FTO gene

Fat mass and obesity-associated protein also known as **alpha-ketoglutarate-dependent dioxygenase FTO** is an enzyme that in humans is encoded by the *FTO* gene located on chromosome 16. As one homolog in the AlkB family proteins, it is the first mRNA demethylase that has been identified.[1] Certain variants of the FTO gene appear to be correlated with obesity in humans.[2]

1 Function

The amino acid sequence of the transcribed FTO protein shows high similarity with the enzyme AlkB which oxidatively demethylates DNA.[3][4] Recombinant FTO protein was first discovered to catalyze demethylation of 3-methylthymine in single-stranded DNA, and 3-methyluridine in single-stranded RNA, with low efficiency.[3] The nucleoside N6-methyladenosine, an abundant modification in RNA, was then found to be a major substrate of FTO.[1][5] The FTO gene expression was also found to be significantly upregulated in the hypothalamus of rats after food deprivation and strongly negatively correlated with the expression of orexigenic galanin-like peptide which is involved in the stimulation of food intake.[6]

Increases in hypothalamic expression of FTO are associated with the regulation of energy intake but not feeding reward.[7]

2 FTO demethylates m6A in mRNA

*N*6-methyladenosine (m^6A) is an abundant modification in mRNA and is found within some viruses,[8][9] and most eukaryotes including mammals,[10][11][12][13] insects,[14] plants,[15][16][17] and yeast.[18][19] It is also found in tRNA, rRNA, and small nuclear RNA (snRNA) as well as several long non-coding RNA, such as *Xist*.[5][20] Adenosine methylation is directed by a large m^6A methyltransferase complex containing METTL3 as the SAM-binding sub-unit.[21] *In vitro*, this methyltransferase complex preferentially methylates RNA oligonucleotides containing GGACU[22] and a similar preference was identified *in vivo* in mapped m^6A sites in Rous sarcoma virus genomic RNA[23] and in bovine prolactin mRNA.[24] In plants, the majority of the m^6A is found within 150 nucleotides before the start of the poly(A) tail.[25]

Mapping of m^6A in human and mouse RNA has identified over 18,000 m^6A sites in the transcripts of more than 7,000 human genes with a consensus sequence of [G/A/U][G>A]m^6AC[U>A/C][5][20] consistent with the previously identified motif.[22] Sites preferentially appear in two distinct landmarks—around stop codons and within long internal exons—and are highly conserved between human and mouse.[5][20] A subset of stimulus-dependent, dynamically modulated sites has been identified. Silencing the m^6A methyltransferase significantly affects gene expression and alternative RNA splicing patterns, resulting in modulation of the p53 (also known as TP53) signalling pathway and apoptosis.

FTO demethylates m^6A containing RNA efficiently in vitro.[1] FTO knockdown with siRNA led to increased amounts of m^6A in polyA-RNA, whereas overexpression of FTO resulted in decreased amounts of m^6A in human cells.[5] FTO partially co-localizes with nuclear speckles, which supports the notion that m^6A in nuclear RNA is a major physiological substrate of FTO. Function of FTO likely affects the processing of pre-mRNA, other nuclear RNAs, or both. The discovery of the FTO-mediated oxidative demethylation of m^6A in nuclear RNA may initiate further investigations on biological regulation based on reversible chemical modification of RNA.[1][5]

3 Tissue distribution

The FTO gene is widely expressed in both fetal and adult tissues.[26]

4 Clinical significance

4.1 Association with obesity

A study of 38,759 Europeans for variants of FTO identified an obesity risk allele.[26] In particular, carriers of one copy of the allele weighed on average 1.2 kilograms (2.6 lb) more than people with no copies. Carriers of two copies (16% of the subjects) weighed 3 kilograms (6.6 lb) more and had a 1.67-fold higher rate of obesity than those with no copies. The association was observed in ages 7 and upwards. This gene is not directly associated with diabetes however increased body-fat also increases the risk of developing type 2 diabetes.[27]

