Diseases associated with the TLR signaling cascade

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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: 82

This document contains 12 pathways (see Table of Contents)
Toll like receptors (TLRs) are sensors of the innate immune system that detect danger signals derived from pathogens (pathogen-associated molecular patterns - PAMP) or damaged cells (damage-associated molecular patterns - DAMP) (Pasare C and Medzhitov R 2005; Barton GM and Kagan JC 2009; Kawai T and Akira S 2010). Signaling by these sensors promotes the activation and nuclear translocation of transcription factors (IRFs, NFkB and AP1). The transcription factors induce secretion of inflammatory cytokines such as IL-6, TNF and pro-IL1beta that direct the adaptive immune response. Inherited or acquired abnormalities in TLR-mediated processes may lead to increased susceptibility to infection, excessive inflammation, autoimmunity and malignancy (Picard C et al. 2010; Netea MG et al. 2012; Varettoni M et al. 2013). Here we describe four primary immunodeficiency (PID) disorders associated with defective TLR-mediated responses. First, MyD88 or IRAK4 deficiency is characterized with a greater susceptibility to pyogenic bacteria in affected patients (Picard C et al. 2003; von Bernuth H et al. 2008). Second, defects in the TLR3 signaling pathway are associated with a greater susceptibility to herpes simplex virus encephalitis (Zhang SY et al. 2013). Third, imunodeficiencies due to defects in NFkB signaling components are linked to impaired TLR-mediated responses (Courtois G et al. 2003; Fusco F et al. 2004). Finally, events are annotated showing constitutive activation of a somatically mutated MyD88 gene which results in malignancy (Varettoni M et al. 2013).

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Interleukin-1 receptor-associated kinase 4 (IRAK4) is a serine/threonine kinase, that mediates activation of transcriptional factors such as NFkB and AP1 downstream of IL-1 receptors and all toll like receptors (TLR) except for TLR3 (Suzuki N et al. 2002). IRAK4 is recruited to the TLR receptor complex through a homophilic interaction of the death domains of IRAK4 and adaptor myeloid differentiation factor 88 protein (MyD88) (Motshwene PG et al. 2009; Lin SC et al. 2010). Studies have identified patients with an autosomal recessive (AR) form of IRAK4 deficiency, a health condition with clinical manifestation in infancy or early childhood, that predisposes affected patients to recurrent pyogenic bacterial infection (e.g., Streptococcus pneumoniae and Staphylococcus aureus) (Picard C et al. 2003; Ku CL et al. 2007; Picard C et al. 2010; Picard C et al. 2011). Leukocytes derived from IRAK4-deficient patients display a lack of production of inflammatory cytokines such as TNF alpha, IL-6 and IL-1 beta by whole blood or a lack of CD62 ligand (CD62L) shedding from granulocytes following activation with the most TLR agonists including those of TLR1/2 (Pam3CSK4), TLR2/6 (Pam2CSK4) and TLR4 (LPS) (Picard C et al. 2003; McDonald DR et al. 2006; Ku CL et al. 2007). However, LPS-induced TLR4-mediated production of some cytokines (IL8 and MIP-1beta) was reduced but not abolished (Ku CL et al. 2007). LPS-stimulated induction of type I IFN via MyD88-IRAK4 independent signaling axis was normal or weakly affected suggesting that TLR4 could induce some responses in IRAK4 deficient patients (Yang K et al. 2005).

Patients with AR IRAK4 deficiency were found to bear homozygous or compound heterozygous mutations in the IRAK4 gene (Picard C et al. 2003; Ku CL et al. 2007; McDonald DR et al. 2006). Here we describe selected mutations, that have been functionally characterized. Cell-based assay as well as in vitro protein-interaction analyses with IRAK4 variants showed that the loss-of-function of defective IRAK4 is caused by either loss of protein production (reported for IRAK4 Q293X and E402X) or an impaired inter-
action with MyD88 as shown for missence mutation IRAK4 R12C (Ku CL et al. 2007; Yamamoto T et al. 2014).

