

## MAD2L1 (mitotic arrest deficient 2, yeast, human homolog like-1)

### Identity

**Note** MAD2L1 was initially (and erroneously) mapped by fluorescence in situ hybridization (FISH) to 5q23-q31. Subsequent comprehensive mapping studies using somatic cell hybrid analysis, radiation hybrid (RH) mapping, and FISH localized it to 4q27. This location was subsequently confirmed by RH analysis and through the Human Genome Project Draft sequence assembly. A related gene, MAD2L2, maps to 1p36, and a MAD2 pseudogene maps to 14q21-q23. Other related family members exist with similar names (eg. MAD2L2, MAD1L1) highlighting the need for using the MAD2L1 nomenclature to avoid confusion (A MAD2L1 pseudogene maps to chromosome 14)

**Other names**

**HsMAD2**

**MAD2**

**MAD2A**

**Hugo**

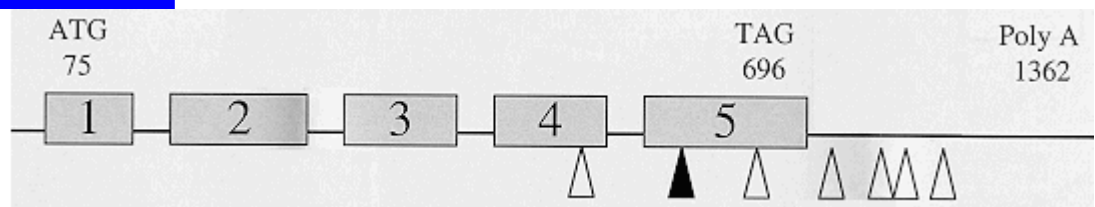
**MAD2L1**

**Location**

4q27

As noted on the GM99-GB4 Chromosome 4 map: Position: 548.24 (cR3000) Lod score: 1.16 Reference Interval: D4S2945-D4S430 (115.1-125.1 cM) It is located within the NCBI BAC genomic contig: NT\_006302.2 which is part of the homo sapiens chromosome 4 sequence segment

### DNA/RNA



Shaded boxes (1-5) depict the 5 exons of MAD2L1. The black triangle indicates a del A mutation that was found in the CAL51 breast cancer cell line. Open triangles depict the locations of identified sequence variants. Figure is not drawn to scale.

**Description** the human MAD2L1 DNA sequence had an open reading frame that was 60% identical to the yeast MAD2 gene.

**Transcription** MAD2L1 has 5 coding exons. No alternative splicing has been described. Regulation of its transcription in human cells is currently poorly understood.

### Protein

**Description** called MAD2A (aliases MAD2-LIKE 1, MD2I, HSMAD2); 205 amino acids; molecular weight: 23,509.95; theoretical pI: 5.02

**Expression** The MAD2L1 protein is widely expressed in all fetal and adult and fetal tissues studied to date.

**Localisation** Localizes to the nucleus and associates with unattached kinetochores during after chromosome condensation.

**Function** Much of what we currently understand about MAD2L1 and its role in the mitotic spindle checkpoint stems from early studies in non-mammalian cells. Several genes have demonstrated critically important, interrelated roles in appropriately responding to aberrant spindle integrity or kinetochore damage by arresting cell cycle progression including BUB (budding uninhibited by benomyl), MAD (mitotic arrest-deficient) genes, additional protein kinase genes, and other cyclin related genes. In budding yeast the mitotic arrest-deficient-2 (MAD2) gene was shown to encode a protein that monitored accurate chromosome segregation via the mitotic spindle checkpoint. The mitotic spindle checkpoint helps regulate cell division to ensure the creation of euploid daughter cells following anaphase and cytokinesis. The checkpoint acts to block cell cycle progression when the mitotic spindle apparatus is not properly assembled or when the kinetochore is not properly attached to the mitotic spindle. The amphibian (*Xenopus*) homolog of MAD2 was identified and it was demonstrated that the MAD2 protein played a critical role in the normal spindle checkpoint assembly as it associated only with unattached kinetochores in prometaphase and in those cells treated with a microtubule inhibitor, nocodazole. MAD2 was absent from kinetochores in normal cells at metaphase

