756).

Orozco G et al. Hum. Mol. Genet. 2010;19:R137-R144

Human
Molecular Genetics

Synthetic association (cont.)

- 29.7k European individuals genotyped on Illumina HumanExome in a PheWAS
  - Genome-wide significant SNPs in GWAS catalogue
  - Mapped the trait to PheWAS phenotype (n=104)
  - Tested all missense and nonsense SNPs with $1\% < MAF < 5\%$ in the gene reported in NHGRI catalogue (1743 genotype-phenotype pairs)
- replicated 66% of NHGRI signals that they had power for:
  - 84 assoc with $p < 0.01$
  - 59 with $OR > 2$ or < 0.5 for 38 unique phenotypes
  - 22 assoc. passing Bonferroni correction
- Conditional GWAS to see whether common could be explain by rare.
- Only replicated NOD2 and Crohn's example.

2. Problem of circularity in deleteriousness predictions of missense variants

- many *in silico* predictors of deleteriousness
- Circularity:
  - Overlapping training and evaluation sets (often not public)
  - Gene-level confounding: most SNPs belong to pure proteins and are annotated the same way
- One cannot properly compare prediction tools
- Polyphen2 seems to be superior to others especially if retrained on Varibench.

3. Application of Clinical Text Data in PheWAS

- Majority of PheWAS used ICD9 diagnostic codes to define case-control status
  - Primarily for billing
  - Limited phenotype granularity
  - Do not allow for other clinically relevant information
- Alt: text-based phenome

Application of Clinical Text Data in PheWAS

- Text based phenome from Marshfield Clinic EMR:
  - 4200 patients
  - 1.5 M clinical notes
  - 423 M words
  - 23k clinically relevant word medical dictionary
  - Five SNPs genotyped

Application of Clinical Text Data in PheWAS

- Performed equally well with ICD9
- AMD SNP
  - Macular degeneration
  - Nonexudative (type)
  - Exudative (type)
  - Visudyne (drug)
- Hashimoto's thyroiditis
  - ICD9 non- significant because term is specific
  - Text based: Hashimoto (1E-12)

4. Warped Linear Mixed Models

- Linear mixed models commonly used in genetics
  - GWAS
  - Heritability estimation
  - Phenotype prediction
- Fundamental assumption is normality of noise (error)
- If violated:
  - Power loss
  - Biased estimate
  - Reduced accuracy
- Current solution:
  application of appropriate transformation pre-processing, which may be challenging (manual, distribution of residual and not phenotype)
- *Fusi et al, Nature communications, 2014*

Warped Linear Mixed Models (WLMM)

- Automatically learns the suitable phenotype transformation
- Tests “infinite” number of transformations to find the best
- Increases power, reduced bias, increases accuracy
- Permits back transformation to the original scale unlike rank based transformations

Summary of method

- y_n : observed non-normal phenotype; z_n : unobserved normal distributed phenotype; f: transformation function

