

TCF7L2

Transcription factor 7-like 2 (T-cell specific, HMG-box) also known as **TCF7L2** or **TCF4** is a protein acting as a transcription factor. In humans this protein is encoded by the *TCF7L2* gene.^{[1][2]} The single nucleotide polymorphism (SNP) within the *TCF7L2* gene, rs7903146, is, to date, the most significant genetic marker^[3] associated with Type 2 diabetes mellitus (T2DM) risk. SNPs in this gene are linked to higher risk to develop type 2 diabetes,^[4] as well as gestational diabetes.^[5]



Structure of complex between TCF7L2 (orange), β -catenin (red), and BCL9 (brown).^[6]

1 Function

TCF7L2 is a transcription factor influencing the transcription of several genes thereby exerting a large variety of functions within the cell. It is a member of the Wnt signaling pathway. Stimulation of the pathway leads to the association of β -catenin with BCL9, translocation to the nucleus, and association with TCF7L2,^[7] which in turn results in the activation of Wnt target genes, specifically repressing proglucagon synthesis in enteroendocrine cells.^{[4][8]}

2 Clinical significance

TCF7L2 is implicated in a large variety of diseases. Several single nucleotide polymorphisms are associated with type 2 diabetes. In European populations it was found to be a major determinant of type 2 risk.^[4]

A frameshift mutation of TCF7L2 is implicated in colorectal cancer.^{[9][10]} Variants of the gene are most likely involved in many other cancer types.^[11]

3 Model organisms

Model organisms have been used in the study of TCF7L2 function. A conditional knockout mouse line called *Tcf7l2^{tm1a(EUCOMM)Wsi}* was generated at the Wellcome Trust Sanger Institute.^[12] Male and female animals underwent a standardized phenotypic screen^[13] to determine the effects of deletion.^{[14][15][16][17]} Additional screens performed: - In-depth immunological phenotyping^[18]

4 Nomenclature

While TCF4 is sometimes misleadingly used as an alias symbol for TCF7L2, it is also the symbol officially approved by the HUGO Gene Nomenclature Committee for the transcription factor 4 gene.

