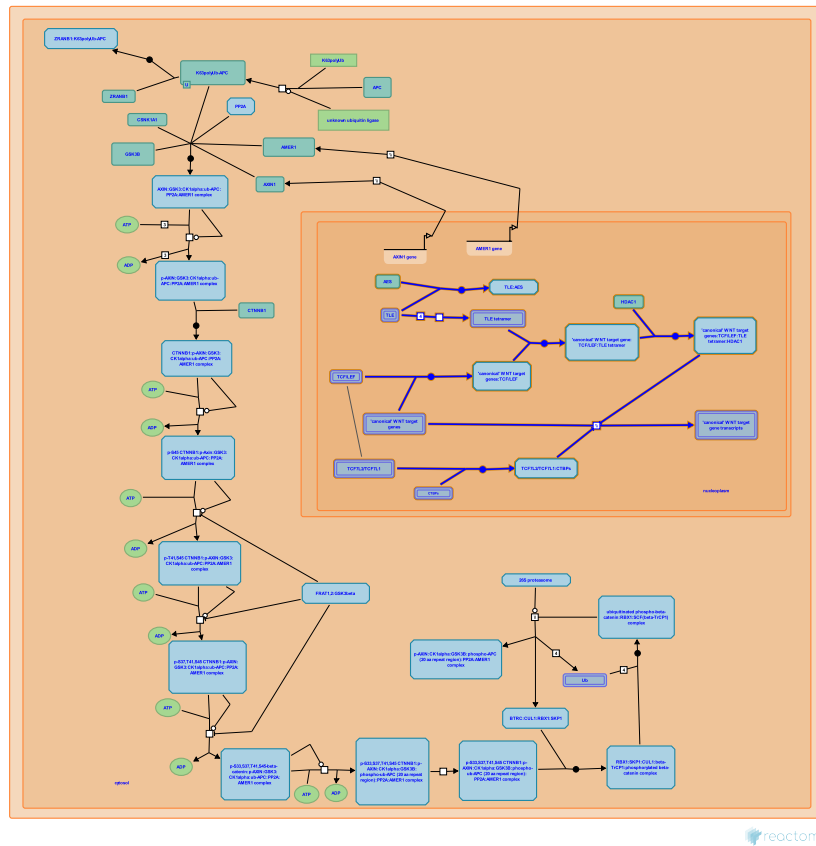


# Repression of WNT target genes



Matthews, L., Rajakulendran, N., Rothfels, K., Salahshor, S., Woodgett, J.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

26/04/2024

## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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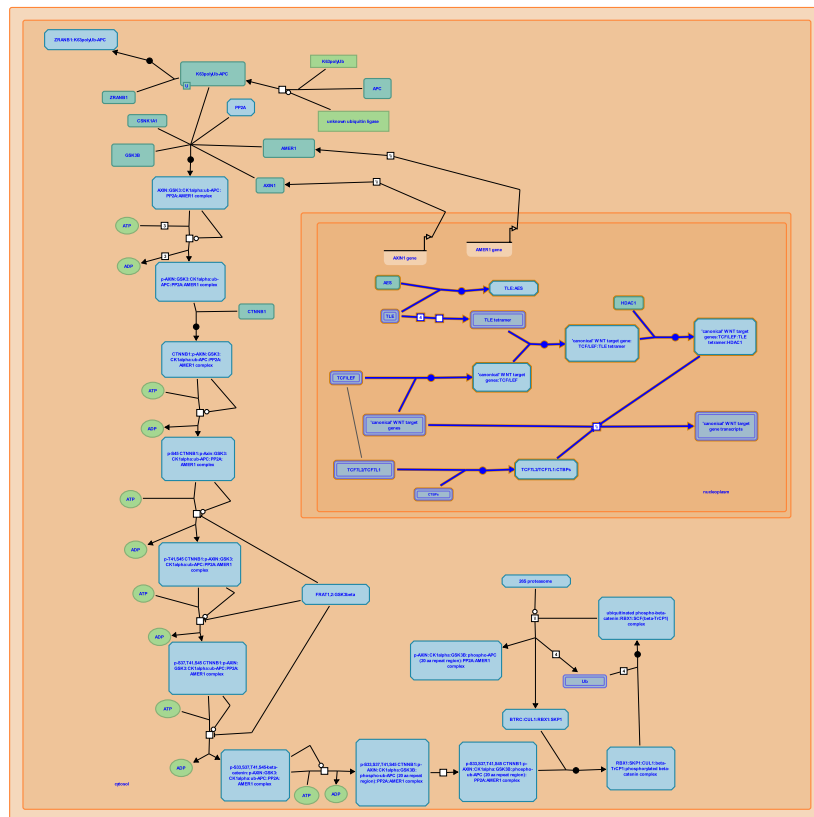
Reactome database release: 88

