Aspects of the molecular pathogenesis of obesity, type 2 diabetes, and insulin resistance

Experimental studies of SHP, MKKS, and SREBF1 based upon the biological candidate gene approach and global gene expression profiling in skeletal muscle

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ABSTRACT

This PhD dissertation is based on three published articles and one prepared manuscript and focuses on aspects of *genetic* and *non-genetic* elements in the molecular pathogenesis of the complex metabolic disorders obesity, type 2 diabetes (T2D) and insulin resistance (IR).

The studies were conducted at Steno Diabetes Center and Hagedorn Research Institute, Gentofte.

Around 80% of all patients with T2D are overweight or obese and this explains why the dramatic increased prevalence over the past decade for both disorders go hand-in-hand. Both obesity and T2D are complex multifactorial disorders with IR being a common feature in both of these metabolic disorders.

Evidence from numerous epidemiological studies demonstrate that factors predisposing to obesity, T2D and IR are of genetic as well as of environmental (non-genetic) origins. Estimates for the genetic basis of phenotypic variations in obesity range from approximately 40 to 70%. Family segregation studies also show that the life-time risk of developing T2D is 40% in offspring of one T2D parent and is as high as 70% if both parents have the disease.

The first study involved the evaluation of the prevalence of Small Heterodimer Partner (*SHP*) gene variants among 750 obese Danish men vs. 795 non-obese subjects. We identified five novel variants in the coding region of *SHP* of which one (G93D) was functional and was identified in only one obese subject.

The second study involves the assessment of the variation of the McKusick-Kaufman Syndrome (*MKKS*) gene and its contribution to common and probably polygenic forms of obesity in 744 obese Danish men and among 378 members of 62 obese families. We identified five variants in the coding region of *MKKS* where one variant (A242S) showed partial co-segregation with obesity in two families. Thus, we find that it is unlikely that *MKKS* variants play a major role in the pathogenesis of common non-syndromic obesity.

The third study involved the evaluation of common variants in Sterol Regulatory Element-Binding Factor 1 (*SREBF1*) by assessing HapMap, in the Inter99 cohort, the Danish ADDITION study and subjects with T2D (a total of 15,734 subjects) with the association of T2D. We found an association between *SREBF1* mutations and a modestly increased predisposition to T2D.

The fourth study involved the evaluation of the independent contributions of non-genetic factors in relation to IR per se by analyzing global gene expression in skeletal muscle from metabolically characterized monozygotic twins discordant for whole-body insulin sensitivity. We did not find a significant difference in overall OXPHOS mitochondrial gene expression between insulin sensitive twins and its IR co-twin.

Overall, these studies add to the growing knowledge of molecular genetics in the molecular pathogenesis of common metabolic phenotypes.