Simultaneously, a study in 2,900 affected individuals

and 5,100 controls of French descent, together with 500 trios (confirming an association independent of population stratification) found association of SNPs in the very same region of FTO (rs1421085).[28] The authors found that this variation, or a variation in strong LD with this variation explains 1% of the population BMI variance and 22% of the population attributable risk of obesity. The authors of this study claim that while obesity was already known to have a genetic component (from twin studies), no replicated previous study has ever identified an obesity risk allele that was so common in the human population. The risk allele is a cluster of 10 single nucleotide polymorphism in the first intron of FTO called rs9939609. According to HapMap, it has population frequencies of 45% in the West/Central Europeans, 52% in Yorubans (West African natives) and 14% in Chinese/Japanese. Furthermore, morbid obesity is associated with a combination of FTO and INSIG2 single nucleotide polymorphisms.[29]

In 2009 variants in the FTO gene were further confirmed to associate with obesity in two very large genome wide association studies of body mass index (BMI).[30][31]

In adult humans it was shown that adults bearing the at risk AT and AA alleles at rs9939609 consumed between 500 and 1250 kJ more each day than those carrying the protective TT genotype (equivalent to between 125 and 280 kcal per day more intake).[32] The same study showed that there was no impact of the polymorphism on energy expenditure. This finding of an effect of the rs9939609 polymorphism on food intake or satiety has been independently replicated in five subsequent studies (in order of publication).[33][34][35][36][37] Three of these subsequent studies also measured resting energy expenditure and confirmed the original finding that there is no impact of the polymorphic variation at the rs9939609 locus on energy expenditure. A different study explored the effects of variation in two different SNPs in the FTO gene (rs17817449 and rs1421085) and suggested there might be an effect on circulating leptin levels and energy expenditure, but this latter effect disappeared when the expenditure was normalised for differences in body composition.[38] The accumulated data across seven independent studies therefore clearly implicates the FTO gene in humans as having a direct impact on food intake but no effect on energy expenditure.

The obesity-associated noncoding region within the FTO gene interacts directly with the promoter of IRX3, a homeobox gene, and IRX5, another homeobox gene. The noncoding region of FTO interacts with the promoters of IRX3 and FTO in human, mouse and zebrafish, and with IRX5. Results suggest that IRX3 and IRX5 are linked with obesity and determine body mass and composition. This is further supported by the fact that obesity-associated single nucleotide polymorphisms, in which cytosine is substituted for thymine, are involved in the expression of IRX3 and IRX5 (not FTO) in human brains. The enhanced expression of IRX3 and IRX5 resulting from this single nucleotide alteration promoted a shift from energy-dissipating beige adipocytes to energy-storing white adipocytes and a subsequent reduction in mitochondrial thermogenesis by a factor of 5.[39][40] Another study found indications that the FTO allele associated with obesity represses mitochondrial thermogenesis in adipocyte precursor cells in a tissue-autonomous manner, and that there is a pathway for adipocyte thermoregulation which involves the proteine ARID5B, the single-nucleotide variant rs1421085, and the IRX3 and IRX5 genes.[41]

4.2 Association with Alzheimer's disease

Recent studies revealed that carriers of common FTO gene polymorphisms show both a reduction in frontal lobe volume of the brain[42] and an impaired verbal fluency performance.[43] Fittingly, a population-based study from Sweden found that carriers of the FTO rs9939609 A allele have an increased risk for incident Alzheimer disease.[44]

4.3 Association with other diseases

The presence of the FTO rs9939609 A allele was also found to be positively correlated with other symptoms of the metabolic syndrome, including higher fasting insulin, glucose, and triglycerides, and lower HDL cholesterol. However all these effects appear to be secondary to weight increase since no association was found after correcting for increases in body mass index.[45] Similarly, the association of rs11076008 G allele with the increased risk for degenerative disc disease was reported.[46]

5 Model organisms

Model organisms have been used in the study of FTO function. In contrast to the findings in humans deletion, analysis of the *Fto* gene in mice showed loss of function is associated with no differences in energy intake but greater energy expenditure and this results in a reduction of body weight and fatness.[47]

Another conditional knockout mouse line, called $Fto^{tm1a(EUCOMM)Wtsi}$[53][54] was generated as part of the International Knockout Mouse Consortium program — a high-throughput mutagenesis project to generate and distribute animal models of disease to interested scientists.[55][56][57] Male and female animals from this line underwent a standardized phenotypic screen to determine the effects of deletion.[51][58] Twenty five tests were carried out on mutant mice and only significant skeletal abnormalities were observed, including kyphosis and abnormal vertebral transverse processes, and only in female homozygous mutant animals.[51]

The reasons for the differences in FTO phenotype between humans and different lines of mice is presently uncertain. However, many other genes involved in regulation of energy balance exert effects on both intake and expenditure.

