Albai, G; Nagaraja, R; Schlessinger, D; Jackson, AU; Tuomilehto, J; Collins, FS; Boehnke, M; Mohlke, KL

Titel des Beitrags:
Common variants near MC4R are associated with fat mass, weight and risk of obesity.

Abstract:
To identify common variants influencing body mass index (BMI), we analyzed genome-wide association data from 16,876 individuals of European descent. After previously reported variants in FTO, the strongest association signal (rs17782313, $P = 2.9 \times 10^{-6}$) mapped 188 kb downstream of MC4R (melanocortin-4 receptor), mutations of which are the leading cause of monogenic severe childhood-onset obesity. We confirmed the BMI association in 60,352 adults (per-allele effect = 0.05 Z-score units; $P = 2.8 \times 10^{-15}$) and 5,988 children aged 7-11 (0.13 Z-score units; $P = 1.5 \times 10^{-8}$). In case-control analyses ($n = 10,583$), the odds for severe childhood obesity reached 1.30 ($P = 8.0 \times 10^{-11}$). Furthermore, we observed overtransmission of the risk allele to obese offspring in 660 families ($P$ (pedigree disequilibrium test average; PDT-avg) = $2.4 \times 10^{-4}$). The SNP location and patterns of phenotypic associations are consistent with effects mediated through altered MC4R function. Our findings establish that common variants near MC4R influence fat mass, weight and obesity risk at the population level and reinforce the need for large-scale data integration to identify variants influencing continuous biomedical traits.

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