This document contains 1 pathway and 7 reactions ([see Table of Contents](#))

## Repression of WNT target genes ↗

**Stable identifier:** R-HSA-4641265

**Compartments:** nucleoplasm



reactome

In the absence of a WNT signal, many WNT target genes are repressed by Groucho/TLE. Groucho was initially identified in *Drosophila*, where it has been shown to interact with a variety of proteins to repress transcription (reviewed in Turki-Judeh and Courey, 2012). Groucho proteins, including the 4 human homologues (transducin-like enhancer of split (TLE) 1-4), do not bind DNA directly but instead are recruited to target genes through interaction with DNA-binding transcription factors including TCF/LEF (Brantjes et al, 2001; reviewed in Chen and Courey, 2000). Groucho proteins are believed to oligomerize in a manner that depends on an N-terminal glutamine-rich Q domain, and oligomerization may be important for function (Song et al, 2004; Pinto and Lobe, 1996). Groucho/TLE proteins affect levels of gene expression by interacting with the core transcriptional machinery as well as by modifying chromatin structure through direct interaction with histones and recruitment of histone deacetylases, among other mechanisms (reviewed in Turki-Judeh and Courey, 2012). In addition to the four TLE proteins, human cells also include a truncated TLE-like protein called amino-terminal enhancer of split (AES) which contains the N-terminal Q domain but lacks much of the C-terminal sequence of TLE proteins, including the WD domain which is important for many protein-protein interactions. AES is believed to act as a dominant negative, since it is able to heter-oligomerize with full-length TLE proteins to form non-functional complexes (Brantjes et al, 2001; reviewed in Beagle and Johnson, 2010).

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## **Editions**

2013-09-23	Authored	Rothfels, K.
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2014-04-03	Edited	Matthews, L.

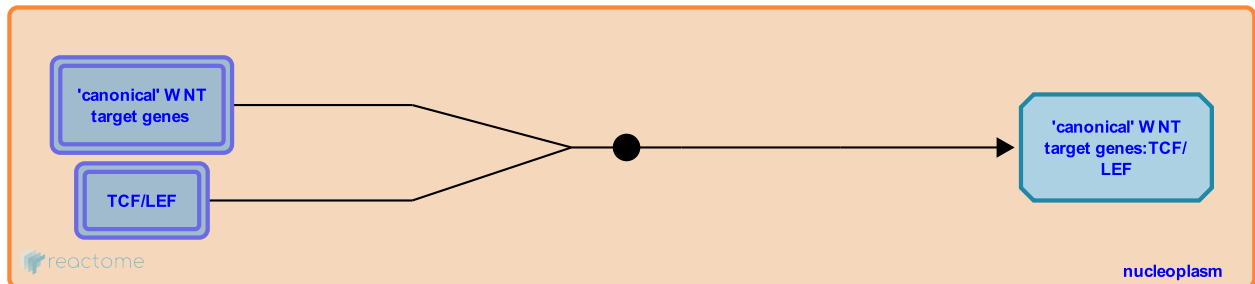
## TCF/LEF binds WNT promoters ↗

**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-8944352

**Type:** binding

**Compartments:** nucleoplasm



TCF7 (TCF1), LEF1, TCF7L1 (TCF3) and TCF7L2 (TCF4) are HMG box-containing DNA-binding proteins that recognize WNT-responsive elements (WREs) in the promoters of WNT target genes. The WRE consensus sequence is CCTTTGWW, where W represents either T or A (reviewed in Brantjes et al, 2002). In the absence of a WNT signal, promoter-bound TCF/LEF is bound by one of four Groucho homologues, TLE1, 2, 3 or 4 (Levanon et al, 1998; Brantjes et al, 2001; Daniels and Weis, 2005). Groucho/TLE proteins are co-repressors for a variety of DNA-binding transcription factors and mediate repression at least in part through their interaction with histone deacetylases such as RPD3/HDAC1 (Arce et al, 2009; Brantjes et al, 2001; Chen et al, 1999; reviewed in Chen and Courey, 2000).