6 Origin of name

By exon trapping, Peters et al. (1999) cloned a novel gene from a region of several hundred kb deleted by the mouse 'fused toes' (FT) mutation. They named the gene 'fatso' (Fto) due to its large size.[59][60]

7 References

[1] Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, Yi C, Lindahl T, Pan T, Yang YG, He C (December 2011). "N6-Methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO". *Nat. Chem. Biol.* **7** (12): 885–7. doi:10.1038/nchembio.687. PMC 3218240. PMID 22002720.

[2] Loos RJ, Yeo GS (2014). "The bigger picture of FTO: the first GWAS-identified obesity gene". *Nat Rev Endocrinol* **10** (1): 51–61. doi:10.1038/nrendo.2013.227. PMC 4188449. PMID 24247219.

[3] Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ (2007). "The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase". *Science* **318** (5855): 1469–72. Bibcode:2007Sci...318.1469G. doi:10.1126/science.1151710. PMC 2668859. PMID 17991826.

[4] Sanchez-Pulido L, Andrade-Navarro MA (2007). "The FTO (fat mass and obesity associated) gene codes for a novel member of the non-heme dioxygenase superfamily". *BMC Biochem.* **8**: 23. doi:10.1186/1471-2091-8-23. PMC 2241624. PMID 17996046.

[5] Meyer KD, Saletore Y, Zumbo P, Elemento O, Mason CE, Jaffrey SR (May 2012). "Comprehensive Analysis of mRNA Methylation Reveals Enrichment in 3' UTRs and near Stop Codons". *Cell* **149** (7): 1635–46. doi:10.1016/j.cell.2012.05.003. PMC 3383396. PMID 22608085.

[6] Fredriksson R, Hägglund M, Olszewski PK, Stephansson O, Jacobsson JA, Olszewska AM, Levine AS, Lindblom J, Schiöth HB (2008). "The obesity gene, FTO, is of ancient origin, upregulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain". *Endocrinology* **149** (5): 2062–71. doi:10.1210/en.2007-1457. PMID 18218688.

[7] Olszewski PK, Fredriksson R, Olszewska AM, Stephansson O, Alsiö J, Radomska KJ, Levine AS, Schiöth HB (October 2009). "Hypothalamic FTO is associated with the regulation of energy intake not feeding reward". *BMC Neurosci* **10**: 129. doi:10.1186/1471-2202-10-129. PMC 2774323. PMID 19860904.

[8] Aloni Y, Dhar R, Khoury G (October 1979). "Methylation of nuclear simian virus 40 RNAs". *J. Virol.* **32** (1): 52–60. PMC 353526. PMID 232187.

[9] Beemon K, Keith J (June 1977). "Localization of N6-methyladenosine in the Rous sarcoma virus genome". *J. Mol. Biol.* **113** (1): 165–79. doi:10.1016/0022-2836(77)90047-X. PMID 196091.

[10] Desrosiers R, Friderici K, Rottman F (October 1974). "Identification of methylated nucleosides in messenger RNA from Novikoff hepatoma cells". *Proc. Natl. Acad. Sci. U.S.A.* **71** (10): 3971–5. Bibcode:1974PNAS...71.3971D. doi:10.1073/pnas.71.10.3971. PMC 434308. PMID 4372599.

[11] Adams JM, Cory S (May 1975). "Modified nucleosides and bizarre 5'-termini in mouse myeloma mRNA". *Nature* **255** (5503): 28–33. Bibcode:1975Natur.255...28A. doi:10.1038/255028a0. PMID 1128665.

[12] Wei CM, Gershowitz A, Moss B (January 1976). "5'-Terminal and internal methylated nucleotide sequences in HeLa cell mRNA". *Biochemistry* **15** (2): 397–401. doi:10.1021/bi00647a024. PMID 174715.