Besides defective TLR2/4 mediated signaling, the Reactome module describes the impact of functional deficiency of IRAK4 on TLR5 pathways. The module does not include defective TLR7, TLR8 and TLR9 signaling events, which are associated mostly with viral infections, although studies using patient-derived blood cells showed abolished cytokine production by peripheral blood mononuclear cells (PBMCs) and lack of CD62 ligand (CD62L) shedding from granulocytes in response to TLR7-9 agonists (McDonald DR et al. 2006; von Bernuth H et al. 2006; Ku CL et al. 2007). In addition to the TLR-NFkB signaling axis, endosomal TLR7-9 activates IFN-alpha/beta and IFN-gamma responses and these are also impaired in IRAK4-deficient PBMC (Yang K et al. 2005). Nevertheless, IFN-alpha/beta and -gamma production in IRAK-4-deficient blood cells in response to 9 of 11 viruses was normal or weakly affected, suggesting that IRAK-4-deficient patients may control viral infections by TLR7-9-independent production of IFNs such as IRAK4-independent antiviral RIGI and MDA5 pathways (Yang K et al. 2005). So it is not yet possible to annotate a definitive molecular pathway between IRAK-4 deficiency and changes in TLR7-9 signaling.

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Devon, RS., Reid, GS., Currie, AJ., MacDonald, KL., Speert, DP., Bharya, S. et al. (2004). Primary immunodeficiency to pneumococcal infection due to a defect in Toll-like receptor signaling. *J. Pediatr.*, 144, 512-8.

Kondo, N., Shirakawa, M., Ohnishi, H., Tochio, H., Kato, Z., Tsutsumi, N. et al. (2014). Functional assessment of the mutational effects of human IRAK4 and MyD88 genes. *Mol. Immunol.*, 58, 66-76.

Ozinsky, A., Dupuis, S., Tufenkeji, H., Al-Rayes, H., Al-Hajjar, S., Lammas, D. et al. (2003). Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science*, 299, 2076-9.

Abel, L., Li, X., von Bernuth, H., Jin, Z., Camcioglu, Y., Pascal, M. et al. (2008). Pyogenic bacterial infections in humans with MyD88 deficiency. *Science*, 321, 691-6.

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Toll like receptor 5 (TLR5) specifically recognizes bacterial infection through binding of flagellin from pathogenic bacteria. Upon ligand binding, TLR5 dimers recruit MyD88 through their TIR domains. Then, MyD88 oligomerizes via its death domain (DD) and TIR domain and interacts with the interleukin-1 receptor-associated kinases (IRAKs) to form the Myddosome complex (MyD88:IRAK4:IRAK1/2) (Motshwene PG et al. 2009; Lin SC et al. 2010). The Myddosome complex transmits the signal leading to activation of transcription factors such as nuclear factor-kappaB (NFkB) and activator protein 1 (AP1). Studies have identified patients with autosomal recessive (AR) form of IRAK4 deficiency, a health condition with clinical manifestation in infancy or early childhood, that predisposes affected patients to recurrent pyogenic bacterial infection (e.g., Streptococcus pneumoniae and Staphylococcus aureus) (Picard C et al. 2003; Ku CL et al. 2007; Picard C et al. 2010; Picard C et al. 2011). Leukocytes derived from IRAK4-deficient patients display a lack of production of inflammatory cytokines such as TNF alpha, IL-6 and IL-1beta or a lack of CD62 ligand (CD62L) shedding from granulocytes following activation with flagellin, the TLR5 agonist (Picard C et al. 2003; McDonald DR et al. 2006; Ku CL et al. 2007). Patients with AR IRAK4 deficiency were found to bear homozygous or compound heterozygous mutations in the IRAK4 gene (Picard C et al. 2003; Ku CL et al. 2007; McDonald DR et al. 2006). Here we describe selective mutations, that have been functionally characterized. Cell-based assays as well as in vitro protein-interaction analyses with IRAK4 variants showed that the loss-of-function of defective IRAK4 can be caused by either an abolished protein production as a result of nonsense mutations (e.g., Q293X and E402X) or an impaired interaction with MyD88 due to missense mutations (e.g., R12C) (Ku CL et al. 2007; Yamamoto T et al. 2014).

