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Titel des Beitrags:
Multi-locus stepwise regression: a haplotype-based algorithm for finding genetic associations applied to atopic dermatitis.

Abstract:
Genome-wide association studies (GWAS) provide an increasing number of single nucleotide polymorphisms (SNPs) associated with diseases. Our aim is to exploit those closely spaced SNPs in candidate regions for a deeper analysis of association beyond single SNP analysis, combining the classical stepwise regression approach with haplotype analysis to identify risk haplotypes for complex diseases. Our proposed multi-locus stepwise regression starts with an evaluation of all pair-wise SNP combinations and then extends each SNP combination stepwise by one SNP from the region, carrying out haplotype regression in each step. The best associated haplotype patterns are kept for the next step and must be corrected for multiple testing at the end. These haplotypes should also be replicated in an independent data set. We applied the method to a region of 259 SNPs from the epidermal differentiation complex (EDC) on chromosome 1q21 of a German GWAS using a case control set (1,914 individuals) and to 268 families with at least two affected children as replication. A 4-SNP haplotype pattern with high statistical significance in the case control set ($p = 4.13 \times 10^{-7}$ after Bonferroni correction) could be identified which remained significant in the family set after Bonferroni correction ($p = 0.0398$). Further
analysis revealed that this pattern reflects mainly the effect of the well-known FLG gene; however, a
FLG-independent haplotype in case control set (OR = 1.71, 95% CI: 1.32-2.23, p = 5.6 × 10(-5)) and
family set (OR = 1.68, 95% CI: 1.18-2.38, p = 2.19 × 10(-3)) could be found in addition. Our approach
is a useful tool for finding allele combinations associated with diseases beyond single SNP analysis in
chromosomal candidate regions.