Structural and Functional Characteristics of the Human Blood-Nerve Barrier with Translational Implications to Peripheral Nerve Autoimmune Disorders

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Abstract Peripheral nerves and nerve roots comprise of three structural compartments: the outer epineurium consisting of longitudinal arrays of collagen fibers responsible for structural integrity and the inner perineurium consisting of multiple concentric layers of specialized epithelioid myofibroblasts that surround the innermost endoneurium which consists of myelinated and unmyelinated axons embedded in a looser mesh of collagen fibers. Axons are responsible for signal transduction to and from the central nervous system required for normal physiological processes and are targeted by the immune system in autoimmune disorders. A highly regulated endoneurial microenvironment is required for normal axonal function. This is achieved by tight junction-forming endoneurial microvessels that control ion, solute, water, nutrient, macromolecule and leukocyte influx and efflux between the bloodstream and endoneurium, and the innermost layers of the perineurium that control interstitial fluid component flux between the epineurium and endoneurium. Endoneurial microvascular endothelium is considered the blood-nerve barrier (BNB) due to direct communication with circulating blood. The mammalian BNB is considered the second most restrictive vascular system after the blood-brain barrier (BBB). Guided by human in vitro studies using primary and immortalized endoneurial endothelial cells that form the BNB, in situ studies in normal and pathologic human peripheral nerves, and representative animal models of peripheral nerve autoimmune disorders, knowledge is emerging on human BNB molecular and functional characteristics, including its array of cytokines/cytokine receptors, selectins, and cellular adhesion and junctional complex molecules that may be employed during normal immune surveillance and altered in autoimmune diseases, providing potential targets of efficacious immunotherapy.

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Abbreviations

BBB	Blood-brain barrier
BNB	Blood-nerve barrier
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
DSP	Distal sensory polyneuropathy
EAN	Experimental autoimmune neuritis
FITC	Fluorescein isothiocyanate
GBS	Guillain-Barré syndrome
GDNF	Glial-derived neurotrophic factor
HIFs	Hypoxia-inducing factors
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICAM-1	Intercellular adhesion molecule-1
IFN-γ	Interferon-γ
IL-1β	Interleukin-1β
IL-2	Interleukin-2
MAPK	Mitogen-activated protein kinase
RET	"rearranged upon transformation"
RNA	Ribonucleic acid
SAPP	Spontaneous autoimmune peripheral polyneuropathy
TEER	Transendothelial electrical resistance
TGF-β	Transforming growth factor-β
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial cell growth factor
ZO	Zonula occludens

Anatomy of Human Peripheral Nerves

Human peripheral nerves serve to facilitate afferent and efferent communication between the central nervous system (brain and spinal cord) and the periphery (internal and external organs, such as the gastrointestinal tract and skin, respectively, secretory organs, and muscle) required for normal physiological processes needed to healthy bodily function. Human peripheral nerves comprise of three compartments: the outer epineurium which consists of longitudinal arrays of collagen fibers that are important for maintaining the structural integrity of the peripheral nerve, the inner perineurium which consists of concentric layers of specialized cells, and the innermost endoneurium which consists of a looser mesh of collagen fibers. A nerve

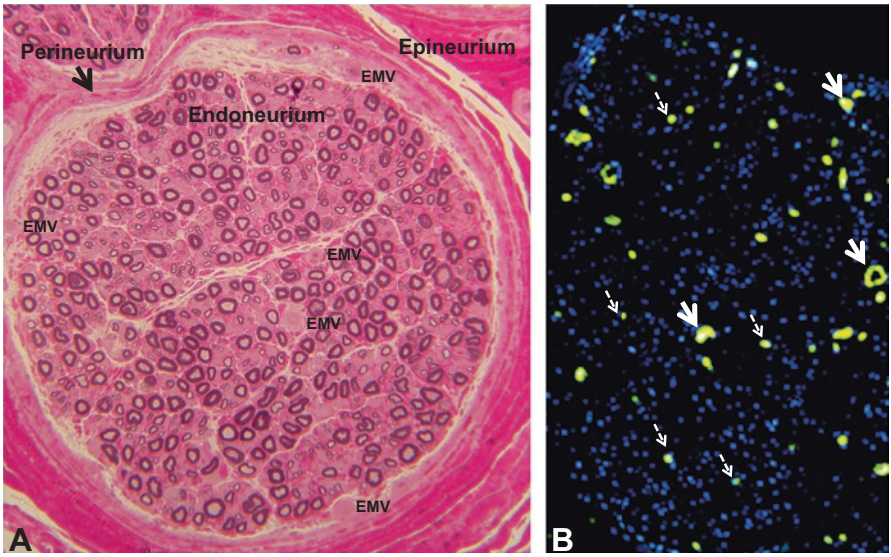

Fig. 1 Digital light photomicrograph of a normal adult sural nerve (plastic embedded semi-thin axial section stained with Toluidine Blue and counterstained with basic fuchsin) showing the three compartments in peripheral nerves and endoneurial microvessels (EMV) that form the BNB (**a**) and an indirect fluorescent digital photomicrograph of a normal adult sural nerve (cryostat thick section stained with fluoresceinated *Ulex europaeus* agglutinin-1) showing epineurial macrovessels (solid arrow) and endoneurial microvessels (broken arrow) (**b**)

fascicle consists of the endoneurium and its surrounding perineurium, initially described in 1876 (Fig. 1a) [1–4].

