

Phenome-wide studies of SNPs from GWAS in a broadly phenotyped population



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Introduction

SNPs associated with one trait may be associated with others (e.g., from shared etiology, correlation between the traits, or different causal variants tagged by one SNP)

Here we present examples from a systematic search for such effects. We looked at

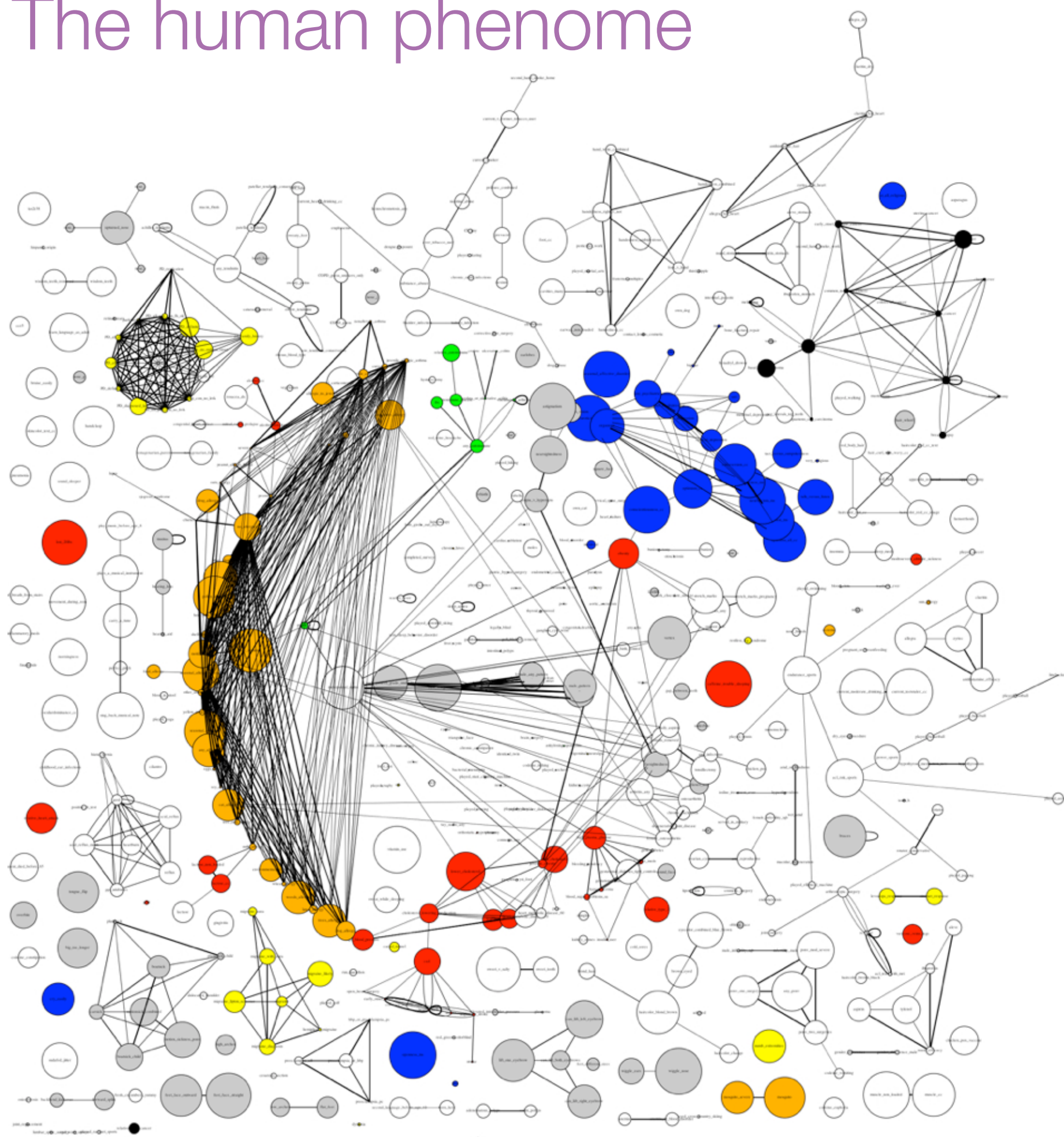
- 1100 phenotypes, self-reported by
 - 65,000 genotyped 23andMe customers, against
 - 2000 SNPs from GWAS and Mendelian disease
- to find novel pleiotropic effects for SNPs that had been previously identified as associated with diseases and traits.

We give five examples where this search has led to new stories about well known associations.

