Psychosocial experiences modulate asthma-associated genes through gene-environment interactions

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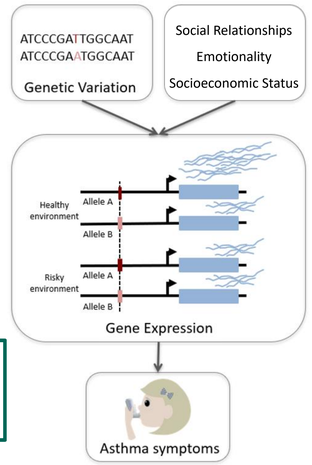
Background

- Low socio-economic status and growing up in risky families correlates with poor health outcomes
- Children living in urban areas and below poverty are most at-risk for asthma[1]
- Social genomics approaches have found pro-inflammatory effects of negative psychosocial experiences on blood gene expression[2,3,4]
- However, these studies did not investigate the whole gamut of psychosocial experiences and did not resolve whether these pathways are causally linked to health outcomes



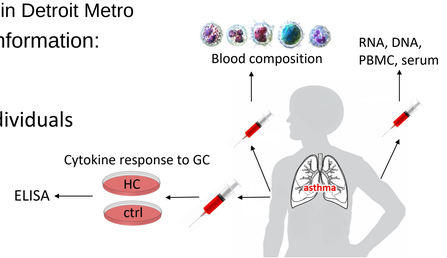
Research question:
What are the specific contributions of the environment and of genetics to asthma-related phenotypes?

Asthma in the Lives of Families Today (ALOFT)

ALOFT (Asthma in the Lives Of Families Today)

- 251 asthmatic children aged 10-17 living in Detroit Metro
- Extensive **medical and psychological** information:
  - Emotionality
  - Social interactions
  - Socio-economic status
  - Blood composition
  - Asthma
  - Glucocorticoid resistance
  - Gene expression
  - Genome-wide genotypes

119 individuals



Transcriptional signatures of traits and environments

We developed a new machine learning approach to de-noise and impute psychosocial effects on gene expression, based on generalized linear models with elastic net regularization (GLMnet[5]) on subset of 119 individuals for whom data was available, according to the following model:

$$\text{Phenotype/Environment} = \mu + \beta_1 \mathrm{E}(\text{gene}_1) + \beta_2 \mathrm{E}(\text{gene}_2) + \ldots + \beta_n \mathrm{E}(\text{gene}_n)$$

We used cross-validation to minimize the mean squared error (MSE) and quantified cross-validated increase in phenotypic variance explained by transcriptomic prediction model (transcriptional signature) over sample mean (Fig. 1b). Using this approach we derived transcriptional signatures that represent the portion of the transcriptome which correlates with each psychosocial factor for all participants.

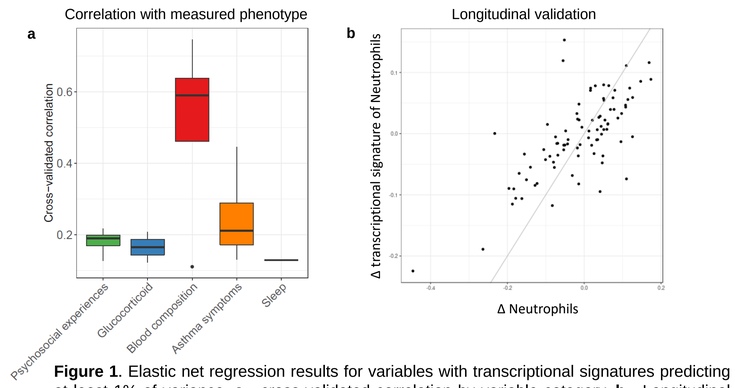


Figure 1. Elastic net regression results for variables with transcriptional signatures predicting at least 1% of variance. **a** - cross-validated correlation by variable category, **b** - Longitudinal change in observed Neutrophils (x axis) and longitudinal change in transcriptional signature of Neutrophils (y axis) (Pearson's rho=0.72, p<0.001, grey=identity line).

Shared transcriptional signatures

We investigated whether psychosocial experiences and asthma symptoms are associated with similar transcriptional signatures. We observed correlations between transcriptional signatures of psychosocial traits and asthma symptoms, which both correlated with transcriptional signatures of blood composition (Fig. 2a). Using bootstrap mediation analysis we found that the effect of self-disclosure on pulmonary function is mediated via blood cell composition (Fig. 2b).