The epineurium consists of arteries, arterioles, venules, and veins that are considered collectively as epineurial macrovessels. The macrovessels are derived from and communicate with the extrinsic vascular supply to individual peripheral nerves known as the vasa nervorum. Lymphatic vessels are also present within the epineurium. The perineurium consists of specialized epithelioid myofibroblasts that form concentric layers, consisting of single cells, around the endoneurium (1–15 layers dependent on nerve diameter), forming fascicles, as well as smaller diameter macrovessels that communicate with the epineurium and endoneurium. The endoneurium consists of axons that are responsible for electrical impulse signal transduction to and from the central nervous system. These axons are myelinated or unmyelinated, are dependent on axonal size and function, and are aligned in the longitudinal axis of the peripheral nerve [1–5].

Schwann cells are the glial cells in peripheral nerves responsible for myelinating segments of large and small diameter axons needed to facilitate rapid salutatory action potential conduction, or surround bundles of small diameter unmyelinated axons (known as a Remak bundle), providing physiological support to these axons [6]. Motor neurons (axonal cell bodies) are located in the brain (for cranial nerves) and spinal cord (for somatic nerves), while sensory neurons are located in collections

of cell bodies called ganglia (e.g., dorsal root ganglia for somatic nerves). The endoneurium also consists of capillary-like microvessels that lack smooth muscle walls (Fig. 1b), as well as rare resident leukocytes (macrophages and mast cells) and fibroblasts [1–5].

The sciatic nerve is the largest nerve in mammals, compromising of 50–80 fascicles in adult humans in the mid-thigh region (and as many as 140 fascicles in the gluteal region) [2, 7, 8] and 1–4 fascicles in adult mice and rats [9–11]. The commonly studied human sural nerve typically consists of 8–10 fascicles in adults [12]. It is important to recognize the rodent sciatic nerve consists of a thin epineurial layer with loose connective tissue in contrast with the more extensive and fibrous human epineurium. This significant structural difference between human and rodent peripheral nerves is important when extrapolating in vivo or in situ experimental observations made in rodents to human peripheral nerves, particularly with reference to nerve injury and local drug delivery (e.g., anesthetics and analgesics).

Identification and Definition of Blood-Nerve Barrier

The importance of maintaining a highly regulated ionic microenvironment to facilitate axonal impulse conduction in peripheral nerves is intuitive and led to the proposal of a blood-nerve barrier (BNB) akin to the blood-brain barrier (BBB). In vivo permeability studies performed in different animal species following intravenous Evans blue albumin and fluoresceinated albumin or dextran administration demonstrated restricted macromolecules within endoneurial microvessel lumens without extravasation into the endoneurium despite diffuse entry into the epineurium (which was in contrast with the diffuse lack of brain parenchymal entry), implying that restrictive interfaces exist in peripheral nerves and nerve roots [13–17].

Subsequent ultrastructural assessment of human peripheral nerves demonstrated that the impermeable endoneurial microvessels consist of endothelial cells that form tight intercellular junctions and share their basement membrane with surrounding pericytes, lack fenestrations, and possess very few 50–100 nm pinocytic vesicles. This was in contrast with permeable epineurial macrovessels that contain a layer of endothelial cells that possess fenestrations and are surrounded by a smooth muscle wall. Furthermore, the innermost concentric perineurial cell layers (i.e., closest to the endoneurium) are connect by intercellular tight junctions, lack fenestrations, and possess pinocytic vesicles (with higher density in the outermost layers). Thus, the internal microenvironment of the endoneurium is deemed to be regulated by tight junction-forming endoneurial endothelial cells and the cell layers of the innermost perineurium [2, 3, 5].

Endoneurial endothelial cells are in direct contact with circulating blood, including hematogenous leukocytes, while perineurial cells are in contact with interstitial fluid from the epineurium and endoneurium. As a consequence, endoneurial endothelial cells form the BNB, while perineurial cells form critical interfaces between the endoneurial and epineurial interstitial fluid compartments which are also important

for maintaining peripheral nerve homeostasis. Since cross-talk between the systemic immune system and peripheral nerves largely depends on hematogenously derived circulating leukocytes, it is important to understand the structural, molecular, and functional characteristics of the human BNB in health in order to elucidate biologically relevant alterations that may occur in disease states such as peripheral nerve autoimmune disorders.