IRAK4 mediates immune responses downstream of all TLRs except for TLR3. Besides defective TLR5 sig-
naling, the Reactome module describes the impact of functional deficiency of IRAK4 on TLR2/4 signaling pathways. We did not include defective TLR7, TLR8 and TLR9 signaling events, which are stimulated by nucleic acids upon viral infections, although studies using patients-derived blood cells have showed abolished cytokines production by peripheral blood mononuclear cells (PBMCs) and lack of CD62 ligand (CD62L) shedding from granulocytes in response to TLR7-9 agonists, i.e., 3M-13 (TLR7), 3M-2 (TLR8), R848 (TLR7 and 8) and CpG (TLR9) (McDonald DR et al. 2006; von Bernuth H et al. 2006; Ku CL et al. 2007). In addition to TLR-NFkB signaling axis the endosomal TLR7-9 activate IFN-alpha/beta and IFN-gamma responses, which have been also impaired in IRAK4-deficient PBMC (Yang K et al. 2005). However, IFN-alpha/beta and IFN-gamma production in response to 9 of 11 viruses tested was normal or weakly affected in IRAK-4-deficient blood cells, suggesting that IRAK-4-deficient patients may control viral infections by TLR7-9-independent production of IFNs (Yang K et al. 2005). So it is not yet possible to annotate a definitive molecular pathway between IRAK-4 deficiency and changes in TLR7-9 signaling.

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Ozinsky, A., Dupuis, S., Tufenkeji, H., Al-Rayes, H., Al-Hajjar, S., Lammas, D. et al. (2003). Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science*, 299, 2076-9.

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MyD88 deficiency (TLR2/4)

**Location:** Diseases associated with the TLR signaling cascade

**Stable identifier:** R-HSA-5602498

**Diseases:** primary immunodeficiency disease

Myeloid differentiation primary response (MyD88) is an adaptor protein that mediates intracellular signaling pathways evoked by all Toll-like receptors (TLRs) except for TLR3 and by several interleukin-1 receptors (IL-1Rs) (Medzhitov R et al. 1998). Upon ligand binding, TLRs hetero- or homodimerize and recruit MyD88 through their respective TIR domains. Then, MyD88 oligomerizes via its death domain (DD) and TIR domain and interacts with the interleukin-1 receptor-associated kinases (IRAKs) to form the Myddosome complex (MyD88:IRAK4:IRAK1/2) (Motshwene PG et al. 2009; Lin SC et al. 2010). The Myddosome complex transmits the signal leading to activation of transcription factors such as nuclear factor-kappaB (NFkB) and activator protein 1 (AP1).

Studies have identified patients with autosomal recessive (AR) form of MyD88 deficiency caused by homozygous or compound heterozygous mutations in MYD88 gene leading to abolished protein production (von Bernuth et al. 2008). AR MyD88 deficiency is a type of a primary immunodeficiency characterized by greater susceptibility to pyogenic bacteria (such as Streptococcus pneumoniae, Staphylococcus aureus or Pseudomonas aeruginosa) manifested in infancy and early childhood. Patients with MyD88 deficiency show delayed or weak signs of inflammation (Picard C et al. 2010; Picard C et al. 2011).

Functional assessment of MyD88 deficiency revealed that cytokine responses were impaired in patient-derived blood cells upon stimulation with the agonists of TLR2 and TLR4 (PAM2CSK4 and LPS respectively), although some were produced in response to LPS. (von Bernuth et al. 2008). NFkB luciferase reporter gene assays using human embryonic kidney 293 (HEK293T) cells showed that MyD88 variants, S34Y, E52del, E53X, L93P, R98C, and R196C, were compromised in their ability to enhance NFkB activation (Yamamoto T et al. 2014). The molecular basis for the observed functional effects (reported for selected mutations) probably faulty Myddosome formation due to impaired MyD88 oligomerization and/or in-
teraction with IRAK4 (George J et al. 2011; Nagpal K et al. 2011; Yamamoto T et al. 2014).

While MyD88-deficiency might be expected to perturb MyD88?IRAK4 dependent TLR7 and TLR8 signaling events associated with the sensing viral infections, patients with MyD88 and IRAK4 deficiencies have so far not been reported to be susceptible to viral infection.