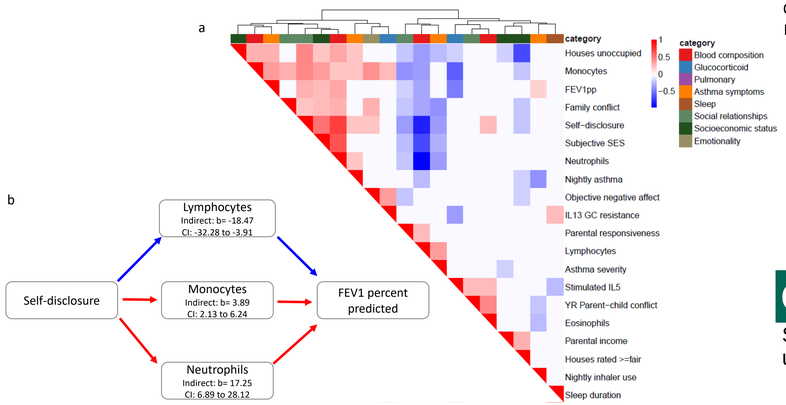


Fig. 2. a - Heatmap of correlations between transcriptional signatures of variables explaining at least 1% of variance. Color indicates strength and direction of correlation; white indicates p-value<0.05, **b** – Result of mediation analysis between transcriptional signature of self-disclosure through transcriptional signatures of cell composition to transcriptional signature of pulmonary function (percent-predicted FEV1).

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GxE, gene expression and asthma

To directly investigate if transcriptional signatures associated with negative psychosocial experiences contribute to inter-individual variation in asthma risk, we used expression quantitative trait locus (eQTLs) combined with transcriptome-wide association analysis (TWAS)[6].

We identified 8590 eGenes with at least one eQTL (10% FDR). Of these 188 are causally associated with asthma and allergic diseases.

To examine the genotype-by-environment effects of psychosocial experiences and blood composition on gene expression (GE), we imputed the transcriptional signatures for the entire cohort of 251, and used the following model:

$$GE = \text{covariates} + \text{genotype dosage}_i * \text{transcriptional signature} + \varepsilon$$

We discovered 349 interaction eQTLs across 136 genes (10% FDR; Fig. 3a). Among the genes causally linked to asthma or allergic disease risk in TWAS, expression of 32 genes is modulated by psychosocial environments; for three genes the genetic effect on gene expression is modulated by psychosocial factors through GxE (e.g. Fig. 3b).

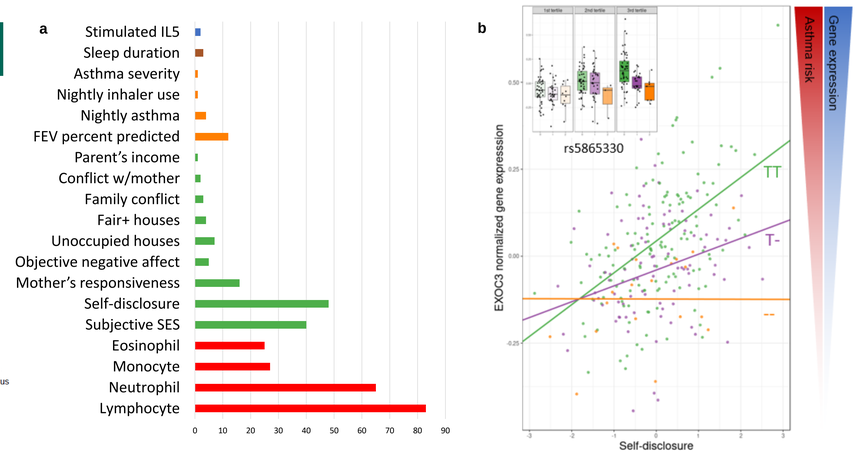

Fig. 3. a - Numbers of significant gene-environment interaction eQTLs (GxE eQTLs, 10% FDR); **b –** Self-disclosure interacts with eQTL rs5865330 T/- to influence expression of EXOC3 gene causally linked to asthma through TWAS.

Conclusions

Social genomics approaches in humans can uncover potential molecular mechanisms underlying health disparities

- Psychosocial experiences and asthma symptoms are reflected in blood gene expression
- We showed sharing of transcriptional signatures between psychosocial and asthma traits
- Psychosocial experiences interact with genetic variants to alter gene expression
- These interactions may lead to increased risk of asthma and other allergic diseases

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