# Mutagenetix Phenotypic Mutation '3d'

<table>
<thead>
<tr>
<th><strong>Allele</strong></th>
<th>3d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutation Type</strong></td>
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</tr>
<tr>
<td><strong>Chromosome</strong></td>
<td>19</td>
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<tr>
<td><strong>Coordinate</strong></td>
<td>3,944,168 bp (GRCm38)</td>
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<tr>
<td><strong>Base Change (assembly)</strong></td>
<td>A ? G</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td>Unc93b1</td>
</tr>
<tr>
<td><strong>Gene Name</strong></td>
<td>unc-93 homolog B1 (C. elegans)</td>
</tr>
<tr>
<td><strong>Synonym(s)</strong></td>
<td>unc-93 homolog B, unc-93 related protein</td>
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<td><strong>Chromosomal Location</strong></td>
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<tr>
<td><strong>Accession Number</strong></td>
<td>NCBI RefSeq: NM_019449; MGI: 1859307</td>
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<tr>
<td><strong>Mapped</strong></td>
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<tr>
<td><strong>Amino Acid Change</strong></td>
<td>Histidine changed to Arginine</td>
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<tr>
<td><strong>Institutional Source</strong></td>
<td>Beutler Lab</td>
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<td><strong>Phenotypic Category</strong></td>
<td>DSS: sensitive day 7, immune system, MCMV susceptibility, response to injected CpG DNA - decreased, TLR signaling defect: hyposensitivity to CpG + IFNg, TLR signaling defect: hyposensitivity to poly I:C, TLR signaling defect: hyposensitivity to poly I:C + IFNg, TLR signaling defect: TNF production by macrophages, TLR signaling defect: type I IFN production by macrophages</td>
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<td><strong>Penetrance</strong></td>
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<td><strong>Alleles Listed at MGI</strong></td>
<td>All alleles(2) : Targeted, knock-out(1) Chemically induced(1)</td>
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**Lab Alleles**

- APN: IGL01088:Unc93b1, IGL02631:Unc93b1, IGL02942:Unc93b1, IGL03149:Unc93b1
- UTSW: R0680:Unc93b1, R1237:Unc93b1, R1557:Unc93b1, R1992:Unc93b1, R2435:Unc93b1, R4016:Unc93b1, R4080:Unc93b1, R4479:Unc93b1, R4829:Unc93b1, R4947:Unc93b1, R4964:Unc93b1, R4966:Unc93b1, R5056:Unc93b1, R5166:Unc93b1, R5441:Unc93b1, R5892:Unc93b1, R6382:Unc93b1, R6556:Unc93b1

**Mode of Inheritance**

- Autosomal Recessive

**Local Stock**

- Live Mice, Embryos, Sperm, gDNA

**Repository**

- MMRRC: 010466-UCD
<table>
<thead>
<tr>
<th>Science Writers</th>
<th>Alyson Mack, Eva Marie Y. Moresco, Anne Murray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors</td>
<td>Koichi Tabeta, Bruce Beutler</td>
</tr>
<tr>
<td>Illustrators</td>
<td>Eva Marie Y. Moresco, Nora G. Smart, Diantha La Vine</td>
</tr>
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<td>03/08/2018 4:40 PM by Diantha La Vine</td>
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Cite this information as follows: Koichi Tabeta, Alyson Mack, Eva Marie Y. Moresco, Anne Murray, Beutler B. Record for 3d, updated Mar 08, 2018. MUTAGENETIX (TM), B. Beutler and colleagues, Center for the Genetics of Host Defense, UT Southwestern Medical Center, Dallas, TX. URL: mutagenetix.utsouthwestern.edu
The 3d phenotype was identified in a screen of G3 mice for altered responses to Toll-like receptor (TLR) ligands (TLR Signaling Screen) (1). Peritoneal macrophages from 3d mice failed to produce normal levels of tumor necrosis factor (TNF)-α in response to exogenous nucleic acid molecules. This diminished response was observed upon stimulation with dsRNA (poly I:C, a TLR3 ligand), ssRNA (resiquimod, a TLR7 ligand), and ssDNA (unmethylated CpG-bearing oligonucleotides, a TLR9 ligand). In contrast, stimulation with lipoteichoic acid, lipopeptides (TLR2/TLR2, TLR2/TLR1, TLR2/TLR6 ligands), and bacterial

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lipopolysaccharide (LPS, a TLR4 ligand) resulted in normal TNF-α production. Type I interferon (IFN) production was also impaired, as was induction of IFN-dependent costimulatory molecules CD40 and CD86. Thus, signaling via TLRs 3, 7, and 9 appeared to be absent in 3d homozygotes, even though normal quantities of the receptors were detected by immunoblot analysis of whole cell extracts (1;2).