5 See also

- TCF/LEF family

6 References

- [1] “Entrez Gene: TCF7L2”.
- [2] Castrop J, van Norren K, Clevers H (1992). “A gene family of HMG-box transcription factors with homology to TCF-1”. *Nucleic Acids Res.* **20** (3): 611. doi:10.1093/nar/20.3.611. PMC 310434. PMID 1741298.
- [3] Vaquero AR, Ferreira NE, Omae SV, Rodrigues MV, Teixeira SK, Krieger JE, Pereira AC (2012). “Using gene-network landscape to dissect genotype effects of TCF7L2 genetic variant on diabetes and cardiovascular risk”. *Physiol. Genomics* **44** (19): 903–14. doi:10.1152/physiolgenomics.00030.2012. PMID 22872755.
- [4] Jin T, Liu L (2008). “The Wnt signaling pathway effector TCF7L2 and type 2 diabetes mellitus”. *Mol. Endocrinol.* **22** (11): 2383–92. doi:10.1210/me.2008-0135. PMID 18599616.
- [5] Zhang C, Bao W, Rong Y, Yang H, Bowers K, Yeung E, Kiely M (2013). “Genetic variants and the risk of gestational diabetes mellitus: a systematic review”. *Hum. Reprod. Update* **19** (4): 376–90. doi:10.1093/humupd/dmt013. PMID 23690305.
- [6] PDB: 2GL7; Sampietro J, Dahlberg CL, Cho US, Hinds TR, Kimelman D, Xu W (October 2006). “Crystal structure of a beta-catenin/BCL9/Tcf4 complex”. *Mol. Cell* **24** (2): 293–300. doi:10.1016/j.molcel.2006.09.001. PMID 17052462.
- [7] Lee JM, Dedhar S, Kalluri R, Thompson EW (2006). “The epithelial-mesenchymal transition: new insights in signaling, development, and disease”. *J. Cell Biol.* **172** (7): 973–81. doi:10.1083/jcb.200601018. PMC 2063755. PMID 16567498.
- [8] Online 'Mendelian Inheritance in Man' (OMIM) 602228
- [9] Slattery ML, Folsom AR, Wolff R, Herrick J, Caan BJ, Potter JD (2008). “Transcription factor 7-like 2 polymorphism and colon cancer”. *Cancer Epidemiol. Biomarkers Prev.* **17** (4): 978–82. doi:10.1158/1055-9965.EPI-07-2687. PMC 2587179. PMID 18398040.
- [10] Hazra A, Fuchs CS, Chan AT, Giovannucci EL, Hunter DJ (2008). “Association of the TCF7L2 polymorphism with colorectal cancer and adenoma risk”. *Cancer Causes Control* **19** (9): 975–80. doi:10.1007/s10552-008-9164-3. PMC 2719293. PMID 18478343.
- [11] Tang W, Dodge M, Gundapaneni D, Michnoff C, Roth M, Lum L (2008). “A genome-wide RNAi screen for Wnt/beta-catenin pathway components identifies unexpected roles for TCF transcription factors in cancer”. *Proc. Natl. Acad. Sci. U.S.A.* **105** (28): 9697–702. Bibcode:2008PNAS..105.9697T. doi:10.1073/pnas.0804709105. PMC 2453074. PMID 18621708.
- [12] 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.
- [13] “International Mouse Phenotyping Consortium”.
- [14] 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 (Jun 2011). “A conditional knockout resource for the genome-wide study of mouse gene function”. *Nature* **474** (7351): 337–42. doi:10.1038/nature10163. PMC 3572410. PMID 21677750.
- [15] Dolgin E (Jun 2011). “Mouse library set to be knockout”. *Nature* **474** (7351): 262–3. doi:10.1038/474262a. PMID 21677718.
- [16] Collins FS, Rossant J, Wurst W (Jan 2007). “A mouse for all reasons”. *Cell* **128** (1): 9–13. doi:10.1016/j.cell.2006.12.018. PMID 17218247.
- [17] White JK, Gerdin AK, Karp NA, Ryder E, Buljan M, Bussell JN, Salisbury J, Clare S, Ingham NJ, Podrini C, Houghton R, Estabel J, Bottomley JR, Melvin DG, Sunter D, Adams NC, Sanger Institute Mouse Genetics Project, Tannahill D, Logan DW, Macarthur DG, Flint J, Mahajan VB, Tsang SH, Smyth I, Watt FM, Skarnes WC, Dougan G, Adams DJ, Ramirez-Solis R, Bradley A, Steel KP (2013). “Genome-wide generation and systematic phenotyping of knockout mice reveals new roles for many genes”. *Cell* **154** (2): 452–64. doi:10.1016/j.cell.2013.06.022. PMC 3717207. PMID 23870131.
- [18] “Infection and Immunity Immunophenotyping (3i) Consortium”.

7 Further reading

- Segditsas S, Tomlinson I (2006). “Colorectal cancer and genetic alterations in the Wnt pathway”. *Oncogene* **25** (57): 7531–7. doi:10.1038/sj.onc.1210059. PMID 17143297.
- Florez JC (2007). “The new type 2 diabetes gene TCF7L2”. *Curr Opin Clin Nutr Metab Care* **10** (4): 391–6. doi:10.1097/MCO.0b013e3281e2c9be. PMID 17563454.
- Castrop J, van Norren K, Clevers H (1992). “A gene family of HMG-box transcription factors with homology to TCF-1”. *Nucleic Acids Res.* **20** (3): 611. doi:10.1093/nar/20.3.611. PMC 310434. PMID 1741298.
- Maruyama K, Sugano S (1994). “Oligo-capping: a simple method to replace the cap structure of eukaryotic mRNAs with oligoribonucleotides”. *Gene* **138** (1-2): 171–4. doi:10.1016/0378-1119(94)90802-8. PMID 8125298.
- Korinek V, et al. (1997). “Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma”. *Science* **275** (5307):