Characteristics of the Human BNB in Health

Basic knowledge of the structural, molecular, and functional characteristics of the human BNB in health and disease is emerging, guided by data from the human BBB and studies performed on peripheral nerve biopsies in situ and primary and immortalized human endoneurial endothelial cells in vitro; however, our knowledge is far from complete. Structurally, human endoneurial endothelial cells that form the BNB possess electron-dense intercellular tight junctions in situ and in vitro (Fig. 2) [3, 7]. In vitro, these tight junctions consist of occludin, members of the claudin family such as claudin-5, as well as cytoplasmic adaptors such as members of the zonula occludens (ZO) family, e.g., ZO-1 and ZO-2 (also known as tight junction proteins 1 and 2, respectively), based on immunocytochemistry of confluent cultures [7, 18–20], while claudin-5 and ZO-1 had been previously demonstrated in situ [21–23]. Data has emerged over the past 15 years on the importance of the

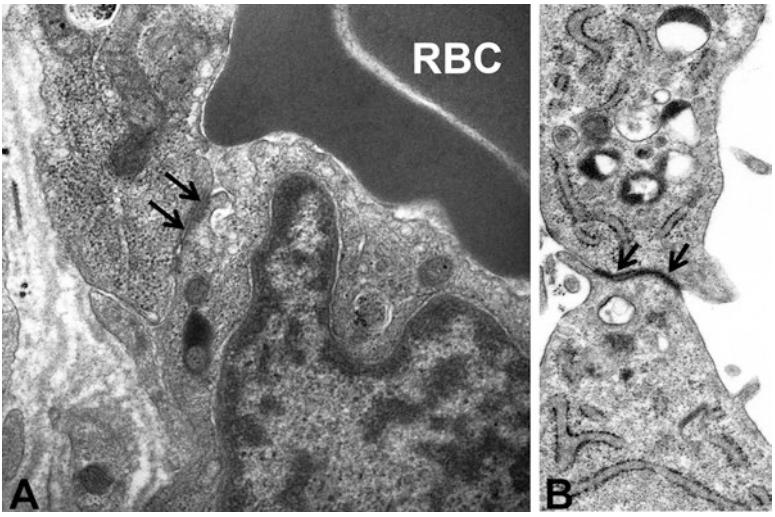

Fig. 2 Digital electron ultramicrographs from an adult sural nerve (**a**) and cultured semipermeable transwell inserts (**b**) showing human endoneurial endothelial cells with electron-dense intercellular tight junctions (black arrows). A red blood cell (RBC) is present in the lumen of the endoneurial microvessel

intercellular junctional complex, consisting of tight, adherens, and gap junctions and their associated adaptor proteins and interacting cytoskeletal components in normal specialized endothelial and epithelial cell function [22, 24–29].

Recent work elucidating the normal adult human BNB transcriptome based on conserved transcripts expressed by early- and late-passage primary human endoneurial endothelial cells and laser-capture microdissected endoneurial microvessels from four histologically normal adult sural nerve biopsies demonstrated expression of 133 intercellular junctional complex molecules (22 tight junction or junction-associated, 45 adherens junction or junction-associated, and 52 cell junction-associated or adaptor molecules), with in situ protein expression of α1 catenin, cadherin-5, cadherin-6, claudin-4, claudin-5, crumbs cell polarity complex component lin-7 homolog A, gap junction protein A1, multiple PDZ domain crumbs cell polarity complex component, protocadherin-1, vezatin, ZO-1, and zyxin demonstrated on endoneurial microvessels by indirect fluorescent immunohistochemistry [22]. This complexity may exist to provide significant molecular redundancy needed to maintain a structurally normal BNB due to its essential homeostatic role in normal peripheral nerve function.

Restrictive intercellular tight junction formation is a critical observation that differentiates endoneurial microvascular endothelial cells from epineurial macrovascular endothelial cells in human peripheral nerves. Endoneurial endothelial cells express receptors for specific mitogens such as glial-derived neurotrophic factor (GDNF, GFRα1), vascular endothelial growth factor (VEGF, VEGFR2), basic fibroblast growth factor (bFGF, FGFR1), transforming growth factor-β (TGF-β, TGFRI/II), and glucocorticoids (GR) [18, 19, 30–32], implying that autocrine or paracrine mitogen secretion by endothelial cells, Schwann cells, pericytes, mast cells, or endoneurial fibroblasts could regulate BNB composition and function in health. Schwann cells, the glial cells of the peripheral nervous system present in the endoneurium, have been shown to secrete GDNF in vitro and in vivo [33, 34], and GDNF has been demonstrated to influence restrictive human BNB characteristics in vitro at low nanomolar concentrations in a dose-dependent manner via RET-tyrosine kinase-mitogen-activated protein kinase (MAPK) signaling and enhance murine BNB restrictive characteristics in vivo following non-transecting nerve injury using a tamoxifen-inducible conditional knockout model [30, 35]. This suggests that GDNF is an essential paracrine regulator of BNB formation that may also have an important role during BNB formation during development and maintenance in health, with some redundancy demonstrated in vitro by other less efficacious mitogens, such as basic fibroblast growth factor.