**Literature references**

Devon, RS., Reid, GS., Currie, AJ., MacDonald, KL., Speert, DP., Bharya, S. et al. (2004). Primary immunodeficiency to pneumococcal infection due to a defect in Toll-like receptor signaling. *J. Pediatr.*, 144, 512-8. ↗

Kondo, N., Shirakawa, M., Ohnishi, H., Tochio, H., Kato, Z., Tsutsumi, N. et al. (2014). Functional assessment of the mutational effects of human IRAK4 and MyD88 genes. *Mol. Immunol.*, 58, 66-76. ↗

Abel, L., Li, X., von Bernuth, H., Jin, Z., Camcioglu, Y., Pascal, M. et al. (2008). Pyogenic bacterial infections in humans with MyD88 deficiency. *Science*, 321, 691-6. ↗

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Myeloid differentiation primary response (MyD88) is an adaptor protein that mediates intracellular signaling pathways evoked by all Toll-like receptors (TLRs) (except for TLR3) and several interleukin-1 receptors (IL-1Rs) (Medzhitov R et al. 1998). Upon ligand binding, TLRs hetero- or homodimerize and recruit MyD88 through their respective TIR domains. Then, MyD88 oligomerizes via its death domain (DD) and TIR domain and interacts with the interleukin-1 receptor-associated kinases (IRAKs) to form the Myddosome complex (MyD88:IRAK4:IRAK1/2) (Motshwene PG et al. 2009; Lin SC et al. 2010). The Myddosome complex transmits the signal leading to activation of transcription factors such as nuclear factor-kappaB (NFkB) and activator protein 1 (AP1).

Studies have identified patients with autosomal recessive (AR) form of MyD88 deficiency caused by homozygous or compound heterozygous mutations in MYD88 gene leading to abolished protein production (von Bernuth et al. 2008). AR MyD88 deficiency is a type of a primary immunodeficiency characterized by greater susceptibility to pyogenic bacteria such as invasive pneumococcal disease manifested in infancy and early childhood. Patients with MyD88-deficiency show delayed or weak signs of inflammatory responses (Picard C et al. 2010; Picard C et al. 2011).

Functional assessment of MyD88 deficiency revealed that cytokine responses were abolished in patient-derived blood cells upon stimulation with bacterial flagellin, which is recognized by TLR5 (von Bernuth et al. 2008). An Nfkb luciferase reporter gene assay using human embryonic kidney 293 (HEK293T) cells showed that MyD88 variants, S34Y, E52del, E53X, L93P, R98C, and R196C, were compromised in the ability to enhance NFkB activation (Yamamoto T et al. 2014). The molecular basis for the observed functional effects (reported for selected mutations) probably faulty Myddosome formation due to impaired MyD88
oligomerization and/or interaction with IRAK4 (George J et al. 2011; Nagpal K et al. 2011; Yamamoto T et al. 2014).

While MyD88 deficiency might be expected to perturb MyD88?IRAK4 dependent TLR7 and TLR8 signaling events associated with the sensing viral infections in the endosome, patients with MyD88 and IRAK4 deficiencies have so far not been reported to be susceptible to viral infection.

**Literature references**

Abel, L., Li, X., von Bernuth, H., Jin, Z., Camcioglu, Y., Pascal, M. et al. (2008). Pyogenic bacterial infections in humans with MyD88 deficiency. *Science, 321*, 691-6.

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Toll like receptor 3 (TLR3) recognizes double-stranded RNA (dsRNA), an intermediate product during viral replication for most viruses. TLR3 is expressed in various tissues and cells including cells of the central nervous system (CNS) (Bsibsi M et al. 2002). TLR3 activity in neurons and glial cells was found to be critical for controlling herpes simplex virus type 1 (HSV-1) infection in CNS (Lafaille FG et al. 2012). Children with inborn errors of TLR3-mediated immunity are prone to HSV-1 encephalitis (HSE), a rare life-threatening complication during HSV-1 infection (Casrouge A et al. 2006; Perez de Diego R et al. 2010; Zhang SY et al. 2007; Herman M et al. 2012; Lafaille FG et al. 2012). The functional defect in HSE patients with TLR3 deficiency is probably due to impaired induction of type I and III interferon (IFN) by cells of the CNS, which appears to be uniquely dependent upon TLR3 for protection against HSV1 (Zhang SY et al. 2007; Guo Y et al. 2011; Lafaille FG et al. 2012). Importantly, blood cells in the periphery produce normal amounts of interferons, even in TLR3-deficient patients, which perhaps can be explained by RIGI or MDA5-mediated antiviral responses.

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UNC93B1 deficiency - HSE

Location: Diseases associated with the TLR signaling cascade

Stable identifier: R-HSA-5602415

Diseases: primary immunodeficiency disease

UNC93B1 is an endoplasmic reticulum protein with 12 membrane-spanning domains. Signaling cascades of nucleotide-sensing endosomal toll like receptors (TLR3 and TLR7-9) depends on functional UNC93B1, which is thought to deliver these TLRs from the ER to the endosome where they recognize specific pathogenic patterns and initiate host immune responses.