3d homozygotes display enhanced susceptibility to microbes, as evinced by the following: (1) elevated virus titers in spleen homogenates and a decreased cytokine (IFN-α, IFN-β/α, IL-12 and TNF-α) response after inoculation with mouse cytomegalovirus (MCMV); (2) a moderate immunodeficiency when challenged with Staphylococcus aureus; and (3) a reduced cytokine (IL-12p40 and TNF-α) induction in response to Listeria monocytogenes infection. The effect of the 3d mutation is most apparent upon infection of macrophages with the Listeria hly strain, which lacks the pore-forming protein listerolysin and is thus confined to the endosome. In addition, 3d mice show diminished adaptive immune responses, in that they fail to present antigen normally: major histocompatibility complex (MHC) class II presentation is partially reduced, and cross-presentation by MHC class I molecules is strongly reduced. No defect in endocytosis or endosomal-lysosomal acidification is observed in 3d mice.

The presence of autoantibodies is a hallmark of systemic lupus erythematosus (SLE) and it has been shown that anti-nuclear antibody production relies on TLR9 and TLR7 (3). Examination of the 3d mice found that the mutation led to suppression of spontaneous anti-nuclear, anti-ribonuclear protein (RNP), and IgM rheumatoid factor (RF) Ab production, glomerulonephritis (GN), and mortality in lupus-prone strains (4). In another study with samples from patients with SLE, the expression of UNC93B mRNA was higher in B cells and peripheral blood mononuclear cells (PBMCs) and the levels of UNC93B correlated with disease activity (5).

Melo et al. have determined that 3d mice are susceptible to infection with the protozoan parasite Toxoplasma gondii (6). TLR11 is a predominantly ER-associated TLR involved in the sensing of an infection by T. gondii. Activation of TLR11 subsequently leads to IL-12-dependent host resistance. A recent study by Pifer et al. has determined that Unc93b1 directly interacts with TLR11 and is essential for TLR11-mediated signaling in dendritic cells (7). Pifer et al. found that 3d mice were unable to activate a TLR11 response (namely production of IL-12) after T. gondii infection as well as after exposure to purified profilin (7). Further observations found that the T. gondii-infected 3d mice had lower numbers of IFN-α-secreting CD4+ and CD8+ T cells and that IL-12 secretion was necessary for survival after infection (6;7).
The 3d locus mapped to a 0.46-Mb interval on Chromosome 19 (1), and corresponds to an A to G transition at position 1273 of the *Unc93b1* transcript, in exon 9 of 11 total exons.

1257 GCTGGGGCAGGACTGCA
407  ACTGCTCACCCTT

The mutated nucleotide is indicated in red lettering, and causes a histidine to arginine substitution at residue 412 of the *Unc93b1* protein.
The 598 amino acid protein Unc93b1 has twelve predicted membrane-spanning domains, with both the N- and C-termini on the cytoplasmic side of the membrane (Figure 2). No ER-targeting KDEL motif is present in the amino acid sequence. A domain of unknown function (DUF895), also found in two predicted paralogs (Unc93a and Unc93c), is present between residues 124 and 189. Unc93b1 contains two putative N-linked glycosylation sites (N251 and N272) on the predicted third extracellular loop. The human UNC93B protein is predicted to contain twelve transmembrane helices, and exhibit weak homology to the bacterial ATP-binding cassette (ABC)-2 type transporter sequence between amino acids 319 and 523. Human and mouse UNC93B proteins share 90% amino acid identity.

TLR9 competes with, and predominates over, TLR7 for Unc93B1-mediated transportation. Characterization of Unc93B1 truncation mutants revealed that the cytosolic N-terminus is essential for negatively regulating TLR7-mediated responses, while enhancing TLR9 responses. A mutation at residue 34 (D34A), resulted in down-regulation of TLR9 trafficking and subsequent TLR9-mediated responses. The 3d mutation causes the substitution of a histidine for an arginine residue (H412R) in the expressed polypeptide. Histidine-412 is positioned in the ninth of twelve membrane-spanning domains, and is invariant in all known vertebrate UNC-93B orthologs; this residue is an asparagine in the C. elegans UNC-93B protein. Protein expression levels and half-life of Unc93b1^3d is similar to those of the wild type protein in bone marrow-derived dendritic cells (BM-DC).
Unc93b1 is highly expressed in both myeloid and lymphoid (i.e., B cells) tissue in mice (1). In humans, it is found at high levels in heart, brain and kidney, and at lower levels in most other tissues (9). Examination of human UNC-93B mRNA expression by microarray and Northern blot analysis determined that UNC-93B is expressed in many tissues, but that expression is highest in antigen presenting cells (APCs) (i.e. monocytes, macrophages, and dendritic cells) (12). Expression of UNC-93B was also high in alveolar macrophages of the lung (12). UNC-93B mRNA generates a single 2.6 kb band by Northern blot (12). Expression of both UNC-93B mRNA and protein could be induced by TLR agonists and was most strongly induced by the TLR3 agonist poly I:C in monocyte-derived dendritic cells (MoDC) and monocyte-derived macrophages (MDM) (12). In C. elegans, it is a membrane-associated muscle cell protein (13).

