A new paradigm for pharmacogenomic discoveries: Capturing drug response during surgery

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Motivation

- Highly penetrant variants for a number of drugs have been identified using pharmacogenomics.
- Findings are primarily limited to drugs used to treat cardiovascular diseases, infectious diseases, and cancer therapies.
- Existing pharmacogenomic studies are confounded by environmental factors, drug compliance, and pre-existing co-morbidities.
- They usually focus on drugs taken for a large amount of time, adverse events or dosing, not on acute response.
- Phenotypic heterogeneity and differences in underlying genetic ancestry are also confounders to current approaches.

Aims

- Measure **real-time drug response** using patient **data collected during surgery** where bias of drug type and dose and pre-existing conditions are known, environmental impact is minimized, and real-time physiological response is collected.
- Systematically describe **differences between patients**.
- Uncover potential **genetic variants** underlying real-time drug response variability.

Phenylephrine drug response

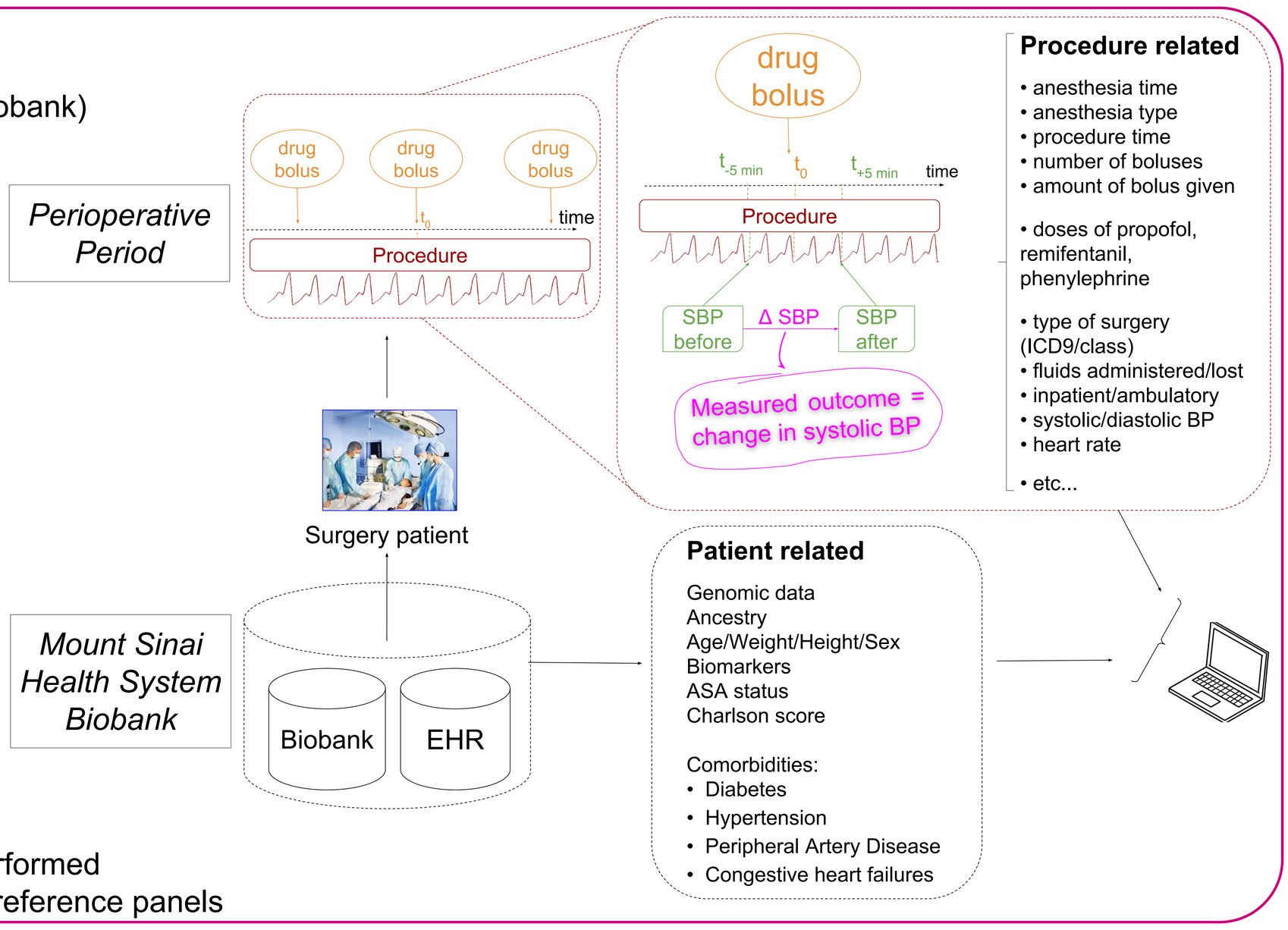
- α_1-adrenergic receptor agonist → known drug target.
- Phenylephrine is responsible for **vasoconstriction of blood vessels** thereby **increasing blood pressure** and is commonly **administered during surgery**.
- Evidence of inter-individual drug response.
- **Genomics** of phenylephrine drug response is **unknown**.