The 23andMe database

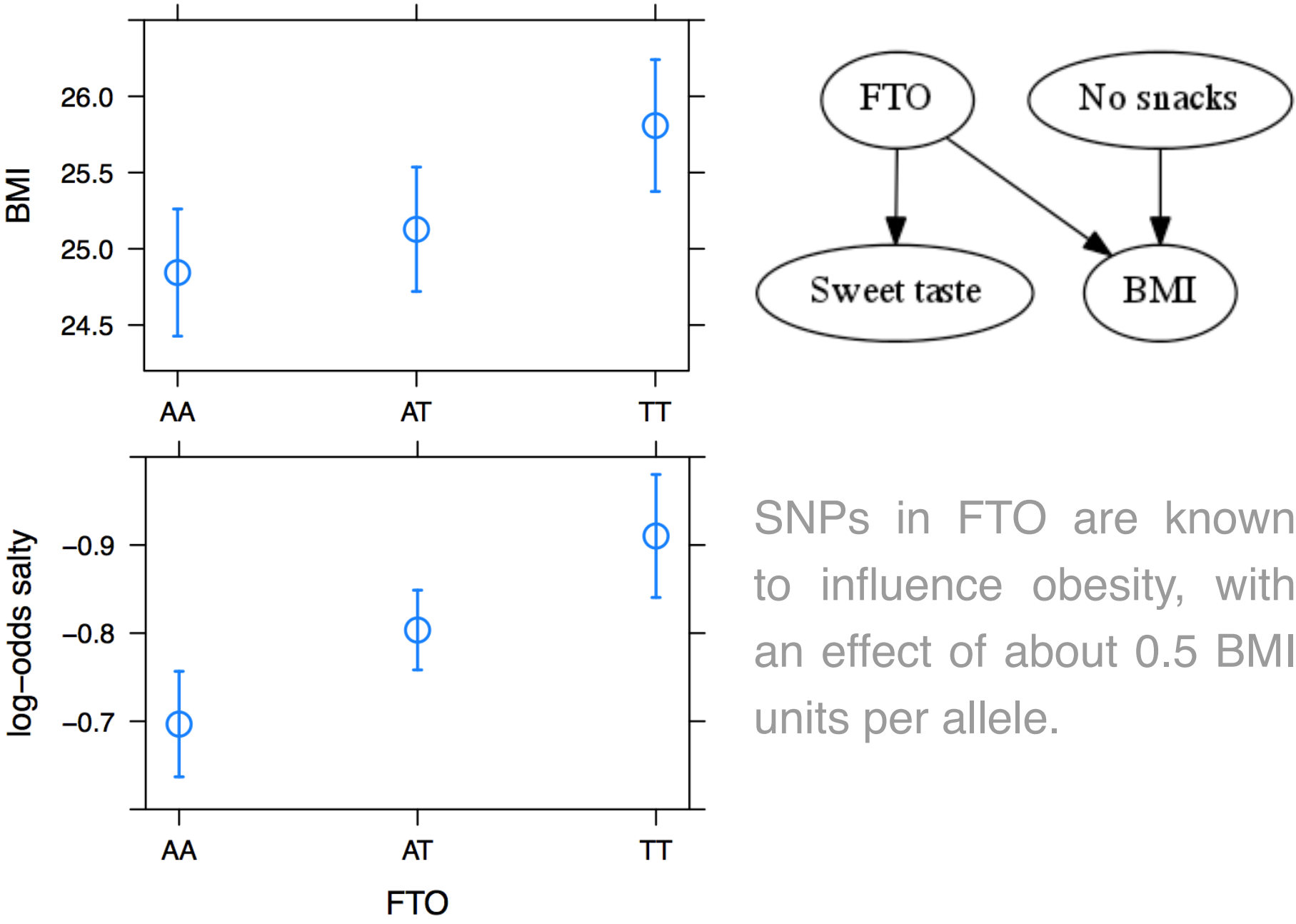
- Over 100,000 genotyped customers
- Over 50 online surveys
- 300+ “snippets” - one off questions
- Over 60% of customers contribute phenotype data.
- Result: over 1100 self-reported phenotypes
- These range from
 - common (migraines) to rare (sarcoma)
 - serious (antidepressant side-effects) to frivolous (mosquito bite reaction).

The human phenome



A snapshot of the human “phenome” according to the 23andMe database. Nodes are phenotypes, size is proportional to prevalence, and two phenotypes are connected with a line if they are over 30% correlated. Some disease types are colored: red nodes are cardiovascular and lipid traits, blue personality, green autoimmune, orange allergy, yellow neurological, and gray morphological.