The human homolog of MAD2, MAD2L1, has been isolated through identification of genes that reduced sensitivity to a chemical mitotic spindle assembly inhibitor, thiabendazole, in yeast that were deficient for a particular kinetochore element, CBF1. The protein encoded by MAD2L1 monitors kinetochore attachments to the mitotic spindle in human cells. Interaction of MAD2L1 and additional checkpoint components with kinetochores unattached to chromosomes blocks the onset of anaphase, preventing missegregation of chromosomes and aneuploidy in resulting daughter cells

The nuclear protein encoded by MAD2L1, MAD2A, is a member of the MAD family of proteins that is a critical component of the mitotic checkpoint. MAD2A is required for proper execution of the mitotic checkpoint. When kinetochore-spindle attachment is not completed properly, anaphase is delayed via activation of the mitotic spindle checkpoint. Anaphase is prevented until all chromosomes are properly aligned at the metaphase plate. Normally, the human MAD2A protein localizes as part of a protein complex at unattached kinetochores after chromosome condensation but not after metaphase. Similarly, MAD2A localizes at the kinetochore upon activation of the mitotic spindle checkpoint and mediates cell cycle arrest by associating with CDC20/p55CDC and the anaphase promoting complex (APC) when chromosomes are not properly attached at the kinetochore. Therefore, MAD2A may regulate the activities of the WD40 protein CDC20 that is necessary for progression through anaphase and exit from mitosis. MAD2A reportedly exist in two states, a monomer and a tetramer, both which are capable of binding CDC20. In vitro studies have suggested, but not conclusively established, that only the tetrameric form of MAD2A is capable of inhibiting CDC20 activation of the APC. A yeast 2-hybrid

assay using cytoplasmic tails of several a disintegrin and metalloproteinase domain (ADAM) bait proteins, demonstrated that MAD2A interacts strongly with TACE (ADAM17) but not with other ADAMs tested, including ADAM9 which interacts with another MAD family member, the MAD2L2 encoded protein MAD2B. A 35-amino acid stretch of TACE that contains a proline-rich SH3-ligand domain (PXPXXP) has been demonstrated as the interaction site with MAD2A.

As noted above, MAD2A is a key protein that functions as part of a larger protein complex that regulates the highly conserved mitotic spindle checkpoint. Appropriate chromosome segregation at anaphase is regulated at least in part by this spindle assembly checkpoint that monitors completion of chromosome-microtubule attachment during metaphase. To further determine the function of Mad2 during normal cell division, Mad2 knockout mice were created and analyzed; day 5.5 embryonic cells lacking Mad2, like mad2 deficient budding yeast cells, grew normally but did not arrest in response to spindle disruption. By d 6.5, the epiblast cells began rapid division associated with widespread chromosome missegregation and subsequent apoptosis. Interestingly, postmitotic trophoblast giant cells survived, however, without Mad2. It was concluded that Mad2 is critical for the spindle assembly checkpoint and accurate chromosome segregation in mitotic mouse cells as well as for embryonic viability, even in the absence of any mitotic spindle damage. Mad2 and the spindle checkpoint in meiosis of *S. cerevisiae* were further characterized by comparing wildtype and mad2 <sup>-/-</sup> yeast that lacked normal checkpoint function. In the mad2 deficient yeast cells, meiosis I missegregation was noted to be significantly increased. These studies suggested that mad2 and the spindle checkpoint in budding yeast are critically important for normal meiotic chromosome segregation, despite the fact that normal mad2 function is largely dispensable in wildtype mitosis of budding yeast.

#### Homology

Homologous sequences: Mouse: Mm.43444 Mad2l1; Mm.9648 ESTs, Highly similar to AF072933\_1 Mad2-like protein [H.sapiens]; Mm.28402 ESTs, Moderately similar to KIAA0280 [H.sapiens]; Rat: Rn.27237 ESTs, Highly similar to AF072933\_1 Mad2-like protein; Rn.34733 ESTs, Weakly similar to mitotic checkpoint component Mad2; Drosophila: Dm.LL.40677 CG2948 CG2948 gene product; Dm.LL.38656 CG17498 CG17498 gene product; Human: Hs.19400 MAD2L2

Related Proteins: H. sapiens: MAD2L2 (27%); M. musculus: MAD2L1 (95%); D. melanogaster: CG17498 (46%); C. elegans: MDF-2 (53%); S. pombe: Mad2p (48%); Spac12d12.09p (26%); S. cerevisiae: Mad2p (43%) [details]