**Followed by:** [TLE tetramers bind TCF/LEF at WNT promoters](#)

### Literature references

- Arce, L., Waterman, ML., Pate, KT. (2009). Groucho binds two conserved regions of LEF-1 for HDAC-dependent repression. *BMC Cancer*, 9, 159. ↗
- Weis, WI., Daniels, DL. (2005). Beta-catenin directly displaces Groucho/TLE repressors from Tcf/Lef in Wnt-mediated transcription activation. *Nat Struct Mol Biol*, 12, 364-71. ↗
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- Paroush, Z., Goldstein, RE., Groner, Y., Tang, H., Bernstein, Y., Levanon, D. et al. (1998). Transcriptional repression by AML1 and LEF-1 is mediated by the TLE/Groucho corepressors. *Proc. Natl. Acad. Sci. U.S.A.*, 95, 11590-5. ↗
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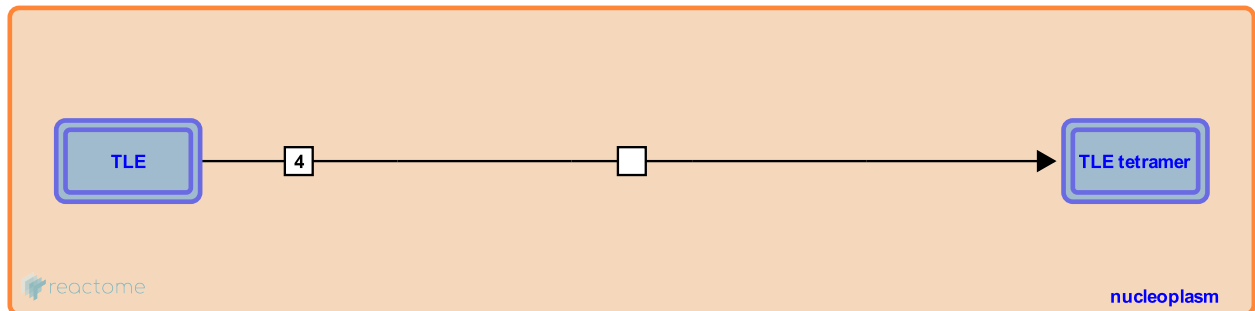
## TLE oligomerizes ↗

**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-4641229

**Type:** transition

**Compartments:** nucleoplasm



TCF1, LEF1, TCF3 and TCF4 are HMG box-containing DNA-binding proteins that recognize WNT-responsive elements (WREs) in the promoters of WNT target genes (reviewed in Brantjes et al, 2002). In the absence of a WNT signal, promoter-bound TCF/LEF is bound by one of four Groucho homologues, TLE1, 2, 3 or 4 (Levanon et al, 1998; Brantjes et al, 2001; Daniels and Weis, 2005). Groucho/TLE proteins are co-repressors for a variety of DNA-binding transcription factors and mediate repression at least in part through their interaction with histone deacetylases such as RPD3/HDAC1 (Arce et al, 2009; Brantjes et al, 2001; Chen et al, 1999; reviewed in Chen and Courey, 2000). Groucho proteins have been shown to homo-tetramerize through a glutamine rich Q domain at the N-terminus, and this oligomerization is required for repression. The Q domain is also sufficient for interaction with TCF/LEF proteins (Brantjes et al, 2001; Chen et al, 1998; Pinto and Lobe, 1996; Song et al, 2004). Studies with purified proteins have shown that human TLE1 and 2 bind to an amino-terminal truncated form of LEF1(69-397) with an affinity comparable to that for full length LEF1 (Daniels and Weis, 2005).

**Followed by:** [TLE tetramers bind TCF/LEF at WNT promoters](#)

## Literature references

- Arce, L., Waterman, ML., Pate, KT. (2009). Groucho binds two conserved regions of LEF-1 for HDAC-dependent repression. *BMC Cancer*, 9, 159. ↗
- Hasson, P., Paroush, Z., Song, H., Courey, AJ. (2004). Groucho oligomerization is required for repression in vivo. *Mol. Cell. Biol.*, 24, 4341-50. ↗
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- Paroush, Z., Goldstein, RE., Groner, Y., Tang, H., Bernstein, Y., Levanon, D. et al. (1998). Transcriptional repression by AML1 and LEF-1 is mediated by the TLE/Groucho corepressors. *Proc. Natl. Acad. Sci. U.S.A.*, 95, 11590-5. ↗
- van De Wetering, M., Clevers, HC., Brantjes, H., Roose, J. (2001). All Tcf HMG box transcription factors interact with Groucho-related co-repressors. *Nucleic Acids Res.*, 29, 1410-9. ↗