UNC93B deficiency has been implicated in the increased susceptibility to herpes simplex virus type 1 (HSV1) encephalitis (HSE), a rare complication during HSV-1 infection of the central nervous system (CNS) (Casrouge A et al. 2006). Patients-derived UNC96B1-deficient fibroblasts showed an impaired production of IFN-beta and -gamma following stimulation with TLR3 agonist poly(I:C) (Casrouge A et al. 2006). These cells were also more susceptible to HSV1 infection, showing rapid viral replication together with high mortality rates. Furthermore, pluripotent stem cells (iPSC) derived from HSE patient dermal fibroblasts were differentiated into populations of neural stem cells (NSC), neurons, astrocytes and oligodendrocytes (Lafaille FG et al. 2012). The impaired induction of IFN beta and gamma was observed in all tested CNS cells upon stimulation with poly(I:C). However, HSV1 infection selectively affected type I and III IFN production in UNC93B1-deficient neurons and oligodendrocytes (Lafaille FG et al. 2012). Thus, impaired TLR3-mediated UNC93B-dependent type I and III IFN production in response to HSV1 infection in CNS, in neurons and oligodendrocytes in particular, may underline the pathogenesis of HSE in patients with UNC93B1 deficiency (Casrouge A et al. 2006; Lafaille FG et al. 2012).

Defective UNC93B1 also impairs the TLR7, TLR8 and TLR9 signaling pathways. Peripheral blood mononuclear cells (PBMCs) from UNC93B-deficient patients did not respond to the stimulation of TLR7, TLR8, or TLR9, in terms of the production of type I and III interferons, and other cytokines tested (Casrouge A et al. 2006). Moreover, no inducible CD62L shedding on granulocytes was detected after stimulation of whole blood cells derived from UNC93B-deficient patients with R-848 (agonist of TLR7 and TLR8) (von Bernuth H. et al. 2008). However, no clinical condition has been so far associated with impaired TLR7, TLR8, TLR9 due to UNC93B1 deficiency so this defect is not annotated here.
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Beutler, B., Abel, L., Alcais, A., Dulac, O., Lebon, P., Lorenzo, L. et al. (2006). Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science*, **314**, 308-12.

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TICAM1 deficiency - HSE

**Location:** Diseases associated with the TLR signaling cascade

**Stable identifier:** R-HSA-5602566

**Diseases:** primary immunodeficiency disease

Inborn errors of interferon immunity due to defects in toll like receptor 3 (TLR3)-mediated signaling underlie pathogenesis of herpes simplex virus type 1 (HSV1) encephalitis (HSE) in some children (Netea MG et al. 2012). Autosomal dominant (AD) and recessive (AR) deficiencies of (TIR) domain-containing adaptor inducing IFN-beta (TRIF or TICAM1) are also associated with impaired IFN production and predisposition to HSE in the course of primary infection by HSV1 (Sancho-Shimizu V et al. 2011).

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Alkhamis, N., Abel, L., Halwani, R., Ghadiri, A., Lebon, P., Al-Muhsen, S. et al. (2011). Herpes simplex encephalitis in children with autosomal recessive and dominant TRIF deficiency. *J. Clin. Invest.*, 121, 4889-902.

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TNF Receptor Associated Factor 3 (TRAF3) is a cytoplasmic adaptor protein utilized by the tumor necrosis factor receptor superfamily and toll-like receptors (TLRs). TRAF3 deficiency is thought to mimic the previously reported TLR3 deficiency in terms of susceptibility to herpes simplex virus type 1 (HSV1) encephalitis (HSE) via impaired TLR3-mediated immunity against HSV1 infection of central nervous system (CNS) (Pérez de Diego R et al. 2010; Guo Y et al. 2011).

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Abel, L., Lebon, P., Bravo, J., Al-Muhsen, S., Pérez de Diego, R., Herman, M. et al. (2010). Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. *Immunity*, 33, 400-11.

