S2 Text. Literature review of 3D interacting genes with the intronic rs5792235 *FADS2* variant.

***BEST1* (bestrophin 1; 11q12.3)**

The *BEST1* gene encodes for bestrophin-1, an integral membrane protein localized basolaterally in the RPE. *BEST1* mutations are responsible for a group of inherited retinal disorders known as bestrophinopathies [1]. SNPs near or contained in *RAB3IL1* and within or downstream of *BEST1* were mainly positively associated with dihomo-γ-linolenic acid (DGLA, a 20-carbon n-6 fatty acid) levels, with a handful of SNPs also related arachidonic acid and linoleic acid levels [2].

***DAGLA* (diacylglycerol lipase alpha; 11q12.2)**

This gene encodes a diacylglycerol lipase. The encoded enzyme is involved in the biosynthesis of the endocannabinoid 2-arachidonoyl-glycerol. The protein coded by *DAGLA* is associated with inflammation and atherosclerosis in mice. The endocannabinoid 2-arachidonoylglycerol (2-AG) is a known modulator of inflammation [3]. *DAGLA* is also related to anxiety, with a proposed link to an association with weight [4]. *Dagla* KO mice demonstrate leanness, mainly due to hypophagia [5].

***DKFZP434K028* (uncharacterized LOC26070; 11q12.2)**

Unknown function. No clear relationship with cardiometabolic traits.

***FEN1* (flap structure-specific endonuclease 1; 11q12.2)**

The protein encoded by this gene removes 5' overhanging flaps in DNA repair and processes the 5' ends of Okazaki fragments in lagging strand DNA synthesis. The protein is a member of the XPG/RAD2 endonuclease family and is one of ten proteins essential for cell-free DNA replication. A recent GWAS for plasma PUFAs showed evidence for association between the SNP rs174537 (*FEN1* 10154G>T) and arachidonic acid. The same paper identified a gene-gene interaction between *APOA5* -1131T>C and *FEN1* 10154G>T on coronary artery disease (CAD) risk. Individuals with the *FEN1* 10154T allele showed lower total cholesterol, malondialdehyde (MDA), ox-LDL, and DGLA than those with the GG genotype [6]. In another study, *FEN1* rs174537 and FADS2 rs2727270 were both associated with PUFAs in serum phospholipids. Males with the *FEN1* rs174537T allele showed a lower proportion of arachidonic acid and lower ratio of arachidonic acid to linoleic acid than those with rs174537 GG genotype. Carriers of the rs174537T allele also showed a significant decrease in IL-6 and a significant increase in ox-LDL [7]. In a Korean study, *FEN1* rs174537 differed in allele frequencies between controls and CAD patients after adjustment for age, BMI, cigarette smoking, alcohol consumption, hypertension, diabetes mellitus, and hyperlipidemia and was associated with multiple serum phospholipids [8].

***INCENP* (inner centromere protein, 11q12.3)**

The inner centromere proteins (INCENPs), the initial members of the passenger protein group, display a broad localization along chromosomes in the early stages of mitosis but gradually become concentrated at centromeres as the cell cycle progresses into mid-metaphase. During telophase, the proteins are located within the midbody in

the intercellular bridge, where they are discarded after cytokinesis. No clear relationship with cardiometabolic traits.

MIR1908 **(microRNA 1908; 11q12.2)**

MIR1908 is a microRNA. miR-1908 was found to be associated with total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride and fasting glucose. In addition, a number of miR-1908 target genes were highlighted as potential mediators [9].

MIR611 **(microRNA 611, 11q12.2)**

MIR611 is a microRNA. No clear relationship with cardiometabolic traits.

MYRF **(myelin regulatory factor, 11q12.2)**

This gene encodes a transcription factor that is required for central nervous system myelination and may regulate oligodendrocyte differentiation. It is thought to act by increasing the expression of genes that effect myelin production but may also directly promote myelin gene expression. *MYRF* has been associated with T2D and its comorbidities, including retinopathy and CAD [10].

RAB3IL1 **(RAB3A interacting protein like 1, 11q12.2-q12.3)**

This gene encodes a guanine nucleotide exchange factor for the ras-related protein Rab3A. The encoded protein binds Rab3a and the inositol hexakisphosphate kinase InsP6K1. SNPs near or contained in *RAB3IL1* and within or downstream of *BEST1* were mainly positively associated with DGLA levels, with a handful of SNPs also related arachidonic acid and linoleic acid levels [2]. Other studies associated the gene

with plasma n-6 PUFAs [11] and oleic acid [12]. In an experimental study, Rab3A blocked the effects of GLP1 on ß-cells (GLP1 enhances glucose sensitivity in ß-cells) [13].

RPLP0P2 **(ribosomal protein lateral stalk subunit P0 pseudogene 2, 11q12.2)**

Unknown function. No clear relationship with cardiometabolic traits, although *RPLP0P2* is upregulated in subjects experiencing weight regain [14].

SCGB1D1 **(secretoglobin family 1D member 1, 11q12.3)**

The protein encoded by this gene is a member of the lipophilin subfamily. This gene product represents one component of a heterodimeric molecule present in human tears whose elution profile is consistent with prostatein, a tetrameric molecule composed of three peptide components in heterodimers. No clear relationship with cardiometabolic traits.

SCGB2A1 **(secretoglobin family 2A member 1, 11q12.3)**

Unknown function. No clear relationship with cardiometabolic traits.

SYT7 **(synaptotagmin 7, 11q12.2)**

This gene is a member of the synaptotagmin gene family and encodes a protein similar to other family members that mediate calcium-dependent regulation of membrane trafficking in synaptic transmission. In humans, expression of this gene has been associated with prostate cancer. Syt7 belongs to a protein family which mediates Ca^{2+}-dependent vesicular trafficking and exocytosis. Ablation of Syt7 in mice has been shown to decrease insulin and glucagon secretion in pancreatic cells [15, 16]. In

human islets, gene expression of *SYT7* has been demonstrated to be lower in islets of T2D donors compared to controls [17]. In another experiment, gene expression of *SYT7* correlated negatively to *in vivo* measurements of HbA1c levels and positively to glucose stimulated insulin secretion *in vitro* in human islets [18]. *SYT7* has also been associated with linoleic and arachidonic acids [11].

TMEM258 **(transmembrane protein 258, 11q12.2)**

Unknown function. Associated with central regulation of intestinal inflammation, but no clear relationship with cardiometabolic traits.

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