MOLECULAR PAIN

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Integrating epigenetic data into molecular casual networks

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Genome-wide association studies (GWAS) have recently identified many risk loci for complex human diseases. However, genetics can explain only a fraction of disease variation. Epigenetics refers to cellular mechanisms that affect gene expression without modifying DNA sequence [1]. Epigenetic mechanisms reflect gene X environment interactions, which contribute to risk for many chronic diseases including obesity [2], hypertension [3], cancers [4], chronic inflammation [5], chronic pain [6], and chronic obstructive pulmonary disease (COPD) [7]. While these studies have provided an initial look into genetic or epigenetic factors affecting disease risk or disease severity, understanding the transcriptional regulation by genetic and epigenetic factors, such as DNA methylation and microRNA, may shed light on understanding the biological processes and molecular mechanisms associated complex human diseases.

By integrating genetic, epigenetic, and transcriptomic data we developed genetic causality tests [8,9] and a novel methylation-based causality test. Then, we developed a method to construct a global Bayesian network [10-12] using the causal test results as priors. As a proof-of-concept, we applied these methods to genome-wide genetic, epigenetic, and transcriptomic data and phenotypic data generated from lung tissues of COPD patients and non-COPD controls, and identified multiple causal regulators for pathways associated with disease severity. We experimentally validated candidate genes in cell lines, mouse models, and in human tissues. Our results suggest that the integrative causal network can provide important insights into understanding the mechanisms underlying epigenetic regulations, altering transcriptional programs that lead to COPD pathogenesis and progression. These approaches can be applied to uncover molecular mechanisms underlying other diseases, such as chronic pain.

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References

1. Ubeda F, Wilkins JF: **Imprinted genes and human disease: an evolutionary perspective.** *Advances in experimental medicine and biology* 2008, **626**:101-115.
2. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH: **Persistent epigenetic differences associated with prenatal exposure to famine in humans.** *Proc Natl Acad Sci U S A* 2008, **105**:17046-17049.
3. de Jonge LL, Harris HR, Rich-Edwards JW, Willett WC, Forman MR, Jaddoe VW, Michels KB: **Parental smoking in pregnancy and the risks of adult-onset hypertension.** *Hypertension* 2013, **61**:494-500.
4. Kanwal R, Gupta S: **Epigenetic modifications in cancer.** *Clin Genet* 2012, **81**:303-311.
5. Bayarsaihan D: **Epigenetic mechanisms in inflammation.** *Journal of dental research* 2011, **90**:9-17.
6. Denk F, McMahon SB: **Chronic pain: emerging evidence for the involvement of epigenetics.** *Neuron* 2012, **73**:435-444.
7. Vucic EA, Chari R, Thu KL, Wilson IM, Cotton AM, Kennett JY, Zhang M, Lonergan KM, Steiling K, Brown CJ, *et al*: **DNA methylation is globally disrupted and associated with expression changes in chronic obstructive pulmonary disease small airways.** *American journal of respiratory cell and molecular biology* 2014, **50**:912-922.
8. Schadt EE, Lamb J, Yang X, Zhu J, Edwards S, Guhathakurta D, Sieberts SK, Monks S, Reitman M, Zhang C, *et al*: **An integrative genomics approach to infer causal associations between gene expression and disease.** *Nat Genet* 2005, **37**:710-717.
9. Millstein J, Zhang B, Zhu J, Schadt EE: **Disentangling molecular relationships with a causal inference test.** *BMC Genet* 2009, **10**:23.
10. Zhu J, Sova P, Xu Q, Dombek KM, Xu EY, Vu H, Tu Z, Brem RB, Bumgarner RE, Schadt EE: **Stitching together multiple data dimensions reveals interacting metabolomic and transcriptomic networks that modulate cell regulation.** *PLoS Biol* 2012, **10**:e1001301.
11. Zhu J, Wiener MC, Zhang C, Fridman A, Minch E, Lum PY, Sachs JR, Schadt EE: **Increasing the Power to Detect Causal Associations by Combining Genotypic and Expression Data in Segregating Populations.** *PLoS Comput Biol* 2007, **3**:e69.
12. Zhu J, Zhang B, Smith EN, Drees B, Brem RB, Kruglyak L, Bumgarner RE, Schadt EE: **Integrating large-scale functional genomic data to dissect the complexity of yeast regulatory networks.** *Nat Genet* 2008, **40**:854-861.

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