Materials and Methods

- Patients enrolled in ***BioMe*** (Mount Sinai biobank)
  - Who have undergone surgery
  - With available genotype
- **Phenotype**: difference in systolic blood pressure due to phenylephrine
- Significant confounders were either used as exclusion criteria or adjusted for:

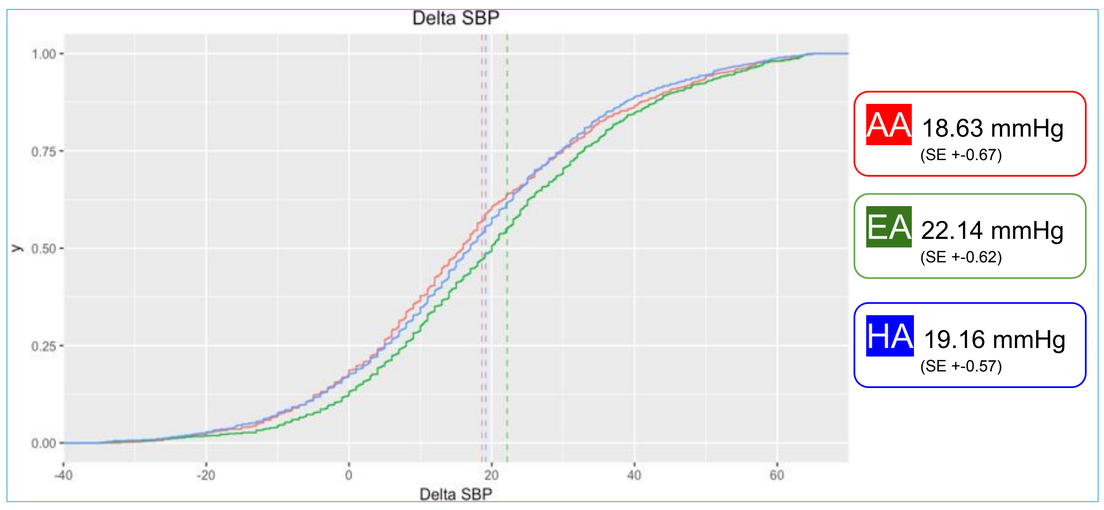
  - Extreme systolic/diastolic, mean arterial pressures, heart rate
  - Emergency procedures, endo-, colonoscopies, intubations, ...
  - Patients w/ blood transfusions or who received > 500 ml fluids
  - Patients who received propofol and phenylephrine within a 10 min interval

- **Diverse population**:
  - African Americans (n = 1217)
  - Hispanic/Latinos (n = 1707)
  - European Americans (n = 1386)
- **Genome-wide association tests** were performed for > 40 million SNPs inputed from 1000G reference panels



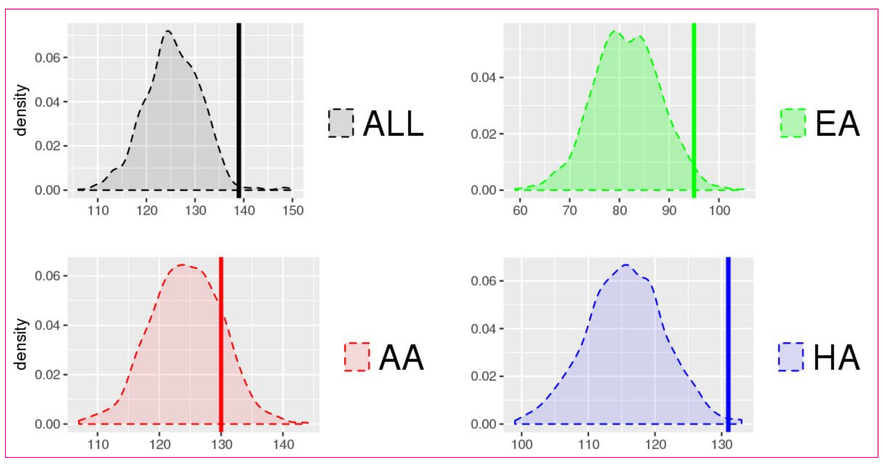
Results

Differential Phenylephrine Drug Response Across Populations



European Americans have a significantly higher increase of blood pressure after phenylephrine than African Americans and Hispanic/Latinos (p-values < 9e-6 and 10e-5)