In addition to the junctional complex, specialized influx and efflux transporters that regulate ionic, water, molecular, nutrient, drug, and xenobiotic entry into or removal from the peripheral nerve endoneurium exist at the human BNB, controlling the endoneurial microenvironment. In vitro, these include alkaline phosphatase, glucose transporter-1 (also known as SLC2A1), monocarboxylate transporter-1 (also known as SLC16A1), creatine transporter (also known as SLC6A8), large amino acid transporter-1 (also known as SLC7A5), γ-glutamyl transpeptidase, and p-glycoprotein (also known as ABCB1) expressed by primary and immortalized

human endoneurial endothelial cells (messenger RNA or protein) [7, 32], with glucose transporter-1 previously demonstrated on human endoneurial microvessels in situ [36].

The human BNB transcriptome demonstrated 509 transporter transcripts, including 196 members of the solute carrier transport family, 76 cation channel, 33 members of the ATP-binding cassette family, 14 zinc transporter, 13 anion channel, 4 solute carrier organic transporter, and 3 aquaporin molecules. ABCA8, ABCB1, AQP1, SLC1A1, SLC2A1, SLC3A2, SLC5A6, SLC16A1, and SLC19A2 were demonstrated on BNB-forming endoneurial endothelial cells in normal human sural nerve biopsies by indirect immunohistochemistry in situ [22]. The extensive repertoire of transcripts that comprise the healthy human BNB cellular components (i.e., cell junction, cell part, extracellular matrix, extracellular region, macromolecular complex, membrane, organelle, and synapse) and their protein classes has been recently published, recognizing that not all transcripts undergo translation to functional protein. Although there are major similarities, structural differences and molecular heterogeneity in the composition of the BNB probably exist between different species [5, 37], limiting the degree of extrapolation feasible between data derived from animal models in vitro and in vivo and the human BNB. Figure 3 depicts a schematic figure summarizing essential structural and molecular components of the human BNB.

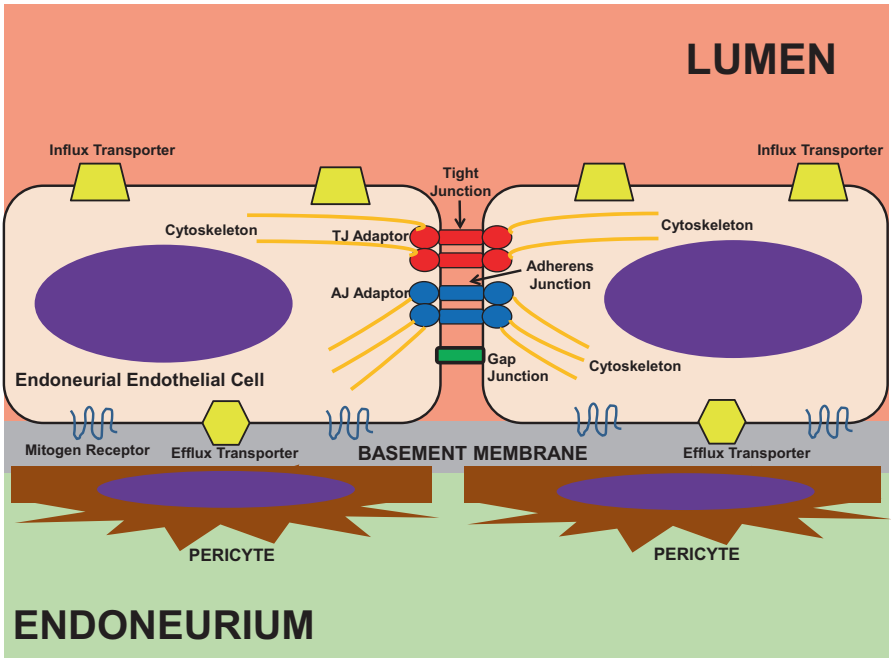

Fig. 3 Schematic figure showing the structural and essential molecular components of the human BNB

Human BNB Physiology

The human BNB, similar to other specialized tight junction-forming microvascular systems such as the BBB, blood-retina barrier, and blood-testis barrier, is expected to possess high transendothelial electrical resistance (TEER), low permeability to solutes and macromolecules, and low transendothelial water flux (hydraulic conductivity). In support of this, comparative animal studies have determined that the BNB is the second most restrictive microvascular tissue barrier in mammals, after the BBB. Unlike the human BBB, supported by the glia limitans (which consists of astrocyte and microglial foot processes), there is no physical support of the BNB by Schwann cells. It has not been conclusively established whether endoneurial microvascular pericytes (that lack intercellular junctions and share a basement membrane with endoneurial endothelial cells) provide trophic support to the human BNB.

The human BNB TEER in vivo is unknown; however, it is expected to be >1500 $\Omega.cm^2$, based on BBB data [38–41]. Similarly, its permeability coefficients and hydraulic conductivity in vivo are also unknown, although some work has been published in other mammalian and nonmammalian species evaluating solute permeability and interstitial fluid flux in peripheral nerves following intravenous electrolyte and tracer injections, followed by timed nerve procurement [17, 42–44]. Human BNB TEER has been measured to be as high as ~180 $\Omega.cm^2$ in confluent cultures by a voltohmmeter applying a direct current across transwell inserts and as high as ~900 Ω when recorded in specialized culture wells with gold electrodes using a fixed alternating current at 4000 Hz via electrical cell impedance sensing [7, 20, 32, 35].