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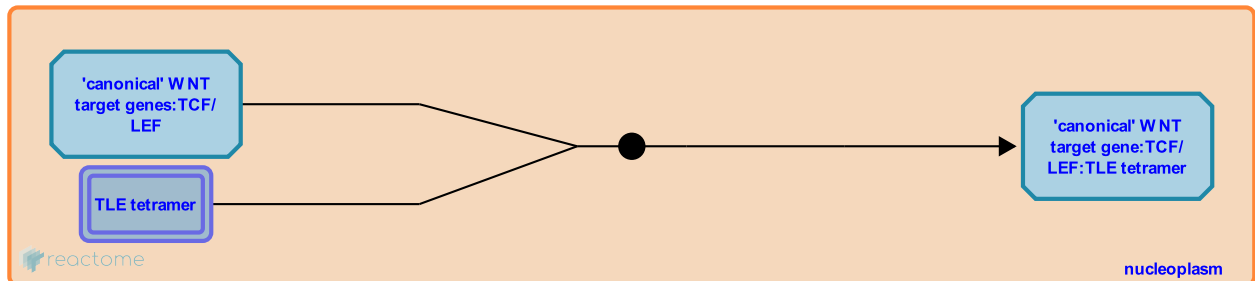
## TLE tetramers bind TCF/LEF at WNT promoters ↗

**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-8944349

**Type:** binding

**Compartments:** nucleoplasm



In the absence of a WNT signal, promoter-bound TCF/LEF is bound by one of four Groucho homologues, TLE1, 2, 3 or 4 (Levanon et al, 1998; Brantjes et al, 2001; Daniels and Weis, 2005). Groucho/TLE proteins are co-repressors for a variety of DNA-binding transcription factors and mediate repression at least in part through their interaction with histone deacetylases such as RPD3/HDAC1 (Arce et al, 2009; Brantjes et al, 2001; Chen et al, 1999; reviewed in Chen and Courey, 2000). Groucho proteins have been shown to homo-tetramerize through a glutamine rich Q domain at the N-terminus, and this oligomerization is required for repression. The Q domain is also sufficient for interaction with TCF/LEF proteins (Brantjes et al, 2001; Chen et al, 1998; Pinto and Lobe, 1996; Song et al, 2004). Studies with purified proteins have shown that human TLE1 and 2 bind to an amino-terminal truncated form of LEF1(69-397) with an affinity comparable to that for full length LEF1 (Daniels and Weis, 2005)

**Preceded by:** [TLE oligomerizes](#), [TCF/LEF binds WNT promoters](#)

**Followed by:** [TLE recruits HDAC1 to WNT promoters](#)

### Literature references

- Arce, L., Waterman, ML., Pate, KT. (2009). Groucho binds two conserved regions of LEF-1 for HDAC-dependent repression. *BMC Cancer*, 9, 159. ↗
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- Paroush, Z., Goldstein, RE., Groner, Y., Tang, H., Bernstein, Y., Levanon, D. et al. (1998). Transcriptional repression by AML1 and LEF-1 is mediated by the TLE/Groucho corepressors. *Proc. Natl. Acad. Sci. U.S.A.*, 95, 11590-5. ↗

### Editions

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## TLE recruits HDAC1 to WNT promoters ↗

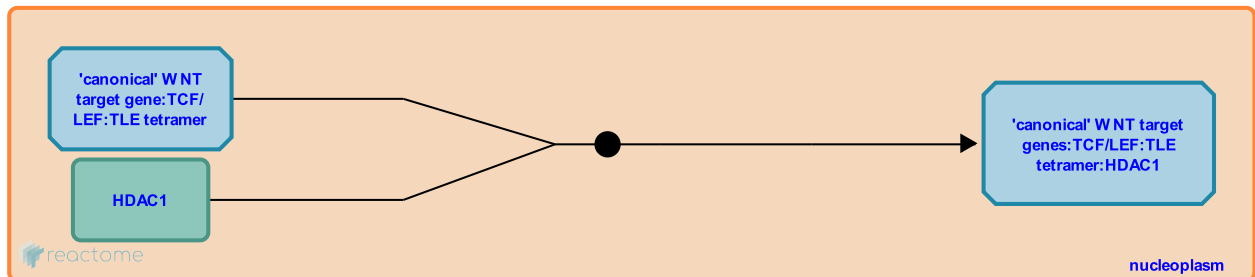
**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-4641231