$$z_n = f(y_n; \psi). \qquad (1)$$

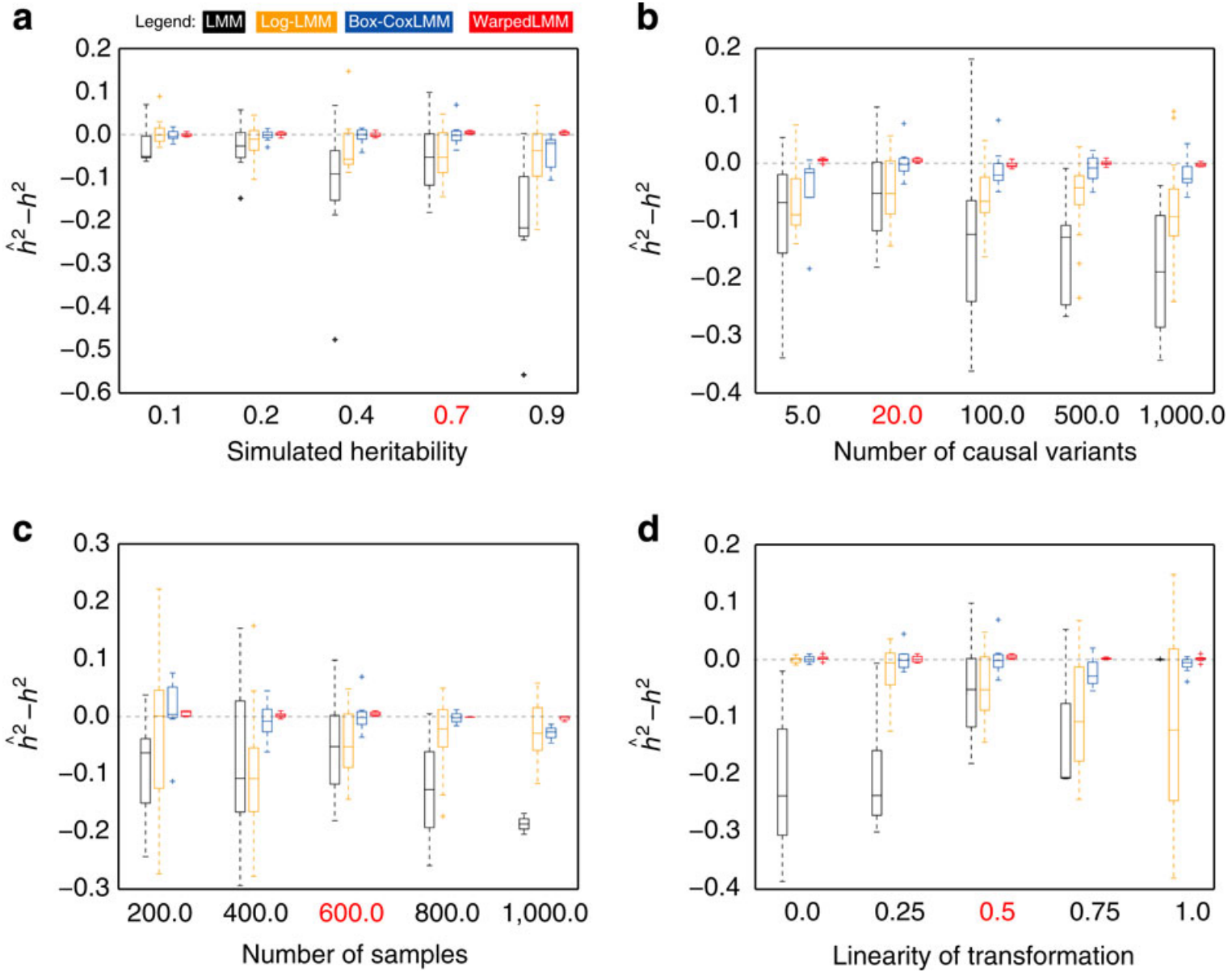
$$z_n = \mathbf{x_n}\beta + u_n^* + \epsilon_n \qquad (3)$$

- Likelihood for vector z for N individuals:

$$\mathbf{z} \sim N\left(\mathbf{X}\beta, \sigma_g^2\mathbf{K} + \sigma_e^2\mathbf{I}\right). \qquad (4)$$