[13] Perry RP, Kelley DE, Friderici K, Rottman F (April 1975). "The methylated constituents of L cell messenger RNA: evidence for an unusual cluster at the 5' terminus". *Cell* **4** (4): 387–94. doi:10.1016/0092-8674(75)90159-2. PMID 1168101.

[14] Levis R, Penman S (April 1978). "5'-terminal structures of poly(A)+ cytoplasmic messenger RNA and of poly(A)+ and poly(A)- heterogeneous nuclear RNA of cells of the dipteran Drosophila melanogaster". *J. Mol. Biol.* **120** (4): 487–515. doi:10.1016/0022-2836(78)90350-9. PMID 418182.

[15] Nichols JL (August 1979). "N6-methyladenosine in maize poly(A)-containing RNA". *Plant Science Letters* **15** (4): 357–361. doi:10.1016/0304-4211(79)90141-X.

[16] Kennedy TD, Lane BG (June 1979). "Wheat embryo ribonucleates. XIII. Methyl-substituted nucleoside constituents and 5'-terminal dinucleotide sequences in bulk poly(AR)-rich RNA from imbibing wheat embryos". *Can. J. Biochem.* **57** (6): 927–31. doi:10.1139/o79-112. PMID 476526.

[17] Zhong S, Li H, Bodi Z, Button J, Vespa L, Herzog M, Fray RG (May 2008). "MTA is an Arabidopsis messenger RNA adenosine methylase and interacts with a homolog of a sex-specific splicing factor". *Plant Cell* **20** (5): 1278–88. doi:10.1105/tpc.108.058883. PMC 2438467. PMID 18505803.

[18] Clancy MJ, Shambaugh ME, Timpte CS, Bokar JA (October 2002). "Induction of sporulation in Saccharomyces cerevisiae leads to the formation of N6-methyladenosine in mRNA: a potential mechanism for the activity of the IME4 gene". *Nucleic Acids Res.* **30** (20): 4509–18. doi:10.1093/nar/gkf573. PMC 137137. PMID 12384598.

[19] Bodi Z, Button JD, Grierson D, Fray RG (September 2010). "Yeast targets for mRNA methylation". *Nucleic Acids Res.* **38** (16): 5327–35. doi:10.1093/nar/gkq266. PMC 2938207. PMID 20421205.

[20] Dominissini D, Moshitch-Moshkovitz S, Schwartz S, Salmon-Divon M, Ungar L, Osenberg S, Cesarkas K, Jacob-Hirsch J, Amariglio N, Kupiec M, Sorek R, Rechavi G (May 2012). "Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq". *Nature* **485** (7397): 201–6. Bibcode:2012Natur.485..201D. doi:10.1038/nature11112. PMID 22575960.

[21] Bokar JA, Shambaugh ME, Polayes D, Matera AG, Rottman FM (November 1997). "Purification and cDNA cloning of the AdoMet-binding subunit of the human mRNA (N6-adenosine)-methyltransferase". *RNA* **3** (11): 1233–47. PMC 1369564. PMID 9409616.

[22] Harper JE, Miceli SM, Roberts RJ, Manley JL (October 1990). "Sequence specificity of the human mRNA N6-adenosine methylase in vitro". *Nucleic Acids Res.* **18** (19): 5735–41. doi:10.1093/nar/18.19.5735. PMC 332308. PMID 2216767.

[23] Kane SE, Beemon K (September 1985). "Precise localization of m6A in Rous sarcoma virus RNA reveals clustering of methylation sites: implications for RNA processing". *Mol. Cell. Biol.* **5** (9): 2298–306. PMC 366956. PMID 3016525.

[24] Horowitz S, Horowitz A, Nilsen TW, Munns TW, Rottman FM (September 1984). "Mapping of N6-methyladenosine residues in bovine prolactin mRNA". *Proc. Natl. Acad. Sci. U.S.A.* **81** (18): 5667–71. Bibcode:1984PNAS...81.5667H. doi:10.1073/pnas.81.18.5667. PMC 391771. PMID 6592581.

[25] Bodi Z, Zhong S, Mehra S, Song J, Graham N, Li H, May S, Fray RG (2012). "Adenosine Methylation in Arabidopsis mRNA is Associated with the 3' End and Reduced Levels Cause Developmental Defects". *Front Plant Sci* **3**: 48. doi:10.3389/fpls.2012.00048. PMC 3355605. PMID 22639649.