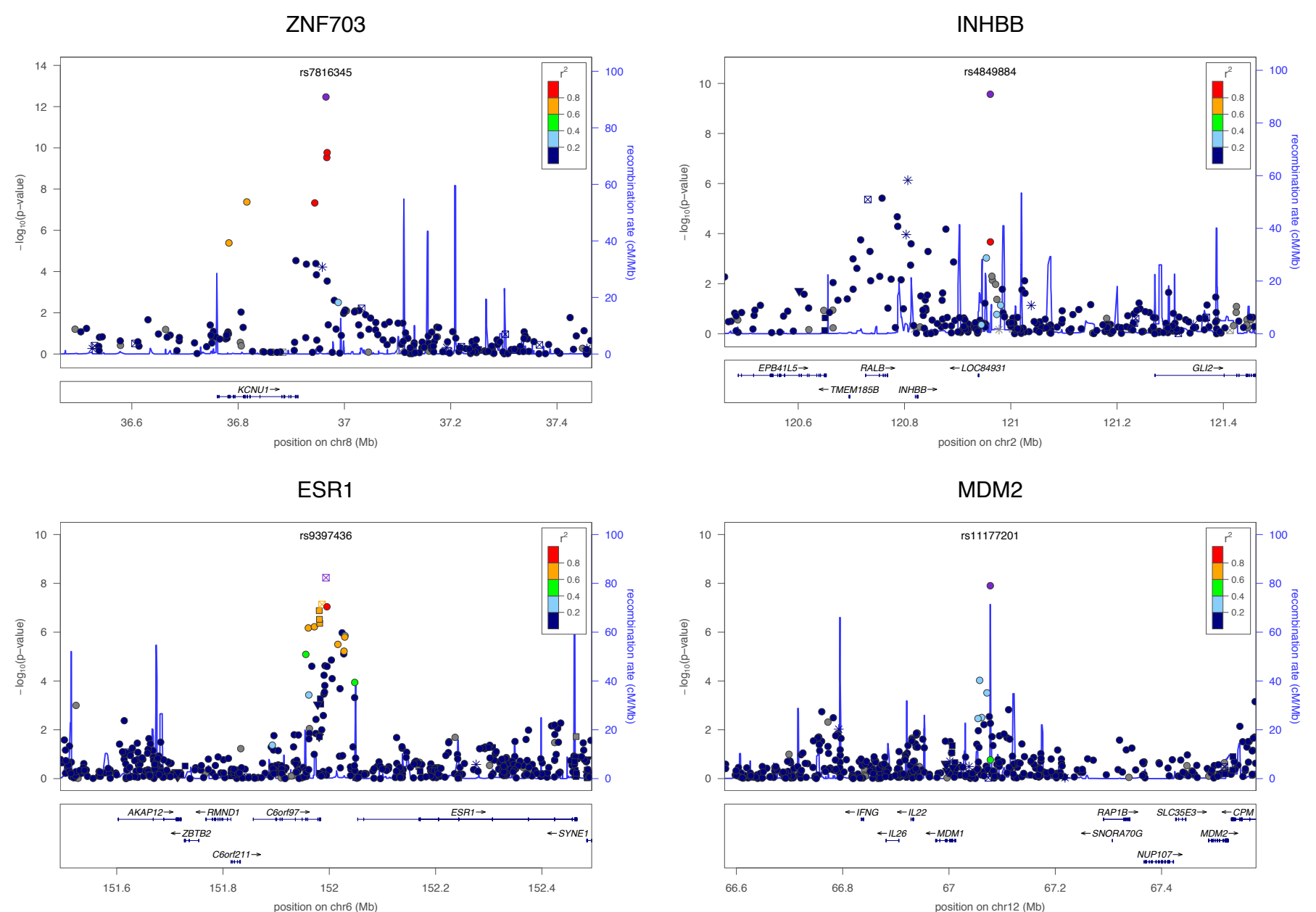
FTO influences sweet taste preference



We find that FTO also affects sweet taste preference independent of BMI, with the AA (skinny) genotype preferring salty snacks. This supports the theory that FTO is involved in obesity through food choice.

We find that people who reach for neither sweet nor salty snacks are 1.3 BMI units skinnier on average.

Breast size and breast cancer



A SNP near ESR1 is associated with both breast size and breast cancer. Genome wide, three other variants in regions with strong links to breast cancer also influence breast size. This is surprising, as breast cancer and breast size are not thought to be closely related.

