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Identification of Rare Mutations in Genes Involved in Monogenic Forms of Obesity and Diabetes in Obese Guadeloupean Children through Next-Generation Sequencing

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Abstract : In the population of Guadeloupe Island (472,124 inhabitants and 80% of subjects of African descent), overweight and obesity were estimated at 23% and 9% respectively among children. High prevalence of diabetes has been reported (~10%) in the adult population. Nevertheless, no study has investigated the contribution of gene mutations to childhood obesity in this population. We aimed to investigate rare genetic mutations in genes involved in monogenic obesity or diabetes in obese Afro-Caribbean children from Guadeloupe Island using next-generation sequencing. The present investigation included unrelated obese children, from a previous study on overweight conducted in Guadeloupe Island in 2013. We sequenced coding regions of 59 genes involved in monogenic obesity or diabetes. A total of 25 obese schoolchildren (with Z-score of body mass index [BMI]: 2.0 to 2.8) were screened for rare mutations (non-synonymous, splice-site, or insertion/deletion) in 59 genes. Mean age of the study population was 12.4 ± 1.1 years. Seventeen children (68%) had insulin-resistance (HOMA-IR > 3.16). A family history of obesity (mother or father) was observed in eight children and three of the accompanying parent presented with type 2 diabetes. None of the children had gonadotrophic abnormality or mental retardation. We detected five rare heterozygous mutations, in four genes involved in monogenic obesity, in five different obese children: MC4R p.Ile301Thr and SIM1 p.Val326Thrfs*43 mutations which were pathogenic; SIM1 p.Ser343Pro and SH2B1 p.Pro90His mutations which were likely pathogenic; and NTRK2 p.Leu140Phe that was of uncertain significance. In parallel, we identified seven carriers of mutation in ABCC8 or KCNJ11 (involved in monogenic diabetes), which were of uncertain significance (KCNJ11 p.Val13Met, KCNJ11 p.Val151Met, ABCC8 p.Lys1521Asn and ABCC8 p.Ala625Val). Rare pathogenic or likely pathogenic mutations, linked to severe obesity were detected in more than 15% of this Afro-Caribbean population at high risk of obesity and type 2 diabetes.

Keywords : childhood obesity, MC4R, monogenic obesity, SIM1
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