[26] Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI (2007). "A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity". *Science* **316** (5826): 889–94. Bibcode:2007Sci...316..889F. doi:10.1126/science.1141634. PMC 2646098. PMID 17434869.

[27] Sandholt CH, Hansen T, Pedersen O (2012). "Beyond the fourth wave of genome-wide obesity association studies". *Nutr Diabetes* **2**: e37. doi:10.1038/nutd.2012.9. PMC 3408643. PMID 23168490.

[28] Dina C, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougnères P, Kovacs P, Marre M, Balkau B, Cauchi S, Chèvre JC, Froguel P (2007). "Variation in FTO contributes to childhood obesity and severe adult obesity". *Nature Genetics* **39** (6): 724–6. doi:10.1038/ng2048. PMID 17496892.

[29] Chu X, Erdman R, Susek M, Gerst H, Derr K, Al-Agha M, Wood GC, Hartman C, Yeager S, Blosky MA, Krum W, Stewart WF, Carey D, Benotti P, Still CD, Gerhard GS (2008). "Association of morbid obesity with FTO and INSIG2 allelic variants". *Arch Surg* **143** (3): 235–40; discussion 241. doi:10.1001/archsurg.2007.77. PMID 18347269.

[30] Thorleifsson G, Walters GB, Gudbjartsson DF, Steinthorsdottir V, Sulem P, Helgadottir A, Styrkarsdottir U, Gretarsdottir S, Thorlacius S, Jonsdottir I, Jonsdottir T, Olafsdottir EJ, Olafsdottir GH, Jonsson T, Jonsson F, Borch-Johnsen K, Hansen T, Andersen G, Jorgensen T, Lauritzen T, Aben KK, Verbeek AL, Roeleveld N, Kampman E, Yanek LR, Becker LC, Tryggvadottir L, Rafnar T, Becker DM, Gulcher J, Kiemeney LA, Pedersen O, Kong A, Thorsteinsdottir U, Stefansson K (January 2009). "Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity". *Nat. Genet.* **41** (1): 18–24. doi:10.1038/ng.274. PMID 19079260.

[31] Willer CJ, Speliotes EK, Loos RJ, Li S, Lindgren CM, Heid IM, Berndt SI, Elliott AL (January 2009). "Six new loci associated with body mass index highlight a neuronal influence on body weight regulation". *Nat. Genet.* **41** (1): 25–34. doi:10.1038/ng.287. PMC 2695662. PMID 19079261.

[32] Speakman JR, Rance KA, Johnstone AM (August 2008). "Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure". *Obesity (Silver Spring)* **16** (8): 1961–5. doi:10.1038/oby.2008.318. PMID 18551109.

[33] Wardle J, Carnell S, Haworth CM, Farooqi IS, O'Rahilly S, Plomin R (September 2008). "Obesity associated genetic variation in FTO is associated with diminished satiety". *J. Clin. Endocrinol. Metab.* **93** (9): 3640–3. doi:10.1210/jc.2008-0472. PMID 18583465.

[34] Timpson NJ, Emmett PM, Frayling TM, Rogers I, Hattersley AT, McCarthy MI, Davey Smith G (October 2008). "The fat mass- and obesity-associated locus and dietary intake in children". *Am. J. Clin. Nutr.* **88** (4): 971–8. PMID 18842783.

[35] Haupt A, Thamer C, Staiger H, Tschritter O, Kirchhoff K, Machicao F, Häring HU, Stefan N, Fritsche A (April 2009). "Variation in the FTO gene influences food intake but not energy expenditure". *Exp. Clin. Endocrinol. Diabetes* **117** (4): 194–7. doi:10.1055/s-0028-1087176. PMID 19053021.

[36] Wardle J, Llewellyn C, Sanderson S, Plomin R (January 2009). "The FTO gene and measured food intake in children". *Int J Obes (Lond)* **33** (1): 42–5. doi:10.1038/ijo.2008.174. PMID 18838977.

[37] Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CN (December 2008). "An obesity-associated FTO gene variant and increased energy intake in children". *N. Engl. J. Med.* **359** (24): 2558–66. doi:10.1056/NEJMoa0803839. PMID 19073975.