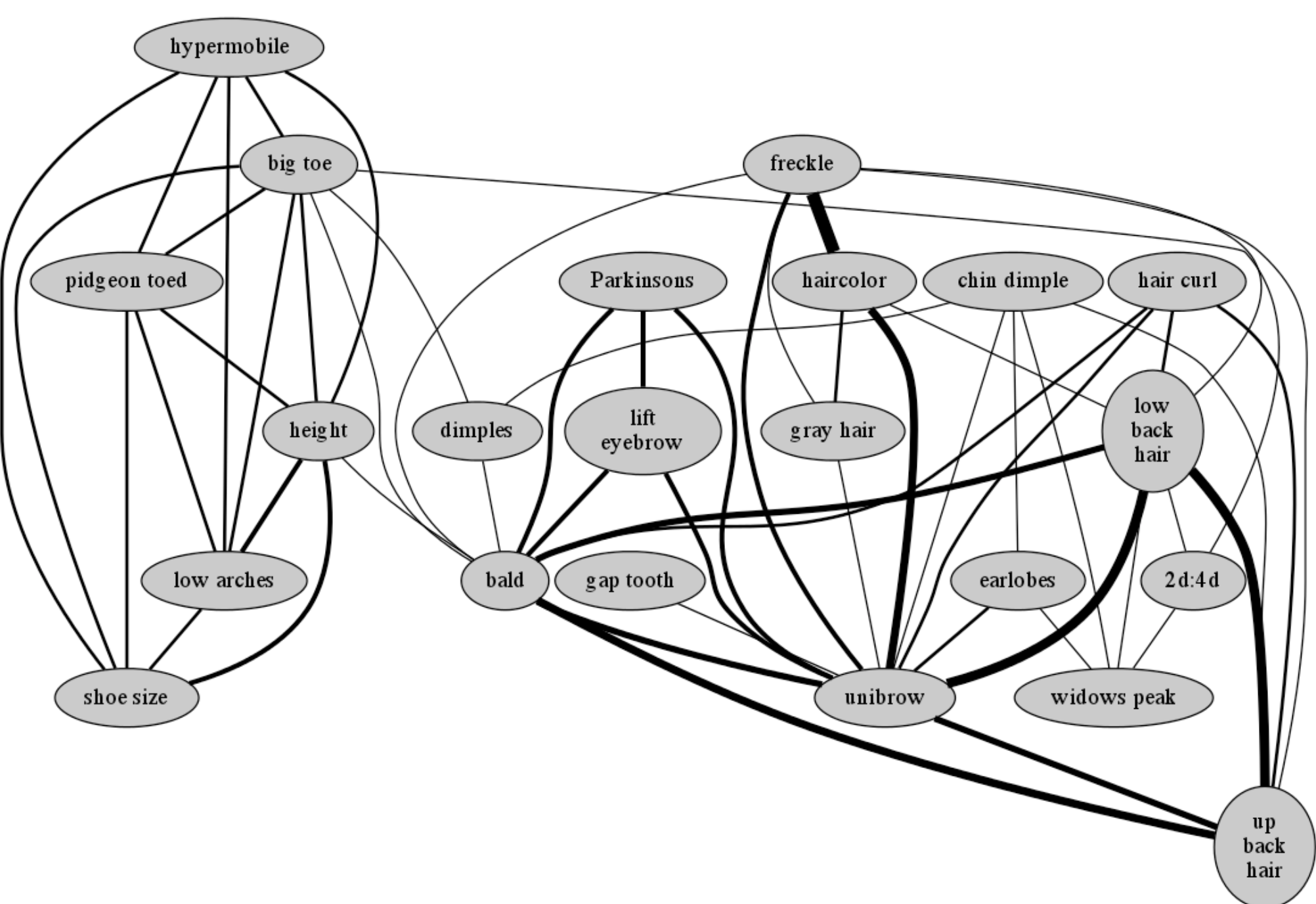
ACTN3 and sport choice

Null mutations in ACTN3 have been shown to explain a small part of the variance in performance of world class sprinters. Based on this information, companies have sprung up purporting to determine what sports people may excel in from their ACTN3 genotype.

Does ACTN3 determine sport choice in the greater population? We surveyed over 15,000 people to determine their history of playing 39 sports.

We find that ACTN3 genotype is **not** significantly associated with choice of any specific sport, with duration of participation, or with a choice of power (football, gymnastics, hockey, basketball, etc) versus endurance (running, rowing, swimming, etc) sports.

