Genetic aspects of human obesity

Studies of the candidate genes: MC4R, GHSR, ghrelin, PPARG2P and ESRRA

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ABSTRACT

A genetic predisposition to obesity has been shown in several studies and recently both monogenic and polygenic types of obesity have been identified. This dissertation focuses on five biological candidate genes.

The melanocortin 4 receptor gene (*MC4R*) was selected for screening for variants in a cohort of Danish men and the frequency of pathogenic *MC4R* mutations among obese individuals with juvenile-onset was 2.5 % in the Danish population. In the growth hormone secretagogue receptor (*GHSR*) and ghrelin genes several variants were identified; however, only one rare mutation in the promoter of *GHSR* co-segregated with late-onset obesity. This mutation increased the transcription of the *GHSR* by introducing an SP-1-like binding site in the promoter.

In the peroxisome proliferator-activated receptor γ (*PPARG*) promoter eight SNPs in the 3000 base pairs upstream from the ATG site in the putative *PPARG* promoter were identified. However, none of the variants were associated with obesity or related quantitative traits. Analysis of the estrogen-related receptor α gene (*ESRRA*) identified three variants that occurred with a minor allele frequency above 5%. These were examined in a large-scale study of genetic epidemiology but no significant associations with any obesity phenotypes were observed nor was there evidence for epistasis between these variants and variants in the genes encoding PGC-1α and PGC-1β.

In conclusion, we have identified a novel form of monogenic obesity in the gene encoding *GHSR* and have established that *MC4R* mutations account for 2.5% of monogenic obesity among young Danish men. We did not find any mutations in the *PPARG* promoter, ghrelin or *EPPA*α, which were significantly associated with obesity or related quantitative traits.