Solute permeability to sodium fluorescein (molecular mass 376 Da) and 70 KDa fluoresceinated dextran (dextran-70-FITC) across primary and immortalized human endoneurial endothelial cells is typically <5% of input at 15 minutes using static transwell systems in vitro, with higher values (~3–15-fold) seen with sodium fluorescein when directly compared to dextran-70-FITC using the same batch of endothelial cells in concurrent experiments [7, 20, 32]. Human BNB transendothelial water flux under the influence of hydrostatic pressure, otherwise known as hydraulic conductivity, has been measured in vitro (~2.0×10^{-7} cm/s/cm H_2O) using a customized transwell diffusion chamber-bubble track system [45]. Consistent with prior observations, the human BNB was the second most restrictive human or mammalian microvascular endothelial cell type after the BBB in terms of water flux [17, 43–45].

Hematogenous leukocyte trafficking across microvascular endothelium in vivo (based on intravital microscopy) or in vitro under flow is a sequential coordinated process that involves leukocyte attraction from circulating blood to the endothelial cell luminal surface (mediated by specific chemokines bound to glycosaminoglycans on the endothelium and chemokine receptors expressed by leukocytes), rolling (mediated by selectins expressed on the endothelium and their glycoproteins or

carbohydrate moiety counterligands expressed on leukocytes), leukocyte arrest and haptotaxis on the endothelial cell surface (mediated by chemokines and chemokine receptors), integrin activation and firm adhesion (via leukocyte integrin binding to endothelial cell adhesion molecules) that induces a conformation change in leukocyte shape from round to flat with formation of pseudopodia, and leukocyte transmigration via the paracellular (i.e., through intercellular junctions) or transcellular (i.e., through endothelial cells) routes followed by basement membrane disruption at the abluminal surface (via secretion of specific matrix metalloproteases) required for complete passage into tissues [46–52]. There is in vitro data using a flow-dependent leukocyte-BNB trafficking model providing evidence that this sequential process (also known as the multistep paradigm of leukocyte trafficking) occurs in peripheral nerves [53–55].

The presence of rare endoneurial macrophages, mast cells, and T lymphocytes in normal human peripheral nerve endoneurium implies some physiological cross talk between the systemic immune compartment and peripheral nerves at the BNB. The human BNB transcriptome supports the expression of human leukocyte antigen (or major histocompatibility complex) class I and II molecules in normal healthy endoneurial microvessels in situ [22], suggesting that the human BNB may directly participate in innate and adaptive immune responses in peripheral nerves (Tables 1 and 2). Furthermore, specific chemokine transcripts were also expressed by the normal healthy adult BNB based on this transcriptome. These include CCL2, CCL14, CCL28, CXCL3, CXCL12, CXCL16, and CX3CL1 [22].

These chemokines could facilitate the interaction of hematogenous monocytes (CCL2, CCL14, CX3CL1), T lymphocytes (CCL2, CX3CL1), natural killer T cells (CXCL16), and neutrophils (CXCL3) with endoneurial microvascular cells during normal immunosurveillance or part of an early immune response to injury, while CXCL12 and CCL28 may be important in endothelial cell migration and vascular repair. A more complex array of chemokines including CXCL9, CXCL10, and CXCL11 that facilitate CXCR3+ CD4+ T-helper 1 lymphocyte migration were expressed by the basal human BNB in vitro [22, 55], implying some degree of endothelial cell activation in vitro or dysregulated chemokine expression in situ.

Endoneurial microvascular endothelial cells also express selectins (e.g., P-selectin, E-selectin) and cell adhesion molecules (e.g., intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), fibronectin Type III connecting segment) under basal conditions that were upregulated or underwent alternative splicing following stimulus with physiological concentrations of pro-inflammatory cytokines tissue necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) in vitro (Fig. 4) [55]. The constitutive expression of these cell adhesion molecules known to facilitate leukocyte adhesion and transmigration supports the notion the endoneurial microvessels participate in cross talk between subsets of circulating leukocytes that are components of systemic immune compartment and peripheral nerves.

