Polygenic Model for Complex Diseases: Genetic Susceptibility and Risk Factor

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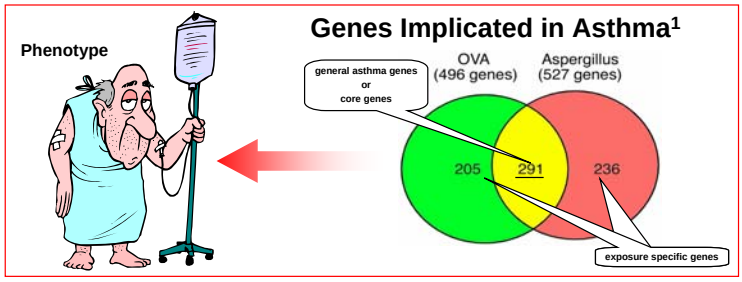
INTRODUCTION

Common diseases, such as asthma, Alzheimer's and cardiovascular diseases, are complex in nature, being variably influenced by physiological, life-style, environmental and genetic factors. As such, variations in individual genes that have the potential to affect a disease generally possess low or incomplete penetrance and, consequently, in epidemiological studies show low risk associations with typical odd ratios around 1.5 - 2.0. The disease phenotype is, in part, a result of joint co-expression of multiple genes. In particular:

- **hundreds of genes** simultaneously shape the susceptible phenotype
- a degree of susceptibility to environmental exposures is determined by the joint effect of unique **combination of genes** specific for a given individual
- how to establish appropriate **risk factors** taking into account subpopulations with genetically susceptible combinations of genes?



METHODS

Population-based genetic association studies deal with relatively small effects against a complex background. Therefore, often they are statistically underpowered and poorly standardized. In the present work[2] source data were extracted from PubMed using the following criteria:

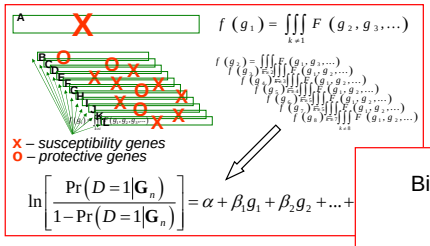
- physician diagnosed asthma as the diagnosis
- case-control study design
- reported associations with $p < 0.05$

For each of 16 genes the following information was collected, e.g.:

Gene	SNP	Reference	Frequency	Odds Ratio
TGF-β	- 509	[3]	0.117	2.456

THEORY

PROBLEM: to estimate gross genetic susceptibility of individual from known single-gene association studies. Mathematically, it narrows down to reconstruction of unknown joint multivariate distribution from known univariate marginals of this distribution.



$$f(g_1) = \iiint_{k \neq 1} F(g_2, g_3, \ldots)$$

$$\ln\left[\frac{\Pr(D=1|\mathbf{G}_n)}{1-\Pr(D=1|\mathbf{G}_n)}\right] = \alpha + \beta_1 g_1 + \beta_2 g_2 + \ldots +$$

- frequencies (p) of genetic markers (minor types) and major types ($q = 1 - p$) enter the model with binomial coefficients

$$f_{genotype} = p_1 p_2 p_3 \ldots \times q_1 q_2 q_3 \ldots$$

- association between a marker and disease is expressed in terms of the standard logistic regression model:

$$\ln\left[\frac{\Pr(Disease=1|g)}{1-\Pr(Disease=1|g)}\right] = \alpha + \beta g$$

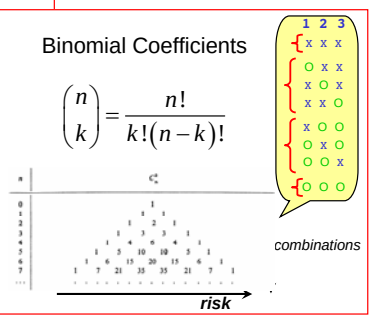
single gene, = 0 or = 1

Odds Ratio (OR)

$$\ln\left[\frac{\Pr(g_1, g_2 \ldots g_n)}{1-\Pr(g_1, g_2 \ldots g_n)}\right] = \alpha + \sum_{i=1}^{n} \beta_i g_i$$