[38] Do R, Bailey SD, Desbiens K, Belisle A, Montpetit A, Bouchard C, Pérusse L, Vohl MC, Engert JC (April 2008). "Genetic variants of FTO influence adiposity, insulin sensitivity, leptin levels, and resting metabolic rate in the Quebec Family Study". *Diabetes* **57** (4): 1147–50. doi:10.2337/db07-1267. PMID 18316358.

[39] Smemo S, Tena JJ, Kim KH, Gamazon ER, Sakabe NJ, Gómez-Marín C, Aneas I, Credidio FL, Sobreira DR, Wasserman NF, Lee JH, Puviindran V, Tam D, Shen M, Son JE, Vakili NA, Sung HK, Naranjo S, Acemel RD, Manzanares M, Nagy A, Cox NJ, Hui CC, Gomez-Skarmeta JL, Nóbrega MA (12 March 2014). "Obesity-associated variants within FTO form long-range functional connections with IRX3". *Nature* **507** (7492): 371–375. Bibcode:2014Natur.507..371S. doi:10.1038/nature13138. PMID 24646999.

[40] http://www.medscape.com/viewarticle/849799

[41] Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, Glunk V, Sousa IS, Beaudry JL, Puviindran V, Abdennur NA, Liu J, Svensson PA, Hsu YH, Drucker DJ, Mellgren G, Hui CC, Hauner H, Kellis M (2015). "FTO Obesity Variant Circuitry and Adipocyte Browning in Humans". *The New England Journal of Medicine* **373**: 895–907. doi:10.1056/NEJMoa1502214. PMID 26287746.

[42] Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, Dinov ID, Toga AW, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen AN, Corneveaux JJ, Stephan DA, DeCarli CS, DeChairo BM, Potkin SG, Jack CR, Weiner MW, Raji CA, Lopez OL, Becker JT, Carmichael OT, Thompson PM (May 2010). "A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly". *Proc. Natl. Acad. Sci. U.S.A.* **107** (18): 8404–9. Bibcode:2010PNAS..107.8404H. doi:10.1073/pnas.0910878107. PMC 2889537. PMID 20404173.

[43] Benedict C, Jacobsson JA, Rönnemaa E, Sällman-Almén M, Brooks S, Schultes B, Fredriksson R, Lannfelt L, Kilander L, Schiöth HB (June 2011). "The fat mass and obesity gene is linked to reduced verbal fluency in overweight and obese elderly men". *Neurobiol. Aging* **32** (6): 1159.e1–5. doi:10.1016/j.neurobiolaging.2011.02.006. PMID 21458110.

[44] Keller L, Xu W, Wang HX, Winblad B, Fratiglioni L, Graff C (2011). "The obesity related gene, FTO, interacts with APOE, and is associated with Alzheimer's disease risk: a prospective cohort study". *J. Alzheimers Dis.* **23** (3): 461–9. doi:10.3233/JAD-2010-101068. PMID 21098976.

[45] Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, Ebrahim S, Shields B, Zeggini E, Weedon MN, Lindgren CM, Lango H, Melzer D, Ferrucci L, Paolisso G, Neville MJ, Karpe F, Palmer CN, Morris AD, Elliott P, Jarvelin MR, Smith GD, McCarthy MI, Hattersley AT, Frayling TM (2008). "Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected, given its effect on BMI". *Diabetes* **57** (5): 1419–26. doi:10.2337/db07-1466. PMC 3073395. PMID 18346983.

[46] Lao L, Zhong G, Li X, Liu Z (Feb 2014). "A preliminary association study of fat mass and obesity associated gene polymorphisms and degenerative disc disease in a Chinese Han population.". *J Int Med Res* **42** (1): 205–12. doi:10.1177/0300060513503761. PMID 24304927.

[47] Fischer J, Koch L, Emmerling C, Vierkotten J, Peters T, Brüning JC, Rüther U (April 2009). "Inactivation of the Fto gene protects from obesity". *Nature* **458** (7240): 894–8. Bibcode:2009Natur.458..894F. doi:10.1038/nature07848. PMID 19234441.

[48] "Radiography data for Fto". Wellcome Trust Sanger Institute.

[49] "*Salmonella* infection data for Fto". Wellcome Trust Sanger Institute.