#### Mutations

Note No proven germline or somatic disease causing mutations; one somatic frameshift mutation has been identified, due to a 1 bp deletion, in one breast cancer cell line, CAL51, that caused truncation of the resulting protein product as assessed by in vitro transcription and translation assays. The functional significance of this alteration in relationship to cancer needs to be determined

#### Implicated in

Disease Like other solid tumors, ovarian cancers, especially those at later

stages, demonstrate significant aneuploidy and multiple regions of chromosome loss and amplification. MAD2L1 maps to 4q27, an area that is unstable in several cancers as revealed by loss of heterozygosity and comparative genomic hybridization studies. Interestingly, some of the malignant tumors in individuals with BRCA1 germline mutations have somatic loss of chromosome 4q, suggesting that alterations of genes in this region may be associated with breast cancer

Cytogenetics	No cytogenetic translocations involving this gene, however, have been reported or have been associated with any disease, including cancer
Hybrid/Mutated Gene	None described
Oncogenesis	Work by several groups have now suggested that dysfunction of MAD2A may lead to malignancy or degeneration of normal cells, but compelling evidence that supports a role for MAD2L1 alterations in human cancers are still lacking. Despite this lack of solid data, there is increasing suggestive evidence to implicate MAD2L1 alterations in association with the development and/or progression of human cancer. First, aneuploidy is a commonly observed phenotype in many solid tumor malignancies, especially in later stage tumors. Chromosomal instability (CIN) correlates with aneuploidy and is thought to contribute to genetic instability. Thus, it is widely hypothesized that genomic instability which leads to aneuploidy may accelerate malignant progression in many solid tumor malignancies. Mutations in the genes controlling the mitotic checkpoint, including MAD2L1, have therefore been implicated to contribute to CIN in the pathogenesis of solid tumor malignancies. By monitoring proper microtubule assembly and attachment at the kinetochore, the mitotic checkpoint genes regulate the cell cycle to ensure accurate chromosome alignment and segregation at anaphase to generate euploid daughter cells. Loss of appropriate chromosome attachments at the kinetochore or defects in the mitotic spindle lead to cell cycle arrest and a block in the initiation of anaphase. Mad2 is just one member of a handful of yeast genes, the budding uninhibited by benomyl BUB and mitotic arrest deficient (MAD) families of genes, that are important regulators of this mitotic spindle checkpoint. Studies in colorectal cell lines suggest that dominant negative mutations in the human ortholog BUB1 may have a role in CIN and aneuploidy led to speculation about the potential role of MAD2L1 in human cancers. However, no MAD2L1 mutations were identified in colon cancer cells. Human breast tumor cell line T47D has reduced MAD2 expression and it fails to arrest in mitosis after nocodazole treatment. That loss of MAD2 function might also lead to aberrant chromosome segregation in mammalian cells was suggested. A truncation mutation in MAD2L1 in breast cancer with altered protein expression was subsequently reported but no functional studies have yet demonstrated a functional role in oncogenesis has been demonstrated. Studies of Brca2 deficient murine cells further supported a putative role for these genes in cancer as Bub1

mutations were demonstrated to potentiate growth and cellular transformation (Lee et al., 1999). Secondly, the studies of Mad2 knockout mice have demonstrated that embryonic cells lacking Mad2 fail to arrest in response to microtubule inhibitors and that loss of the checkpoint results in chromosome missegregation and apoptosis. It has subsequently been reported that deletion of one allele results in a defective mitotic checkpoint in both human cancer cells and murine primary embryonic fibroblasts. Checkpoint-defective cells show premature sister chromatid separation in the presence of spindle inhibitors and an elevated rate of chromosome missegregation events in the absence of these agents. Furthermore, Mad2 +/- mice develop lung tumors at high rates after long latencies, implicating defects in the mitotic checkpoint in tumorigenesis.