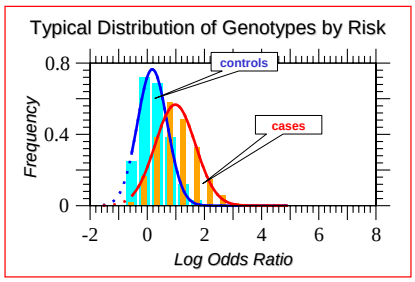
Binomial Coefficients

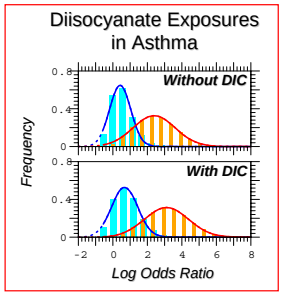
$$\binom{n}{k} = \frac{n!}{k!(n-k)!}$$



RESULTS

- Modelling joint impact of the multiple disease variants provides a pseudo-continuous log-normal relative disease risk distribution in the population.

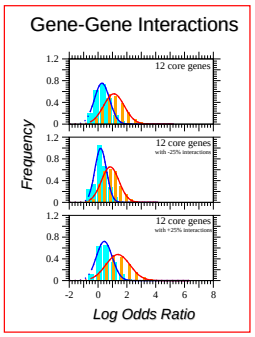


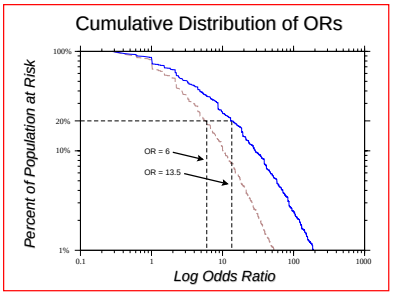


As the number of jointly considered genes increases,

- the distribution of risk further shifts towards the higher risk;
- the standard deviation of disease risk in the population increases;
- the separation between disease population and controls increases.

- **Gene-environment** interactions enter in the model by means of exposure-sensitive genes, *NAT1* in the shown example, which is sensitive to diisocyanates.





- Cumulative distribution quantifies population at risk (" with risk higher than …")
- Mock simulations do not suggest overwhelming effect of **gene-gene** interactions in the model

CONCLUSIONS

A computational approach has been presented, which allows estimation of the **joint contribution of variations** in individual genes to the risk of developing a disease. As an example, variants of 16 asthma susceptibility genes, including those associated with asthma mediators, atopy and chemical metabolism, were analyzed. A 6-fold increased risk of developing asthma for 20% in the general population occurred when only gene variants of asthma mediators were considered. The disease risk was more than doubled (OR=13.5) when the atopy variants were added. Inclusion of all variants resulted in the increased odds ratio of 24. The model helps establish the relative changes in risk associated with **genetic-risk profiles** in the population and provides a framework for comprehensive genetic risk assessment. The software is available on the CDC Intranet, http://158.111.214.63

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[2] E. Demchuk, B. Yucesoy, V.J. Johnson, A. Weston, D. Germolec, C.T. De Rosa & M.I. Luster (2007) A statistical model to assess genetic susceptibility as a risk factor in multifactorial diseases: Lessons from occupational asthma. *Environ. Health Persp.* **115**:231–234.
[3] E.S. Silverman, L.J. Palmer, V. Subramaniam, A. Hallock, S. Mathew, J. Vallone, D.S. Faffe, T. Shikanai, B.A. Raby, S.T. Weiss & S.A. Shore (2004) Transforming growth factor-beta1 promoter polymorphism C-509T is associated with asthma. *Am. J. Respir. Crit. Care Med.* **169**:214-219.

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