- 1784–7. doi:10.1126/science.275.5307.1784. PMID 9065401.
- Suzuki Y, et al. (1997). “Construction and characterization of a full length-enriched and a 5'-end-enriched cDNA library”. *Gene* **200** (1-2): 149–56. doi:10.1016/S0378-1119(97)00411-3. PMID 9373149.
 - He TC, et al. (1998). “Identification of c-MYC as a target of the APC pathway”. *Science* **281** (5382): 1509–12. Bibcode:1998Sci...281.1509H. doi:10.1126/science.281.5382.1509. PMID 9727977.
 - Barker N, Huls G, Korinek V, Clevers H (1999). “Restricted high level expression of Tcf-4 protein in intestinal and mammary gland epithelium”. *Am. J. Pathol.* **154** (1): 29–35. doi:10.1016/S0002-9440(10)65247-9. PMC 1853446. PMID 9916915.
 - Omer CA, Miller PJ, Diehl RE, Kral AM (1999). “Identification of Tcf4 residues involved in high-affinity beta-catenin binding”. *Biochem. Biophys. Res. Commun.* **256** (3): 584–90. doi:10.1006/bbrc.1999.0379. PMID 10080941.
 - Giannini AL, Vivanco MM, Kypta RM (2000). “Analysis of beta-catenin aggregation and localization using GFP fusion proteins: nuclear import of alpha-catenin by the beta-catenin/Tcf complex”. *Exp. Cell Res.* **255** (2): 207–20. doi:10.1006/excr.1999.4785. PMID 10694436.
 - Duval A, Busson-Leconiat M, Berger R, Hamelin R (2000). “Assignment of the TCF-4 gene (TCF7L2) to human chromosome band 10q25.3”. *Cytogenet. Cell Genet.* **88** (3-4): 264–5. doi:10.1159/000015534. PMID 10828605.
 - Duval A, et al. (2000). “The human T-cell transcription factor-4 gene: structure, extensive characterization of alternative splicings, and mutational analysis in colorectal cancer cell lines”. *Cancer Res.* **60** (14): 3872–9. PMID 10919662.
 - Brantjes H, Roose J, van De Wetering M, Clevers H (2001). “All Tcf HMG box transcription factors interact with Groucho-related co-repressors”. *Nucleic Acids Res.* **29** (7): 1410–9. doi:10.1093/nar/29.7.1410. PMC 31284. PMID 11266540.
 - Palacino JJ, et al. (2001). “Presenilin 1 regulates beta-catenin-mediated transcription in a glycogen synthase kinase-3-independent fashion”. *J. Biol. Chem.* **276** (42): 38563–9. doi:10.1074/jbc.M105376200. PMID 11504726.
 - Miravet S, et al. (2002). “The transcriptional factor Tcf-4 contains different binding sites for beta-catenin and plakoglobin”. *J. Biol. Chem.* **277** (3): 1884–91. doi:10.1074/jbc.M110248200. PMID 11711551.
 - Graham TA, et al. (2001). “Tcf4 can specifically recognize beta-catenin using alternative conformations”. *Nat. Struct. Biol.* **8** (12): 1048–52. doi:10.1038/nsb718. PMID 11713475.
 - Poy F, Lepourcelet M, Shivdasani RA, Eck MJ (2001). “Structure of a human Tcf4-beta-catenin complex”. *Nat. Struct. Biol.* **8** (12): 1053–7. doi:10.1038/nsb720. PMID 11713476.
 - Thiele A, et al. (2001). “Regulation and possible function of beta-catenin in human monocytes”. *J. Immunol.* **167** (12): 6786–93. doi:10.4049/jimmunol.167.12.6786. PMID 11739494.
 - Marchenko GN, Marchenko ND, Leng J, Strongin AY (2002). “Promoter characterization of the novel human matrix metalloproteinase-26 gene: regulation by the T-cell factor-4 implies specific expression of the gene in cancer cells of epithelial origin”. *Biochem. J.* **363** (Pt 2): 253–62. doi:10.1042/0264-6021:3630253. PMC 1222473. PMID 11931652.
 - Leung JY, et al. (2002). “Activation of AXIN2 expression by beta-catenin-T cell factor. A feedback repressor pathway regulating Wnt signaling”. *J. Biol. Chem.* **277** (24): 21657–65. doi:10.1074/jbc.M200139200. PMID 11940574.

8 External links

- TCF7L2 here called TCF4 features on this Wnt pathway web site: [Wnt signalling molecules TCFs](#)
- Structure determination of TCF7L2: [PDB entry 2GL7](#) and related publication on [PubMed](#)
- [PubMed GeneRIFs](#) (summaries of related scientific publications) -
- [Weizmann Institute GeneCard for TCF7L2](#)

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