Table 1 List of known molecules involved in the innate immune response expressed by the human BNB transcriptome in health that may be relevant in physiological cross-talk between the systemic immune compartment and peripheral nerve endoneurium and in peripheral nerve autoimmune disorders

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 9066|UniProtKB = P16885	ENSG00000197943	1-Phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2; PLCG2; ortholog	1-PHOSPHATIDYLINOSITOL 4,5-BISPHOSPHATE PHOSPHODIESTERASE GAMMA-2 (PTHR10336:SF25)	Calcium-binding protein(PC00060); guanyl-nucleotide exchange factor(PC00113); phospholipase(PC00186); signaling molecule(PC00207)
HUMAN|HGNC = 9553|UniProtKB = P62333	ENSG00000100519	26S protease regulatory subunit 10B; PSMC6; ortholog	26S PROTEASE REGULATORY SUBUNIT 10B (PTHR23073:SF31)	Hydrolase(PC00121)
HUMAN|HGNC = 9547|UniProtKB = P62191	ENSG00000100764	26S protease regulatory subunit 4; PSMC1; ortholog	26S PROTEASE REGULATORY SUBUNIT 4 (PTHR23073:SF24)	Hydrolase(PC00121)
HUMAN|HGNC = 9549|UniProtKB = P17980	ENSG00000165916	26S protease regulatory subunit 6A; PSMC3; ortholog	26S PROTEASE REGULATORY SUBUNIT 6A (PTHR23073:SF7)	Hydrolase(PC00121)
HUMAN|HGNC = 9551|UniProtKB = P43686	ENSG00000013275	26S protease regulatory subunit 6B; PSMC4; ortholog	26S PROTEASE REGULATORY SUBUNIT 6B (PTHR23073:SF8)	Hydrolase(PC00121)
HUMAN|HGNC = 9548|UniProtKB = P35998	ENSG00000161057	26S protease regulatory subunit 7; PSMC2; ortholog	26S PROTEASE REGULATORY SUBUNIT 7 (PTHR23073:SF13)	Hydrolase(PC00121)
HUMAN|HGNC = 9552|UniProtKB = P62195	ENSG00000087191	26S protease regulatory subunit 8; PSMC5; ortholog	26S PROTEASE REGULATORY SUBUNIT 8 (PTHR23073:SF12)	Hydrolase(PC00121)

HUMAN|HGNC = 9554|UniProtKB = Q99460	ENSG00000173692	26S proteasome non-ATPase regulatory subunit 1; PSMD1; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 1 (PTHR10943:SF2)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9555|UniProtKB = O75832	ENSG00000101843	26S proteasome non-ATPase regulatory subunit 10; PSMD10; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 10 (PTHR24126:SF24)	
HUMAN|HGNC = 9556|UniProtKB = O00231	ENSG00000108671	26S proteasome non-ATPase regulatory subunit 11; PSMD11; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 11 (PTHR10678:SF2)	
HUMAN|HGNC = 9557|UniProtKB = O00232	ENSG00000197170	26S proteasome non-ATPase regulatory subunit 12; PSMD12; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 12 (PTHR10855:SF1)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9558|UniProtKB = Q9UNM6	ENSG00000185627	26S proteasome non-ATPase regulatory subunit 13; PSMD13; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 13 (PTHR10539:SF0)	Enzyme modulator(PC00095)
HUMAN|HGNC = 16889|UniProtKB = O00487	ENSG00000115233	26S proteasome non-ATPase regulatory subunit 14; PSMD14; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 14 (PTHR10410:SF5)	Metalloprotease(PC00153); transcription factor(PC00218)
HUMAN|HGNC = 9559|UniProtKB = Q13200	ENSG00000175166	26S proteasome non-ATPase regulatory subunit 2; PSMD2; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 2 (PTHR10943:SF1)	Enzyme modulator(PC00095)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 9560|UniProtKB = O43242	ENSG00000108344	26S proteasome non-ATPase regulatory subunit 3; PSMD3; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 3 (PTHR10758:SF2)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9561|UniProtKB = P55036	ENSG00000159352	26S proteasome non-ATPase regulatory subunit 4; PSMD4; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 4 (PTHR10223:SF0)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9563|UniProtKB = Q16401	ENSG00000095261	26S proteasome non-ATPase regulatory subunit 5; PSMD5; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 5 (PTHR13554:SF10)	
HUMAN|HGNC = 9564|UniProtKB = Q15008	ENSG00000163636	26S proteasome non-ATPase regulatory subunit 6; PSMD6; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 6 (PTHR14145:SF1)	
HUMAN|HGNC = 9565|UniProtKB = P51665	ENSG00000103035	26S proteasome non-ATPase regulatory subunit 7; PSMD7; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 7 (PTHR10540:SF7)	Metalloprotease(PC00153)
HUMAN|HGNC = 9566|UniProtKB = P48556	ENSG00000099341	26S proteasome non-ATPase regulatory subunit 8; PSMD8; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 8 (PTHR12387:SF0)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9567|UniProtKB = O00233	ENSG00000110801	26S proteasome non-ATPase regulatory subunit 9; PSMD9; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 9 (PTHR12651:SF1)	Enzyme modulator(PC00095)