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** [xTLE4 binds HDAC1 \(Homo sapiens\)](#)



Groucho/TLE mediates repression of WNT target genes in part by recruiting a histone deacetylase to the promoter. The weakly conserved central GP domain of Groucho/TLE has been shown to interact with the histone deacetylase RPD3/HDAC1 (Brantjes et al, 2001; Chen et al, 1999). Knockdown of *rp3* in *Drosophila* cells, or treatment of human or *Drosophila* cells with the histone deacetylase inhibitor Trichostatin A significantly decreases repression of a Groucho/TLE dependent reporter gene, and Groucho and RPD3 have been shown to co-localize to chromatin of target genes by ChIP leading to deacetylation of H3K9, H3K14, K4K5, H4K8 and H4K12 (Chen et al, 1999; Choi et al 1999; Winkler et al, 2010).

**Preceded by:** [TLE tetramers bind TCF/LEF at WNT promoters](#)

**Followed by:** [Transcription of canonical WNT targets is repressed by the TLE:HDAC and TCF/CTBP complexes](#)

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### Editions

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2014-04-03	Edited	Matthews, L.



## TLE forms non-functional complexes with AES ↗

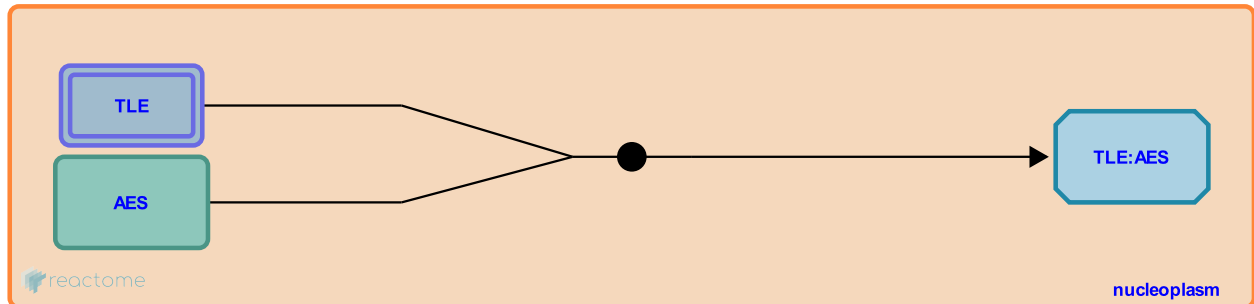
**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-4649028

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** [Gro binds Aes \(Drosophila melanogaster\)](#)



AES is a naturally occurring truncated form of TLE that contains only the Q and GP domain. AES has been shown to have a dominant negative effect on TLE-mediated repression (Miyasaka et al, 1993; Roose et al, 1998; Ren et al, 1999; Swingler et al, 2004). AES is believed to form oligomers with full length TLE proteins mediated by the Q domains; because AES is unable to interact with HDAC1, these oligomers are thought to be non-functional (Muhr et al, 2001; Brantjes et al, 2001).

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### Editions

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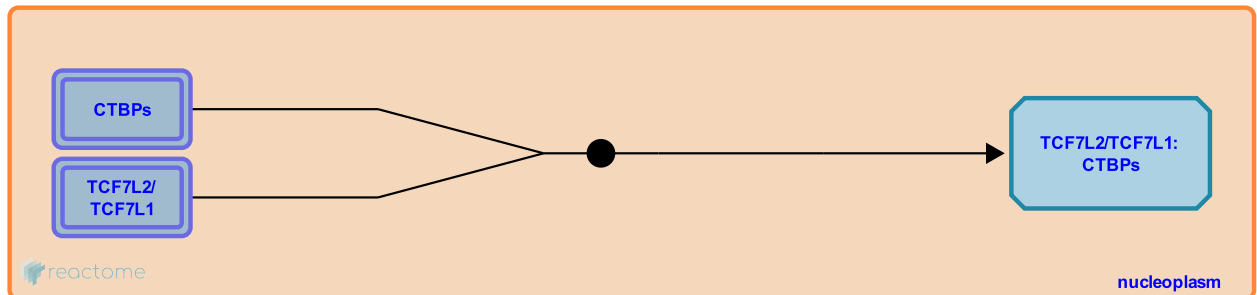
## TCF7L2/TCF7L1 bind CTBP1 to repress WNT target genes ↗