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IKBKG deficiency causes anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) (via TLR)

**Location:** Diseases associated with the TLR signaling cascade

**Stable identifier:** R-HSA-5603027

**Diseases:** primary immunodeficiency disease

Many signaling pathways rely on the activation of nuclear factor kappa B (NFkB), which is critical for the induction of the appropriate cellular function in response to various stimuli such as inflammatory cytokines, microbial products or various types of stress (Lawrence T 2009; Hoesel B and Schmid JA 2013). The NFkB family of transcription factors is kept inactive in the cytoplasm by inhibitor of kappa B (IkB) family members (Oeckinghaus A and Ghosh S 2009). Canonical NFkB activation depends on the phosphorylation of IkB by the I kappa B kinase (IKK) complex, which contains two catalytic subunits named IKK alpha, IKK beta and a regulatory subunit named NFkB essential modulator (NEMO or IKBKG) (Rothwarf DM et al. 1998). Phosphorylation of IkB leads to K48-linked ubiquitination and proteasomal degradation of IkB, allowing translocation of NFkB factor to the nucleus, where it can activate transcription of a variety of genes participating in the immune and inflammatory response, cell adhesion, growth control, and protection against apoptosis (Collins T et al. 1995; Kaltschmidt B et al. 2000; Lawrence T 2009).

IKBKG is encoded by an X-linked gene. Null alleles of the gene are lethal in hemizygous males, whereas hypomorphic alleles typically result in the impaired NFkB signaling in patients with a broad spectrum of clinical phenotypes in terms of both developmental defects and immunodeficiency (Döffinger R et al. 2001; Hanson EP et al. 2008). Several categories of mutations affecting IKBKG have been reported in humans (Döffinger R et al. 2001; Vinolo E et al. 2006; Fusko F et al. 2008). The first category of these mutations consists of hypomorphic mutations typically involving the zinc finger domain and nearby C-terminal regions and causing hypohidrotic ectodermal dysplasia with immune deficiency (HED-ID) in males (Jain A et al. 2001; Shifera AS 2010). The second category consists of amorphic mutations causing incon-
tinentia pigmenti (IP) in females and, generally, prenatal death in males (Aradhya S et al. 2001; Fusco F et al. 2004). The third category is composed of hypomorphic mutations involving the stop codon causing anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID), osteopetrosis and lymphedema (OL-EDA-ID) in males (Döffinger R et al. 2001). Also some patients with a defective IKBKG gene can develop immunodeficiency without ectodermal dysplasia (Orange JS et al. 2004). This module describes several EDA-ID-associated hypomorphic IKBKG mutations that have been reported to affect inflammatory responses initiated by toll like receptors (TLR).

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Four patients with early-onset, life-threatening microbial infections and failure to thrive were found to carry a homozygous duplication c.1292dupG in exon 13 of IKBKB gene that results in a lack of expression of IKBKB (Pannicke U et al. 2013). IKBKB deficiency is associated with severe combined immunodeficiency (SCID), a health condition characterized by low levels of immunoglobulins (hypogammaglobulinemia). Further phenotype assessment revealed that patients peripheral-blood B cells and T cells had normal counts but were almost exclusively of naive phenotype. Regulatory T cells and gamma delta T cells were absent.

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The nuclear factor kappa B (NFkB) family of transcription factors is kept inactive in the cytoplasm by the inhibitor of kappa B (IkB) family members IKBA (IkB alpha, NFKBIA), IKBB (IkB beta, NFKBIB) and IKBE (IkB epsilon, NFKBIE) (Oeckinghaus A and Ghosh S 2009). Multiple stimuli such as inflammatory cytokines, microbial products or various types of stress activate NFkB signaling leading to stimuli-induced phosphorylation of IkB molecule (Scherer DC et al. 1995; Alkalay I et al. 1995; Lawrence T 2009; Hoesel B and Schmid JA 2013). The phosphorylation of IkB proteins triggers their polyubiquitination and subsequent degradation by 26S proteasome, allowing free NFkB dimer to translocate to the nucleus where it directs the expression of target genes. Studies have identified an autosomal dominant form of ectodermal dysplasia with immunodeficiency (AD-EDA-ID) caused by a hypermorphic heterozygous mutation of NFKBIA/IKBA gene. The IKBA defects prevent the phosphorylation and degradation of IKBA protein resulting in gain-of-function condition with the enhanced inhibitory capacity of IKBA in sequestering NFkB dimers in the cytoplasm (Courtois G et al. 2003; Lopes-Granados E et al. 2008; Schimke LF et al. 2013).

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