HUMAN|HGNC = 8816|UniProtKB = O15530	ENSG00000140992	3-Phosphoinositide-dependent protein kinase 1; PDPK1; ortholog	3-PHOSPHOINOSITIDE-DEPENDENT PROTEIN KINASE 1-RELATED (PTHR24356:SF163)	Annexin(PC00050); calmodulin(PC00061); non-receptor serine/threonine protein kinase(PC00167); transfer/carrier protein(PC00219)
HUMAN|HGNC = 5261|UniProtKB = P10809	ENSG00000144381	60 kDa heat shock protein, mitochondrial; HSPD1; ortholog	60 KDA HEAT SHOCK PROTEIN, MITOCHONDRIAL (PTHR45633:SF3)	
HUMAN|HGNC = 23575|UniProtKB = O75179	ENSG00000132466	Ankyrin repeat domain-containing protein 17; ANKRD17; ortholog	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 17 (PTHR23206:SF1)	
HUMAN|HGNC = 16608|UniProtKB = Q9ULZ3	ENSG00000103490	Apoptosis-associated speck-like protein containing a CARD; PYCARD; ortholog	APOPTOSIS-ASSOCIATED SPECK-LIKE PROTEIN CONTAINING A CARD (PTHR10454:SF203)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 590|UniProtKB = Q13490	ENSG00000110330	Baculoviral IAP repeat-containing protein 2; BIRC2; ortholog	BACULOVIRAL IAP REPEAT-CONTAINING PROTEIN 2 (PTHR10044:SF79)	Protease inhibitor(PC00191)
HUMAN|HGNC = 591|UniProtKB = Q13489	ENSG00000023445	Baculoviral IAP repeat-containing protein 3; BIRC3; ortholog	BACULOVIRAL IAP REPEAT-CONTAINING PROTEIN 3 (PTHR10044:SF99)	Protease inhibitor(PC00191)
HUMAN|HGNC = 712|UniProtKB = P32121	ENSG00000141480	Beta-arrestin-2; ARRB2; ortholog	BETA-ARRESTIN-2 (PTHR11792:SF20)	Enzyme modulator(PC00095)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 29938|UniProtKB = Q8WUQ7	ENSG00000105298	Cactin; CACTIN; ortholog	CACTIN (PTHR21737:SF6)	
HUMAN|HGNC = 9380|UniProtKB = P17612	ENSG00000072062	cAMP-dependent protein kinase catalytic subunit alpha; PRKACA; ortholog	CAMP-DEPENDENT PROTEIN KINASE CATALYTIC SUBUNIT ALPHA (PTHR24353:SF82)	
HUMAN|HGNC = 9381|UniProtKB = P22694	ENSG00000142875	cAMP-dependent protein kinase catalytic subunit beta; PRKACB; ortholog	CAMP-DEPENDENT PROTEIN KINASE CATALYTIC SUBUNIT BETA (PTHR24353:SF116)	
HUMAN|HGNC = 16393|UniProtKB = Q9BXL7	ENSG00000198286	Caspase recruitment domain-containing protein 11; CARD11; ortholog	CASPASE RECRUITMENT DOMAIN-CONTAINING PROTEIN 11 (PTHR14559:SF4)	
HUMAN|HGNC = 16391|UniProtKB = Q9H257	ENSG00000187796	Caspase recruitment domain-containing protein 9; CARD9; ortholog	CASPASE RECRUITMENT DOMAIN-CONTAINING PROTEIN 9 (PTHR14559:SF3)	
HUMAN|HGNC = 1509|UniProtKB = Q14790	ENSG00000064012	Caspase-8; CASP8; ortholog	CASPASE-8 (PTHR10454:SF162)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 2527|UniProtKB = P07858	ENSG00000164733	Cathepsin B; CTSB; ortholog	CATHEPSIN B (PTHR12411:SF16)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 2536|UniProtKB = P43235	ENSG00000143387	Cathepsin K; CTSK; ortholog	CATHEPSIN K (PTHR12411:SF55)	Cysteine protease(PC00081); protease inhibitor(PC00191)