Drug Response Significantly Associated with Systolic Blood Pressure Genes

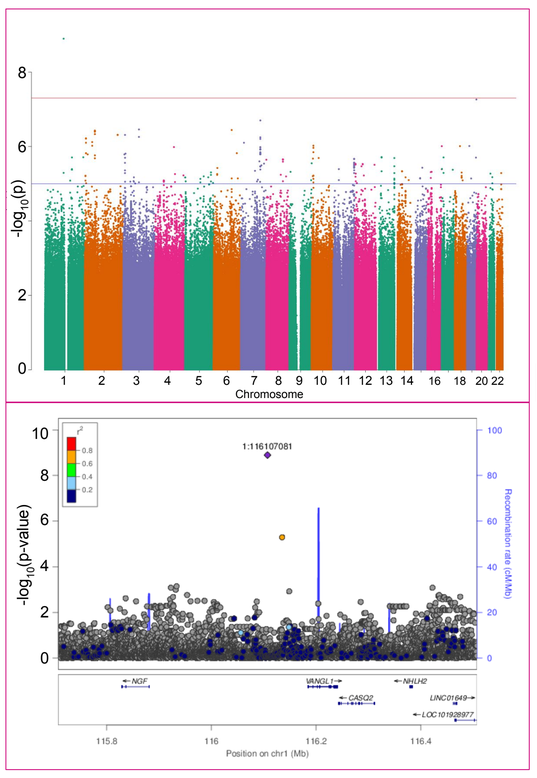


165 genes associated with systolic blood pressure in the *UK BioBank* cohort are enriched for association with phenylephrine response in the *BioMe* cohort in European Americans (p-val = 0.016) and Hispanic Latinos (p-val = 0.005).

Lower association in African Americans from our cohort is consistent with mostly European cohort from the UK BioBank.

Novel Genome-Wide Significant Hits for Phenylephrine Drug Response

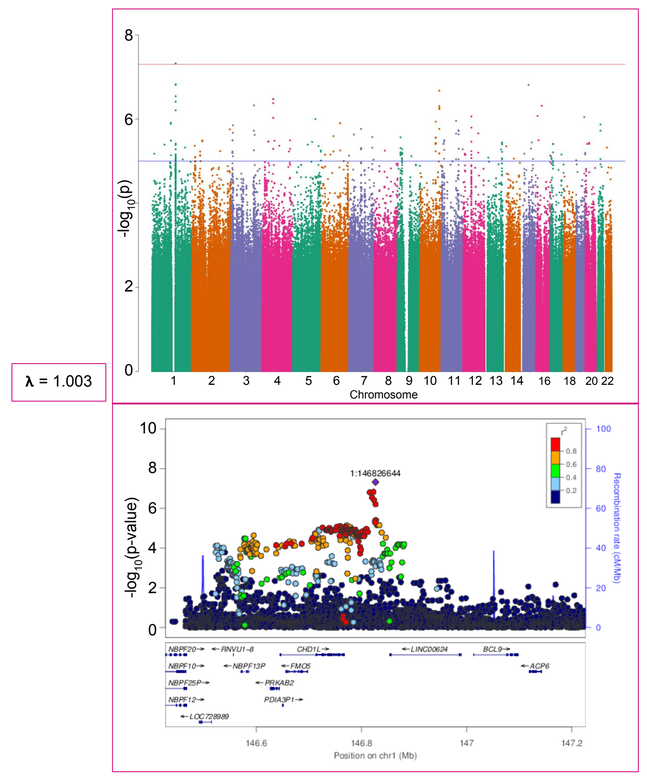
rs561909485 (p-val=1.27e-9) in full cohort



GWAS hit downstream of *VANGL1*

(VANGL1 (+/-) mice show aberrant subclavian artery)

rs17356680 (p-val=4.77e-8) in Hispanics/Latinos



GWAS hit near *CHD1L* (highly expressed in arterial tissues) ; eQTLs w/ rs17356680 and CHD1L in skeletal muscles and arteries.

Conclusions

- We established a robust definition for real-time drug response that can be applied to successfully conduct large-scale pharmacogenomic studies.
- We identified inter-population differences of phenylephrine response.
- We discovered putative novel associations near genes *CHD1L* and *VANGL1*.
- Systolic blood pressure genes are enriched in association with drug response.