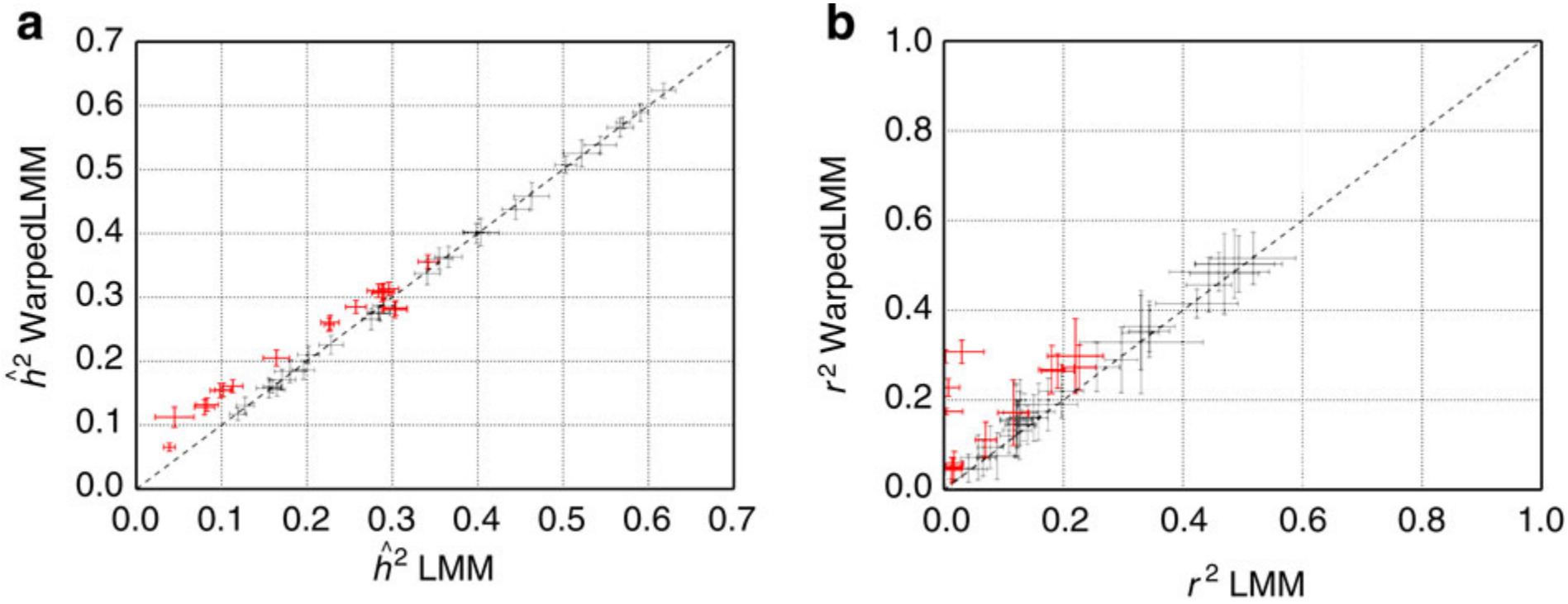
- K is the genetic relatedness matrix for S SNPs
- WLMM identifies the most probable transformation (f) by maximizing likelihood (4) using a warping function proposed by Snelson et al.