**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-5334050

**Type:** binding

**Compartments:** nucleoplasm



In addition to repressing WNT-dependent targets through Groucho/TLE proteins, some TCF/LEF transcription factors may also work by recruiting the CTBP1 and CTBP2 repressors (Duval et al, 2000). CTBP-binding regions are present in the 'E-form' splice variants of TCF7L2 and in TCF7L1 and in vitro interactions have been demonstrated in *Xenopus* and mammals, although the in vivo relevance of these interactions is unclear (Brannon et al, 1999; Valenta et al, 2003; Cuilliere-Dartigues et al, 2006; Tang et al, 2008; Hamada and Bienz, 2004). Abrogation of the interaction interface results in a loss of TCF-CTBP colocalization and increased expression of a TCF-dependent reporter gene (Cuilliere-Dartigues et al, 2006; Tang et al, 2008).

**Followed by:** [Transcription of canonical WNT targets is repressed by the TLE:HDAC and TCF/CTBP complexes](#)

### Literature references

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### Editions

2014-02-18	Authored	Rothfels, K.
2014-04-03	Edited	Matthews, L.
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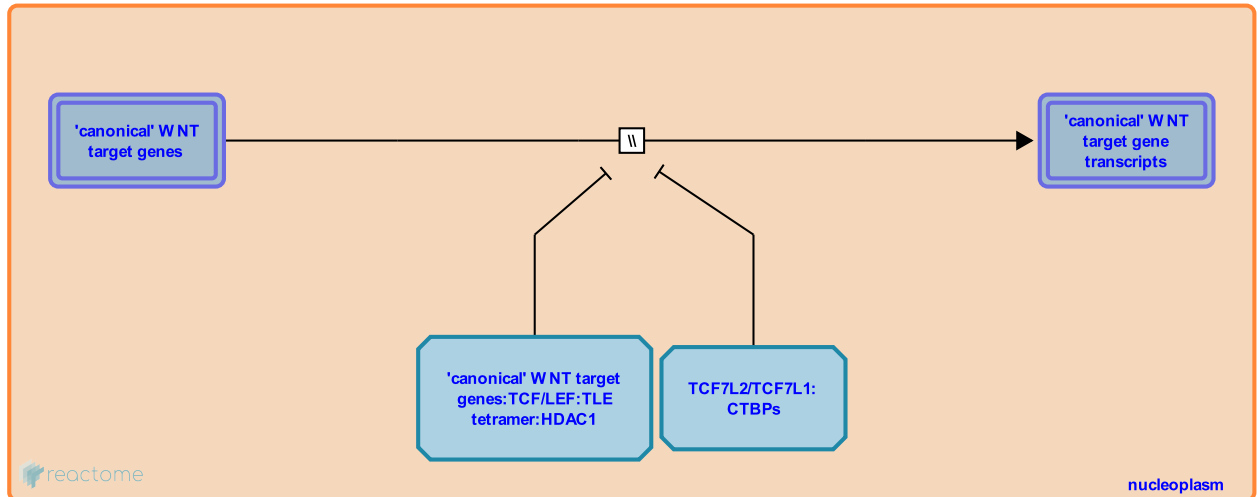
# Transcription of canonical WNT targets is repressed by the TLE:HDAC and TCF/CTBP complexes ↗

**Location:** [Repression of WNT target genes](#)

**Stable identifier:** R-HSA-5229348

**Type:** omitted

**Compartments:** nucleoplasm



Transcription of WNT genes is repressed in the absence of WNT signal by TLE:HDAC complexes (reviewed in Cinnamon and Paroush, 2008; Saito-Diaz et al, 2013). Repression may also be mediated by CTBP proteins binding to TCF7L1 and TCF7L3 (Duval et al, 2000; Cuilliere-Dartigues et al, 2006; Tang et al, 2008).

**Preceded by:** [TLE recruits HDAC1 to WNT promoters](#), [TCF7L2/TCF7L1 bind CTBP1 to repress WNT target genes](#)

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- Dodge, M., Lum, L., Gundapaneni, D., Michnoff, C., Tang, W., Roth, M. (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, 9697-702. ↗

## Editions

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