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Titel des Beitrags: Dilution of candidates: the case of iron-related genes in restless legs syndrome.

Abstract: Restless legs syndrome (RLS) is a common multifactorial disease. Some genetic risk factors have been identified. RLS susceptibility also has been related to iron. We therefore asked whether known iron-related genes are candidates for association with RLS and, vice versa, whether known RLS-associated loci influence iron parameters in serum. RLS/control samples (n = 954/1814 in the discovery step, 735/736 in replication 1, and 736/735 in replication 2) were tested for association with SNPs located within 4 Mb intervals surrounding each gene from a list of 111 iron-related genes using a discovery threshold of P = 5 × 10(-4). Two population cohorts (KORA F3 and F4 with together n = 3447) were tested for association of six known RLS loci with iron, ferritin, transferrin, transferrin-saturation, and soluble transferrin receptor. Results were negative. None of the candidate SNPs at the iron-related gene loci was confirmed significantly. An intronic SNP, rs2576036, of KATNAL2 at 18q21.1 was significant in the first (P = 0.00085) but not in the second replication step (joint nominal P-value = 0.044). Especially, rs1800652 (C282Y) in the HFE gene did not associate with RLS. Moreover, SNPs at the known RLS loci did not
significantly affect serum iron parameters in the KORA cohorts. In conclusion, the correlation between RLS and iron parameters in serum may be weaker than assumed. Moreover, in a general power analysis, we show that genetic effects are diluted if they are transmitted via an intermediate trait to an end-phenotype. Sample size formulas are provided for small effect sizes.