Immunostaining of tagged Unc93b1, or direct visualization of GFP-tagged Unc93b1, shows a subcellular localization to the endoplasmic reticulum (ER) in unstimulated RAW 264.7 macrophages, and in BM-DC (1;2). A similar localization is observed for both wild type Unc93b1 and Unc93b1<sup>3d</sup> (2) as well as in human MoDC and MDM cells (12). However, while wild type Unc93b1 translocates to endolysosomes upon CpG stimulation, mutant Und93b1<sup>3d</sup> remains in the ER (14).

**Background**

TLRs are type I transmembrane proteins that sense molecules of microbial origin and trigger host cell responses. There are 12 TLRs in mice, and 10 in humans, and each receptor recognizes a distinct microbial ligand. Stimulation of the nucleic acid sensors TLR3, TLR7, TLR8, and TLR9, which may occur upon viral infection, initiates signaling through the MyD88- and Trif-dependent pathways and the subsequent local inflammatory response [reviewed in (15;16)]. This response includes the induction of cytokines controlled by the transcription factors NF-κ B, MAPK, IRF7, and IRF3, and the upregulation of costimulatory molecules, such as CD80 and CD86, in professional antigen-presenting cells. Costimulation, in turn, leads to an adaptive immune response, which is activated when specific T cell receptors recognize antigens presented by DCs and macrophages.
Figure 3. Unc93b1 is necessary for TLR3, 7, and 9 trafficking from the endoplasmic reticulum (ER) to the endosome. Other proteins that are necessary for TLR maturation and trafficking are gp96 and PRAT4A (protein associated with TLR4). Gp96 is important for all TLR maturation, while PRAT4A is involved in trafficking of specific TLRs, including TLR7 and TLR9. In the endosome, TLR7 recognizes single-stranded RNA, TLR9 binds to CpG DNA, and TLR3 binds to double-stranded RNA. Proteolysis of both TLR7 and TLR9 is known to occur, and at least in the case of TLR9, is required for function. This image is interactive. Click on the image to view mutations found within the pathway (red) and the genes affected by these mutations (black). Click on the mutations for more specific information.

While some TLRs are expressed on the cell surface, TLR3, TLR7, TLR8, and TLR9, are intracellular receptors residing in the ER and trafficking to the endosomal/lysosomal compartment. The function of each of these receptors depends on its proper localization in the ER and the ability to be recruited to lysosomes in a ligand-dependent manner (17-21). Within lysosomes, they encounter their endocytosed nucleic acid ligands, and become activated to initiate downstream signaling. The recruitment of MyD88 to TLR9 upon CpG stimulation (19), and the activation of c-Src kinase after dsRNA stimulation of TLR3 (21) has been demonstrated to occur within lysosomes. These findings support the existence of a regulated mechanism for the ligand-activated movement of nucleic acid-sensing TLRs from the ER to the endosomal/lysosomal compartment.

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For TLR7 and TLR9, such a mechanism has recently been demonstrated to depend on the function of Unc93b1 (14). Wild type Unc93b1, but not the mutant Unc93b13d, physically interacts with TLRs 3, 7, 9 and 13 via their transmembrane domains, and associates with these TLRs in the ER (2;14). These data support previous findings implicating the TLR7 and TLR9 transmembrane domains and the TLR3 juxtamembrane domain (the linker between transmembrane and TIR domain) in their proper subcellular localization (22;23). Upon TLR activation, Unc93b1 is required to deliver the TLRs from the ER to endolysosomes, translocating with them in the process (Figure 3). Mutant Unc93b13d fails to travel to the ER after TLR stimulation (14). A chimeric TLR with the ectodomain of TLR9 fused to the transmembrane and intracellular domains of TLR4 resides at the cell surface, and confers responsiveness to CpG stimulation on 3d BM-DC, demonstrating that Unc93b1 is not required for TLR ligand recognition or signal initiation (14). In addition, the interactions between Unc93b1 and TLRs, as determined by coimmunoprecipitation, are not affected by TLR stimulation (2). Thus, Unc93b1 is solely required for trafficking of TLRs from the ER to endolysosomes, where they initiate MyD88- or Trif-dependent signaling.

