ABSTRACT

Genetic factors play a substantial role in susceptibility to common diseases such as type 2 diabetes (T2DM) and obesity-related disorders. The current investigation was undertaken to examine the association of genetic variants that indirectly affect diabetes-related traits through their effects on birth weight and adiposity in South Asian Indians. Additionally, the thesis was extended to examine the plausibility of differences in body composition in Asian Indians, compared to the West, as a contributing factor to premature cardio-metabolic risk in Indians.

The first study investigated the association of two birth-weight lowering genetic variants in the *ADCY5* and near *CCNL1* locus with birth weight and adult glycemic traits. Although the significant associations between both genetic variants and birth weight as observed in Western cohorts were not seen, the *ADCY5* variant displayed an association with increased glucose and decreased fasting insulin response, which supports the fetal-insulin hypothesis proposing a common genetic factor linking birth weight and adult T2DM traits. Recent GWAS have shown that associations of certain variants with birth weight is secondary to their effects on adiposity, and the strong link between obesity and T2DM stimulated further examination of the effect of genetic variants on obesity and diabetes-related traits. In Paper II, it was confirmed that the common *FTO* variant exerts an effect on obesity traits in adult Indians similar to that in Caucasians. A subsequent investigation (Paper III) of the effects of *FTO* and *MC4R* in adolescents (mean ± SD age, 17.1 ±1.9 years) demonstrated an association with waist-hip ratio, providing evidence that the preferential accumulation of central fat in Indians is regulated by *FTO* in younger age groups. This could be a constitutional Asian Indian effect, and underpins the importance of ethnic-specific differences in fat distribution. These *FTO* associations with obesity and T2DM traits in adults were further strengthened by a meta-analysis of ~23,000 Asian Indians (Paper IV), in which a consistent obesity-related effect was observed, in addition to an effect on T2DM which seemed to be partially mediated through body mass index (BMI). The strong association of *FTO* with waist circumference and subcutaneous adipose tissue (SAT) proxies led to an investigation of the differences in abdominal adiposity depots in Indians compared to Caucasians, using dual energy X-ray absorptiometry (DXA) as described in Paper V. Compared with a BMI-, gender- and age-matched Western cohort, Asian Indians exhibited relatively less visceral fat accumulation and more subcutaneous fat, reinforcing that ethnic differences in fat distribution need to be appreciated when analyzing the connection between obesity and T2DM.

In conclusion, the effect of *ADCY5* on glucose regulation confirms that impaired glucose homeostasis in adulthood is related to birth weight mediated through mechanisms that involve fetal-insulin signaling. Regarding genetic effects on adiposity, the effect estimate of the *FTO* locus on obesity and diabetes-related traits in Asian Indians is similar to that in Western ethnicities. The relative absence of differences in visceral adiposity, and a predominance of subcutaneous fat accumulation along with lower muscle mass and higher overall body fat in Asian Indians, provides novel insights to investigate the role of specific adipose depots and skeletal muscle in relation to heightened cardio-metabolic risk in this population.