Polygenic Model for Complex Diseases: Genetic Susceptibility and Risk Factors

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Common diseases are polygenic in nature. Although, variations in individual genes that influence the disease are often of low penetrance and variable expressivity, and therefore show small risk associations, typically with odds ratios of 1.5 – 3, the joint effect in combination of genes may be significant in some genetically predisposed individuals. A combinatorial model is proposed to estimate polygenic disease risk in relation to the frequency of polygenotypes within the population. The model infers the joint odds ratios of the disease from the odds ratios and frequencies of idiosyncratic genetic markers. Essentially it attempts to reconstruct the unknown joint multivariate distribution of genetic risk, which depends on multiple genetic markers, from known univariate marginals of this distribution, which correspond to idiosyncratic genetic markers. Since common diseases, such as asthma, are strongly influenced by environmental, workplace and life-style factors, the genetic differences in the population may induce shifts in the dose-response curves for multiple effects. The proposed method estimates the magnitude of possible shifts for the population at risk. Application of the model to gene-environment interactions in asthma is illustrated using occupational exposures to diisocyanates.