Human morphology is highly pleiotropic



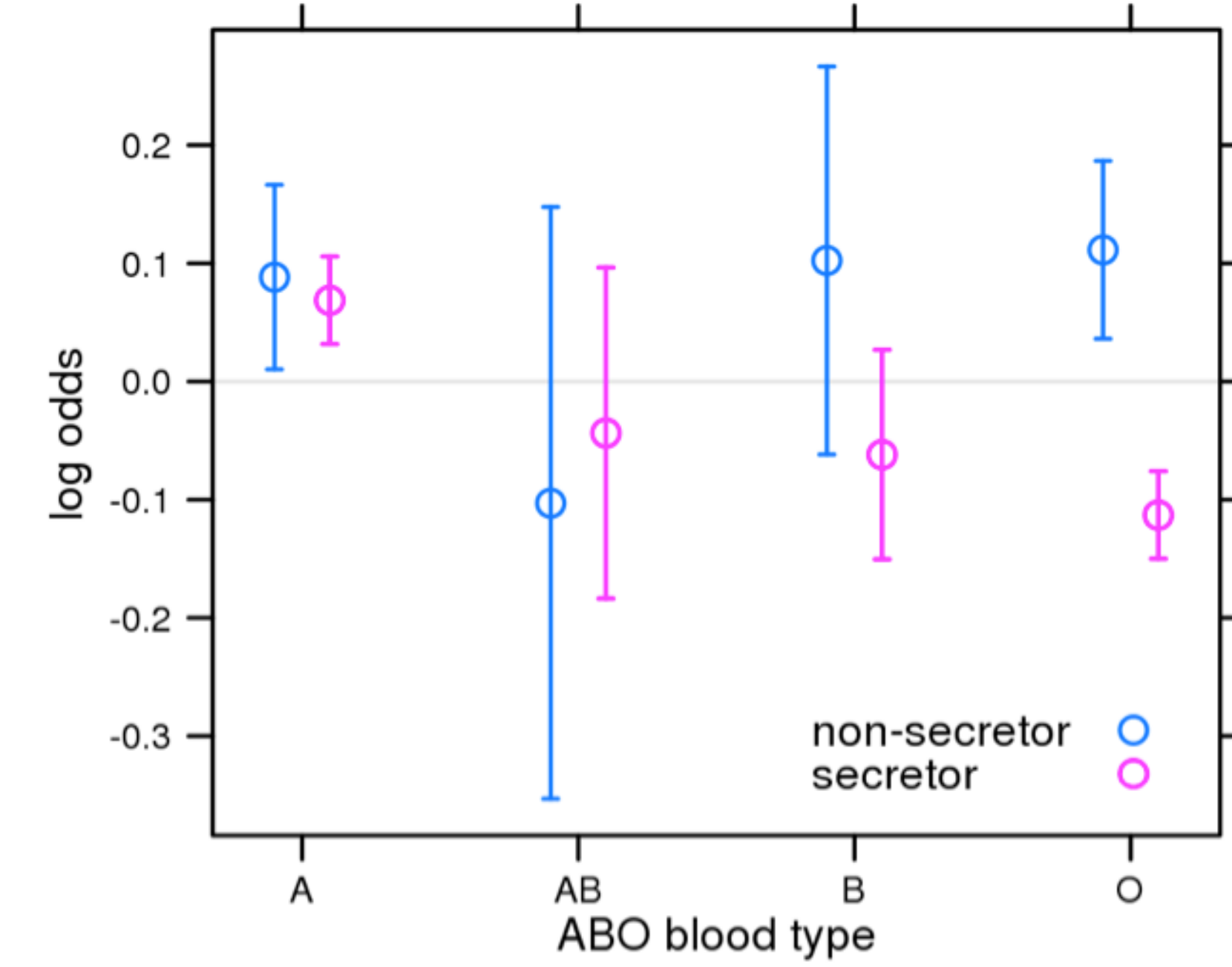
We have broadly surveyed basic human morphological traits in several categories:

- pigmentation
- hair growth and morphology
- skeletal traits

We see many SNPs associated with several distinct morphological traits. For example, a SNP near ZEB2 (rs10427255) originally associated with photic sneeze reflex is also associated with chin dimple, widow’s peak, and attached earlobes.

The graph above shows the pleiotropy across morphological traits. Traits are displayed as nodes, with edges if SNPs is significantly associated with both traits (edgewidth is proportional to the number of shared SNPs). “2d:4d” refers to ring to index finger ratio.

FUT2 and ABO



rs601338 in FUT2 is the main determinant of the ABO non-secretor phenotype in Europeans and has been previously associated with norovirus resistance and Crohn’s disease.

We find an association for FUT2 with mumps and suggestive evidence for other infectious diseases (colds, ear infections), as well as a consistent direction of effect against autoimmune diseases. We also see an association with cholesterol levels and an interaction with ABO blood type.