[50] "*Citrobacter* infection data for Fto". Wellcome Trust Sanger Institute.

[51] Gerdin AK (2010). "The Sanger Mouse Genetics Programme: High throughput characterisation of knockout mice". *Acta Ophthalmologica* **88**: 925–7. doi:10.1111/j.1755-3768.2010.4142.x.

[52] Mouse Resources Portal, Wellcome Trust Sanger Institute.

[53] "International Knockout Mouse Consortium".

[54] "Mouse Genome Informatics".

[55] Skarnes WC, Rosen B, West AP, Koutsourakis M, Bushell W, Iyer V, Mujica AO, Thomas M, Harrow J, Cox T, Jackson D, Severin J, Biggs P, Fu J, Nefedov M, de Jong PJ, Stewart AF, Bradley A (2011). "A conditional knockout resource for the genome-wide study of mouse gene function". *Nature* **474** (7351): 337–342. doi:10.1038/nature10163. PMC 3572410. PMID 21677750.

[56] Dolgin E (2011). "Mouse library set to be knockout". *Nature* **474** (7351): 262–3. doi:10.1038/474262a. PMID 21677718.

[57] Collins FS, Rossant J, Wurst W (2007). "A Mouse for All Reasons". *Cell* **128** (1): 9–13. doi:10.1016/j.cell.2006.12.018. PMID 17218247.

[58] van der Weyden L, White JK, Adams DJ, Logan DW (2011). "The mouse genetics toolkit: revealing function and mechanism". *Genome Biol.* **12** (6): 224. doi:10.1186/gb-2011-12-6-224. PMC 3218837. PMID 21722353.

[59] Peters T, Ausmeier K, Rüther U (October 1999). "Cloning of Fatso (Fto), a novel gene deleted by the Fused toes (Ft) mouse mutation". *Mamm. Genome* **10** (10): 983–6. doi:10.1007/s003359901144. PMID 10501967.

[60] Kim B, Kim Y, Cooke PS, Rüther U, Jorgensen JS (2011). "The fused toes locus is essential for somatic-germ cell interactions that foster germ cell maturation in developing gonads in mice". *Biol Reprod* **84** (5): 1024–32. doi:10.1095/biolreprod.110.088559. PMID 21293032.

8 External links

- FTO protein, human at the US National Library of Medicine Medical Subject Headings (MeSH)
- Catharine Paddock (2007-04-13). "Obesity Gene Discovered". Medical News Today. Retrieved 2008-03-22.

9 Text and image sources, contributors, and licenses

9.1 Text

- **FTO gene** *Source:* https://en.wikipedia.org/wiki/FTO_gene?oldid=697566218 *Contributors:* Carlossuarez46, Discospinster, Rich Farmbrough, Billymac00, Arcadian, GregorB, Rjwilmsi, Bgwhite, Aaron Schulz, Zythe, Fang Aili, SmackBot, Saulbey, Rogermw, Rockpocket, T g7, David@sickmiller.com, Cydebot, Fisherjs, Wikid77, Bigwyrm, Z10x, Hb2019, Boghog, Cdamama, Jrcla2, Philip Trueman, Andrew Su, Duncan.Hull, ProteinBoxBot, Fratrep, SchreiberBike, Polly, Aitias, Addbot, DOI bot, Bragiw, Yobot, Blindkijin, C5813, AnomieBOT, Apollo1758, Citation bot, LilHelpa, FrescoBot, Ericr1954, Tofazzalh~enwiki, Cdina, Citation bot 1, Trappist the monk, Amkilpatrick, 21user, Whoadrp, RjwilmsiBot, Dcirovic, ZéroBot, RE73, Alectronn, Teaktl17, ClueBot NG, Bibcode Bot, Diracseawave, CarrieVS, Melrose312, Capped&tailed, Bruno A. Novais, Monkbot, Mmaloca, Sagr123 and Anonymous: 31

9.2 Images

- **File:TPI1_structure.png** *Source:* https://upload.wikimedia.org/wikipedia/commons/1/1c/TPI1_structure.png *License:* Public domain *Contributors:* based on 1wyi (http://www.pdb.org/pdb/explore/explore.do?structureId=1WYI), made in pymol *Original artist:* →AzaToth

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