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Abstract Topic:- Complex traits and polygenic disorders

Abstract Title:- Unravelling the Genetic Landscape of Childhood Obesity in Indian Adolescents

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Aims:-Identification of common genetic variants associated with childhood obesity in Indian urban adolescents

Methods:- A two-staged genome-wide association study with discovery phase (1391 samples) and a replication phase (4391 samples) was performed to uncover polymorphisms regulating childhood obesity in Indian urban adolescents. After imputation, association testing was performed using generalized linear model in PLINK, adjusting for age, sex, and the first ten principal components assuming additive effect. The observed associations were fortified by integrating gene expression profiles, eQTL mapping, protein-altering consequences, chromatin state and interactions, etc. of underlying genes.

Results:- We identified six novel variants at GWAS significance ($p < 5 \times 10^{-8}$) shaping obesity in Indian adolescents, and reaffirmed the universality of FTO and MC4R in childhood obesity. One of these genes (associated with BMI, weight and hip) showed chromatin interaction with GPAM, an acyl transferase having catalytic role in glycerolipid synthesis, and acts as an eQTL for ACSL5 important in fatty acid metabolism. Another gene (associated with BMI, and weight), is a mitochondrial protease overexpressed in unfolded protein response in POMC neurons potentially impacting obesity. Another gene (associated with BMI, weight and hip), highly expressed in adipose tissue is crucial in AKT pathway important in obesity. One gene (associated with weight) showed highest expression in adipose tissue shows chromatin interaction with genes influencing adipogenesis. Another gene (associated with weight and waist) shows brain-specific expression and ensures proper termination of diacylglycerol signalling. One of the variants (associated with weight), acts as a splice QTL for itself in both subcutaneous and visceral adipose tissue, with opposing effects in these tissues. It also shows chromatin interaction with FAM3B, a regulator of glucose and lipid metabolism.

Conclusions:- Our findings are suggestive of potential regulatory role of the six identified genes in obesity modulated via adipogenesis, lipid metabolism, unfolded protein response, etc. The study mirrors the polygenic nature of childhood obesity and the importance of ethnicity-specific studies in overcoming missing heritability of GWAS.

Keywords:- childhood obesity, genome-wide association study, obesity genetics, complex disease, systems biology