An SH2B1 mutation causing obesity and declining school performance

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We report a 22 year old man with a history of progressive weight gain starting in his mid teens. The weight gain occurred in spite of attempts at strict dieting and regular often extreme exercise. He started to have problems with his school performance around 15 years of age. There was no family history of note. On examination he was noted to have generalised obesity (BMI 38.6 kg/m2) and prominent acanthosis nigricans. He had a normal blood pressure and no Cushingoid features. Biochemical and hormonal investigations were normal, apart from a profound hyperinsulinaemia. Patient continued to be troubled by obesity. He was commenced on metformin with no response in weight terms. He was also seen by psychiatrists and was treated with various drugs including antidepressants.

Genetic testing for all known forms of Mendelian obesity variants followed by searching for novel variants in the known obesity genes and regions was performed using whole exome (WES) followed by Sanger sequencing. A candidate variant, C539T/p.S180F in the SH2B1 gene was identified in the proband.

Sanger sequencing revealed that the missense mutation, C539T/p.S180F, was present in the heterozygous status in the proband and his father, while non-carrier status in the mother, which matches the wild type. The variant is predicted to be pathogenic by SIFT and CADD (Score of 23). In the Genome Aggregation Database (gnomAD), there were a total of three individuals with the same variant. The minor allele frequency (MAF) in gnomAD is 0.00002175 and in 1000 genome project is 0.0001996.

The identification of this variant in one of well-known candidate obesity genes suggests that the mutation may have contributed to the development of the diseases. Further functional study of this mutation is needed to elucidate the mechanism of the disease.