Although an interaction of TLR-3, -7, and -9 with Unc93B1 had been shown (1), an interaction with TLR8 had not been definitively proven. However, a recent study has shown that TLR8 is primarily localized to the early endosome and the ER, but not the late endosome or lysosome of myeloid DCs (24). Examination of TLR8-mediated signaling upon transfection of a human UNC93B1 mutant with a H412R mutation found that the mutant did not interact with human TLR8 (24). In addition, the association of UNC93B1 with TLR8 via His412 was necessary for TLR8-mediated NF-?B activation (24).

siRNA-mediated knockdown of Unc93b1 in HEK293T cells decreases the amount of TLR3 at the cell surface, but does not change total TLR3 accumulation (25). Furthermore, TLR3-mediated signaling was reduced in the siRNA-treated cells (25). The effects of Unc93b1 knockdown on the secretion of the TLR3 ectodomain was also examined and it was observed that the secretion of the ectodomain was reduced (25). Expression of an Unc93b1 that did not have the first 36 residues also reduced the secretion of the TLR3 ectodomain (25). Further studies will determine if the interaction with the ectodomain is direct or indirect.

In developing B cells, the expression of activation-induced cytidine deaminase (AID) during ongoing class switch recombination has been demonstrated to require TLR signaling, and in particular, the function of Unc93b1 (26). B cell activation by B cell receptor (BCR) engagement is the major signal for AID induction in immature B cells. 3d mice display a reduction in AID expression in both pre-B cells and immature B cells, suggesting that TLR-mediated signals initiated by nucleic acids may play a dominant role in AID expression before the rearrangement of the BCR is complete (26).
after stimulation by poly I:C (12). Assessment of DC viability and function by examination of DC activation markers revealed that the cells were unaffected by knockdown of UNC-93B (12). Furthermore, upon reduction in UNC-93B expression did not result in defects in antigen-dependent proliferation of a CD4 T-cell clone (12). Koehn et al. speculate that an observed change in TLR3-mediated TNF production, but no observed change in MHC II-mediated responses indicates that there may be a certain level at which UNC-93B must be expressed to mediate functions in innate or adaptive immunity (12). Alternatively, they also suggest that the functionality of murine versus human UNC-93B may be different.

A role for UNC-93B in resistance to recurrent human herpes simplex virus-1 (HSV-1) encephalitis (HSE) has been reported (8) (OMIM #610551). HSV-1 occurs commonly among young adults, and HSE is a rare complication of this viral infection. Among a group of families in which at least one individual previously had recurrent HSE, two patients displayed reduced production of IFN-?, -? and -? in response to stimulation of peripheral blood mononuclear cells (PBMCs) with HSV or other DNA and RNA viruses (8). Further investigation revealed a specific impairment in type I IFN, TNF-?, IL-1? and IL-6 production in response to TLR7, TLR8 and TLR9 ligands, but not to a TLR3 ligand (8). Both patients had homozygous mutations of UNC93B1, which resulted in the absence of expressed transcript, and defective activation of IRF-3, NF-?B and MAPK (8). Unlike the murine Unc93b1 mutant phenotype, PBMCs from the human patients retained the ability to respond to poly I:C with normal cytokine production, possibly through a TLR3-independent mechanism (8). Antigen presentation was not tested in the human patients.

**Putative Mechanism**

In *C. elegans*, mutations of *unc-93* cause defects in motility, hence the designation *unc*oooordinated (13; 27). The nematode UNC-93 protein has been postulated as a regulatory subunit of a tripartite two-pore K+ channel encoded by *sup-9*, although definitive evidence is lacking for this conclusion (28). Suppression of the *unc*-93 phenotype can be achieved by mutations in *sup-9* (27). Thus, it is thought that UNC-93 acts as a regulatory subunit of a channel that controls muscle contraction in worms. As 3d mice show no defects in neuromuscular function, it seems unlikely that the protein has the same role in a mammalian context.
compartment, but the mechanism by which this occurs remains unknown. One study suggests that TLR9 delivery to endosomes occurs at least in part through a pathway similar to ER-mediated phagocytosis, in which ER fusion with the plasma membrane and subsequent phagocytosis mediates the internalization of various particles and the recycling of membrane components (29). Similarly, TLR9 may be delivered from the ER to the plasma membrane and then to the endosome during phagocytosis (19). In support of this hypothesis, TLR9 is recruited to phagosomal membranes when wild type, but not 3d, BM-DCs are incubated with polystyrene beads, and wild type Unc93b1 colocalizes with TLR9 in phagosomes (14). In addition, no contribution of the secretory pathway through the Golgi apparatus has been demonstrated for TLR9 ER-to-endosome movement (19). It has been postulated that an unidentified ER protein interacts with Unc93b1 to facilitate trafficking of Unc93b1-TLR complexes (14). The 3d mutation, within the ninth transmembrane segment of Unc93b1, may disrupt such an interaction, causing mislocalization of both Unc93b1 and its interacting TLRs.

