DEFICIENCY OF PICORNAVIRUS HOST FACTOR AND OBESITY REGULATOR PLAAT3 CAUSES A NOVEL TYPE OF FAMILIAL PARTIAL LIPODYSTROPHY

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BACKGROUND PLAAT3 (also known as PLA2G16) is a phospholipid modifying enzyme mainly expressed in white adipose tissue (WAT). PLAAT3 represents an important potential drug target as its deficiency in mice protects against picornavirus infection and diet-induced obesity. The consequences of PLAAT3 deficiency in humans are not known. METHODS Unbiased genome-wide approaches including homozygosity mapping, whole exome and genome sequencing were applied to identify the causal mutation in 4 patients from two consanguineous families with unexplained partial lipodystrophy. Lipidomics and histopathological analysis of patient WAT were performed. RESULTS In the first family we identified a homozygous 5092 bp deletion encompassing exon 2 of the PLAAT3 gene (c.16-4823_118+167del, p.Pro6ValfsTer15) within a shared ~43 Mb homozygous region at 11q12.3. In the second family a homozygous duplication of a single base leading to a frameshift in exon 3 of PLAAT3 (c.286dupG, p.Ala96GlyfsTer16) was observed. The patients presented clinically with partial lipodystrophy, severe insulin resistance and hyperlipidemia. Demyelinating neuropathy and chronic pain were additional disabling features. PLAAT3-deficient WAT showed inflammation, irregular adipocyte morphology and an abnormal lipidomic profile indicative of a failure to liberate arachidonic acid (AA) from membrane phosphatidylcholines (PC) resulting in increased levels of AA containing lyso-PCs (LPC). CONCLUSIONS Genetic PLAAT3 deficiency in humans causes a novel type of autosomal recessive familial partial lipodystrophy. This finding introduces an important caveat when considering PLAAT3 as a therapeutic target.