## External links

	<b>Nomenclature</b>	
<a href="#">Hugo</a>	<a href="#">MAD2L1</a>	
<a href="#">GDB</a>	<a href="#">MAD2L1</a>	
<a href="#">Entrez_Gene</a>	<a href="#">MAD2L1</a>	<a href="#">4085</a> MAD2 mitotic arrest deficient-like 1 (yeast)
	<b>Cards</b>	
<a href="#">Atlas</a>	<a href="#">MAD2L1ID304</a>	
<a href="#">GeneCards</a>	<a href="#">MAD2L1</a>	
<a href="#">Ensembl</a>	<a href="#">MAD2L1</a>	
<a href="#">CancerGene</a>	<a href="#">MAD2L1</a>	
<a href="#">Genatlas</a>	<a href="#">MAD2L1</a>	
<a href="#">GeneLynx</a>	<a href="#">MAD2L1</a>	
<a href="#">eGenome</a>	<a href="#">MAD2L1</a>	
<a href="#">euGene</a>	<a href="#">4085</a>	
	<b>Genomic and cartography</b>	
<a href="#">GoldenPath</a>	<a href="#">MAD2L1</a> - <a href="#">4q27</a> <a href="#">chr4:121338195-121345566</a> - <a href="#">4q27</a> (hg17-May_2004)	
<a href="#">Ensembl</a>	<a href="#">MAD2L1</a> - <a href="#">4q27</a> [ <a href="#">CytoView</a> ]	
<a href="#">NCBI</a>	<a href="#">Genes Cyto</a>	<a href="#">Gene Seq</a> [ <a href="#">Map View</a> - NCBI]
<a href="#">OMIM</a>	<a href="#">Disease map</a> [ <a href="#">OMIM</a> ]	
<a href="#">HomoloGene</a>	<a href="#">MAD2L1</a>	
	<b>Gene and transcription</b>	
<a href="#">Genbank</a>	<a href="#">AB056160</a> [SRS]	<a href="#">AB056160</a> [ENTREZ]
<a href="#">Genbank</a>	<a href="#">AF202273</a> [SRS]	<a href="#">AF202273</a> [ENTREZ]
<a href="#">Genbank</a>	<a href="#">AF394735</a> [SRS]	<a href="#">AF394735</a> [ENTREZ]
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<a href="#">Genbank</a>	<a href="#">BC000356</a> [SRS]	<a href="#">BC000356</a> [ENTREZ]
<a href="#">RefSeq</a>	<a href="#">NM_002358</a> [SRS]	<a href="#">NM_002358</a> [ENTREZ]
<a href="#">RefSeq</a>	<a href="#">NT_086653</a> [SRS]	<a href="#">NT_086653</a> [ENTREZ]
<a href="#">AceView</a>	<a href="#">MAD2L1</a> <a href="#">AceView</a> - NCBI	
<a href="#">TRASER</a>	<a href="#">MAD2L1</a> <a href="#">Traser</a> - Stanford	
<a href="#">Unigene</a>	<a href="#">Hs.533185</a> [SRS]	<a href="#">Hs.533185</a> [NCBI] <a href="#">HS533185</a> [spliceNest]
	<b>Protein : pattern, domain, 3D structure</b>	
<a href="#">SwissProt</a>	<a href="#">Q13257</a> [SRS]	<a href="#">Q13257</a> [EXPASY] <a href="#">Q13257</a> [INTERPRO]
<a href="#">Prosite</a>	<a href="#">PS50815</a> <a href="#">HORMA</a> [SRS]	<a href="#">PS50815</a> <a href="#">HORMA</a> [Expasy]
<a href="#">Interpro</a>	<a href="#">IPR003511</a> <a href="#">DNAbind</a> <a href="#">HORMA</a> [SRS]	<a href="#">IPR003511</a> <a href="#">DNAbind</a> <a href="#">HORMA</a> [

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### Polymorphism : SNP, mutations, diseases

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### General knowledge

[Family Browser](#) [MAD2L1](#) [UCSC Family Browser]  
[SOURCE](#) [NM\\_002358](#)  
[SMD](#) [Hs.533185](#)  
[SAGE](#) [Hs.533185](#)  
[Amigo](#) [process|cell cycle](#)  
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[Amigo](#) [process|mitotic checkpoint](#)  
[Amigo](#) [component|nucleus](#)  
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### Other databases

#### Probes

[Probe](#) [MAD2L1 Related clones \(RZPD - Berlin\)](#)

#### PubMed

[PubMed](#) [16 Pubmed reference\(s\) in LocusLink](#)

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