Unc93b1 is required for exogenous antigen processing, affecting both MHC class II antigen presentation and cross-presentation in the context of MHC class I (1). Prior to the discovery that mutation of a single gene, Unc93b1, causes defects in both TLR signaling and antigen presentation, these processes were considered distinct and independent. However, both in fact depend on the endosomal-lysosomal pathway, as TLRs encounter ligands (19-21;30) and antigens are hydrolyzed for MHC class II loading in the acidified endosome (31). Cross-presentation requires exogenous protein antigens for MHC class I loading to pass through the endosome on their way to the ER as peptide fragments (32). During this process, proteins acquired through phagocytosis or pinocytosis exit the endocytic pathway, enter the cytosol, and are degraded by the proteasome. The resulting peptides are translocated to the ER via the transporter associated with antigen processing (TAP) transporter and loaded into MHC class I molecules (32). Because mutations that inactivate TAP prevent expression of class I molecules, it has been proposed that the incorporated peptide is required to stabilize the class I molecule (32;33). However, in 3d mutant cells, MHC class I expression and localization appear normal even though ovalbumin-derived peptide cannot be incorporated into class I molecules (1;14). This normal MHC class I expression suggests that endogenous antigen processing and presentation are relatively unimpaired, raising the possibility that Unc93b1 facilitates the movement of exogenous antigens from the phagosome or endosome to the cytosol. The 3d mutation abolishes Unc93b1 localization to phagosomes, consistent with this possibility. Finally, Unc93b1 may itself function as an ER transporter channel. In this role, Unc93b1 would not be predicted to affect TLR signaling.
they may be further processed before TAP-mediated translocation back into the ER and re-loading into class I MHC. The machinery that extracts peptides from the ER remains poorly understood. The Sec61 complex (also translocon) translocates polypeptides from the cytosol into the ER (34), and some data suggest that it may also serve as a retrotranslocator, moving proteins from the ER to the cytosol (35-37). Recent data suggests that peptide retrotranslocation by Sec61 is required for antigen cross-presentation (38). Derlin-1 is another retrotranslocator (39-40). Unc93b1 may also be a retrotranslocating peptide channel, but this has not been tested.
3d genotyping is performed by amplifying the region containing the mutation using PCR, followed by sequencing of the amplified region to detect the single nucleotide change. The same primers are used for PCR amplification and for sequencing.

**Primers for PCR amplification**

3d(F): 5’-GGGAGTTAATACCAGGAGACCCAG-3’
3d(R): 5’-ATGCTAACAGTTCTGAGCCACCTAG-3’

**PCR program**

1) 94°C  2:00
2) 94°C  0:15
3) 60°C  0:20
4) 68°C  1:00
5) repeat steps (2-4) 35X
6) 68°C  5:00
7) 4°C  ?

The following sequence of 465 nucleotides (from Genbank genomic region NC_000085 for linear genomic sequence of Unc93b1) is amplified:

8700 8701  ggagttataa ccaggagacc cagagaggac aggtgtgaac taaaacggga
taatgtgtgg
8761 8762  gaccaaccg gcctcctccc ttagggctac gccgtgtggt
8821 8822  gcatacgctg gactggtgca gacccctgca ctggttcctgt
8881 8882  gcctcaggtg ggtgttgctc ttagggctac gccgtgtggt
8941 8942  cactggtgtg cacccctgcc ttagggctac gccgtgtggt
9001 9002  ccctggtttt gccccgtgct ccctcctgcc ttagggctac gccgtgtggt
9061 9062  acaagacccg acttagcagt gagtacagct taggtggctt gctggttgcc
gagcgtctca
9121 9122  aggaggggag tggacagcag gatgtggttc ttaggtggtc
gccccctca
gagcgtctca
gagcttggtc
gctggtgtt
gctgtgcaagcttggtgctc
gccccctca

Primer binding sites are underlined; the mutated A is highlighted in red.

**References**


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