Simulation of heritability estimate



Heritability study in mouse

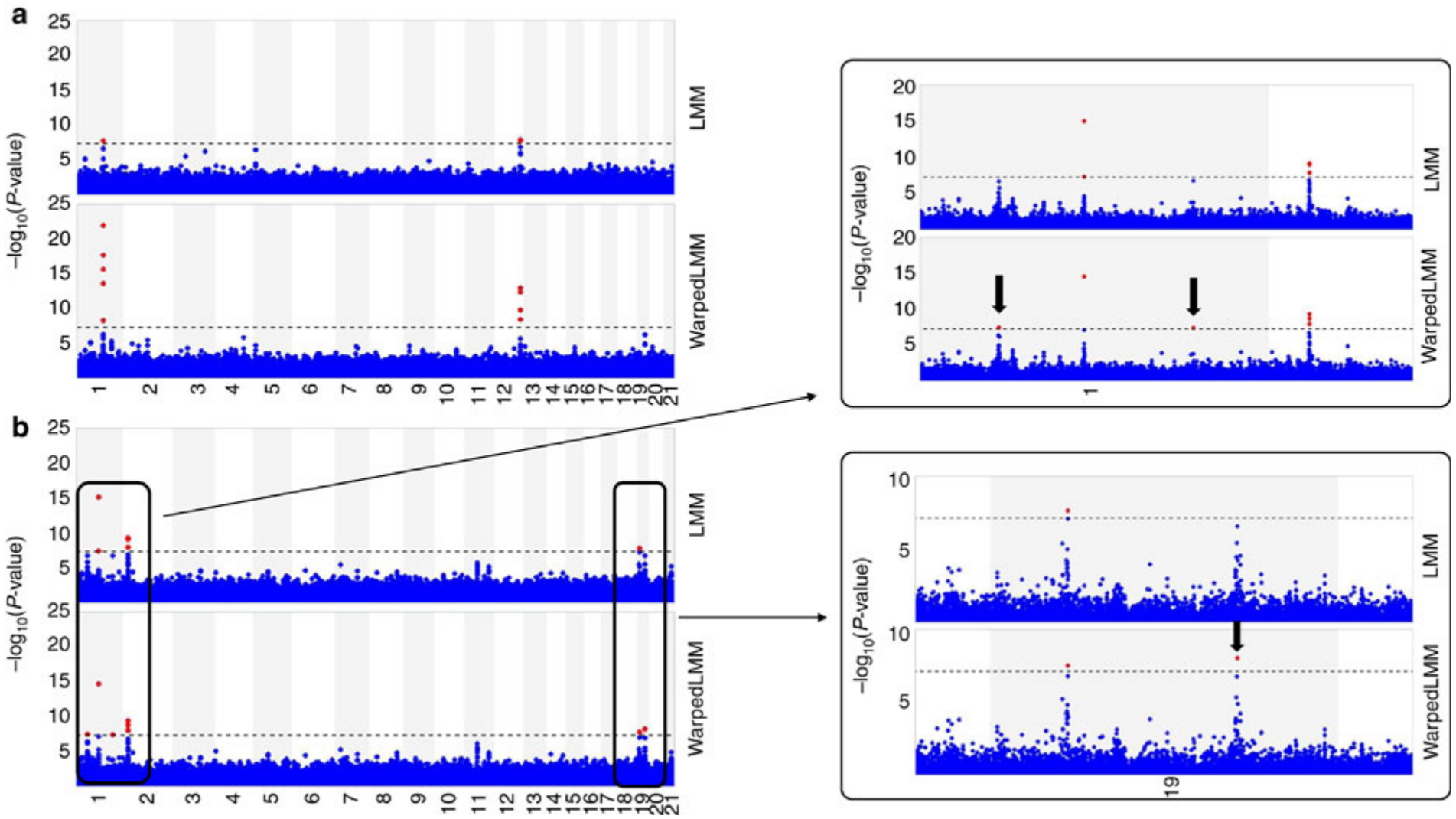
- 58 phenotypes in mice, manually transformed
- Compared heritability estimates in the original paper using LMM with WLMM.
- 18 of 47 phenotypes the two estimates were significantly different and in 17/18 of these WLMM yielded higher heritability estiamtes
- Because no gold standard: used training and validation in 90% vs 10% of data which WLMM was superior



(**a**) Heritability estimates using a LMM on the untransformed phenotype versus the heritability estimates obtained by WarpedLMM. Empirical error bars were obtained from ten bootstrap replicates, using 90% of the data in each replicate. Significant differences are coloured in red (paired *t*-test, α=0.05). (**b**) Out-of-sample prediction accuracy assessed by the squared correlation coefficient r^2, considering either a LMM on the untransformed data or a WarpedLMM. Prediction accuracies were assessed from ten random train-test splits. Phenotypes with significant deviations in prediction accuracy of the LMM and the WarpedLMM are highlighted in red (paired *t*-test, *P*-value≤0.05).

WLMM for GWAS

- Analyzed for metabolic traits
  - HDL (linear vs WLMM)
  - LDL (linear vs WLMM)
  - TG (log transformed vs WLMM)
  - CRP (log transformed vs WLMM)
- Overall WLMM increased GWAS power
- An implementation of WarpedLMM in python is available at http://github.com/pmbio/warpedLMM.



(**a**) The GWAS results for C-reactive protein, and (**b**) the GWAS results for low-density lipoprotein. Red circles denote significant associations (α<5 × 10^{-8}, marked on the plots with a dashed line). The two rightmost panels show an enlarged view of interesting regions in chromosomes 1 and 19, with black arrows highlighting loci that were identified only when using WarpedLMM.