HUMAN|HGNC = 2537|UniProtKB = P07711	ENSG00000135047	Cathepsin L1; CTSL; ortholog	CATHEPSIN L1 (PTHR12411:SF411)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 2545|UniProtKB = P25774	ENSG00000163131	Cathepsin S; CTSS; ortholog	CATHEPSIN S (PTHR12411:SF525)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 1527|UniProtKB = Q03135	ENSG00000105974	Caveolin-1; CAV1; ortholog	CAVEOLIN-1 (PTHR10844:SF18)	G-protein modulator(PC00022); membrane traffic protein(PC00150); structural protein(PC00211); transmembrane receptor regulatory/adaptor protein(PC00226)
HUMAN|HGNC = 16016|UniProtKB = Q5KU26	ENSG00000158270	Collectin-12; COLEC12; ortholog	COLLECTIN-12 (PTHR24023:SF910)	
HUMAN|HGNC = 1243|UniProtKB = Q07021	ENSG00000108561	Complement component 1 Q subcomponent-binding protein, mitochondrial; C1QBP; ortholog	COMPLEMENT COMPONENT 1 Q SUBCOMPONENT-BINDING PROTEIN, MITOCHONDRIAL (PTHR10826:SF1)	
HUMAN|HGNC = 2348|UniProtKB = Q92793	ENSG00000005339	CREB-binding protein; CREBBP; ortholog	CREB-BINDING PROTEIN (PTHR13808:SF1)	Acetyltransferase(PC00038); chromatin/chromatin-binding protein(PC00077); transcription cofactor(PC00217)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 13257|UniProtKB = Q9UMR7	ENSG00000111729	C-type lectin domain family 4 member A; CLEC4A; ortholog	C-TYPE LECTIN DOMAIN FAMILY 4 MEMBER A (PTHR22802:SF357)	Cell adhesion molecule(PC00069); immunoglobulin receptor superfamily(PC00124)
HUMAN|HGNC = 2551|UniProtKB = Q13616	ENSG00000055130	Cullin-1; CUL1; ortholog	CULLIN-1 (PTHR11932:SF81)	Ubiquitin-protein ligase(PC00234)
HUMAN|HGNC = 21367|UniProtKB = Q8N884	ENSG00000164430	Cyclic GMP-AMP synthase; MB21D1; ortholog	CYCLIC GMP-AMP SYNTHASE (PTHR10656:SF35)	
HUMAN|HGNC = 2577|UniProtKB = P13498	ENSG00000051523	Cytochrome b-245 light chain; CYBA; ortholog	CYTOCHROME B-245 LIGHT CHAIN (PTHR15168:SF0)	
HUMAN|HGNC = 17294|UniProtKB = Q5VWQ8	ENSG00000136848	Disabled homolog 2-interacting protein; DAB2IP; ortholog	DISABLED HOMOLOG 2-INTERACTING PROTEIN (PTHR10194:SF26)	G-protein modulator(PC00022)
HUMAN|HGNC = 215|UniProtKB = P78325	ENSG00000151651	Disintegrin and metalloproteinase domain-containing protein 8; ADAM8; ortholog	DISINTEGRIN AND METALLOPROTEINASE DOMAIN-CONTAINING PROTEIN 8 (PTHR11905:SF20)	Metalloprotease(PC00153)
HUMAN|HGNC = 6846|UniProtKB = P52564	ENSG00000108984	Dual specificity mitogen-activated protein kinase kinase 6; MAP2K6; ortholog	DUAL SPECIFICITY MITOGEN-ACTIVATED PROTEIN KINASE KINASE 6 (PTHR24361:SF40)	

HUMAN|HGNC = 13890|UniProtKB = Q96J02	ENSG00000078747	E3 ubiquitin-protein ligase Itchy homolog; ITCH; ortholog	E3 UBIQUITIN-PROTEIN LIGASE ITCHY HOMOLOG (PTHR11254:SF66)	Ubiquitin-protein ligase(PC00234)
HUMAN|HGNC = 8827|UniProtKB = Q96FA3	ENSG00000197329	E3 ubiquitin-protein ligase pellino homolog 1; PELI1; ortholog	E3 UBIQUITIN-PROTEIN LIGASE PELLINO HOMOLOG 1 (PTHR12098:SF4)	
HUMAN|HGNC = 592|UniProtKB = P98170	ENSG00000101966	E3 ubiquitin-protein ligase XIAP; XIAP; ortholog	E3 UBIQUITIN-PROTEIN LIGASE XIAP (PTHR10044:SF115)	Protease inhibitor(PC00191)
HUMAN|HGNC = 12028|UniProtKB = P14625	ENSG00000166598	Endoplasmin; HSP90B1; ortholog	ENDOPLASMIN (PTHR11528:SF54)	Hsp90 family chaperone(PC00028)
HUMAN|HGNC = 15842|UniProtKB = Q96RT1	ENSG00000112851	Erbin; ERBIN; ortholog	ERBIN (PTHR45752:SF47)	
HUMAN|HGNC = 3573|UniProtKB = Q13158	ENSG00000168040	FAS-associated death domain protein; FADD; ortholog	FAS-ASSOCIATED DEATH DOMAIN PROTEIN (PTHR15077:SF9)	
HUMAN|HGNC = 13607|UniProtKB = Q9UKB1	ENSG00000072803	F-box/WD repeat-containing protein 11; FBXW11; ortholog	F-BOX/WD REPEAT-CONTAINING PROTEIN 11 (PTHR44129:SF4)	
HUMAN|HGNC = 1144|UniProtKB = Q9Y297	ENSG00000166167	F-box/WD repeat-containing protein 1A; BTRC; ortholog	F-BOX/WD REPEAT-CONTAINING PROTEIN 1A (PTHR19854:SF16)	G-protein-coupled receptor(PC00021)
HUMAN|HGNC = 3757|UniProtKB = O75955	ENSG00000137312	Flotillin-1; FLOT1; ortholog	FLOTILLIN-1 (PTHR13806:SF16)	
HUMAN|HGNC = 3758|UniProtKB = Q14254	ENSG00000132589	Flotillin-2;FLOT2;ortholog	FLOTILLIN-2 (PTHR13806:SF20)	

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Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 6570|UniProtKB = O00182	ENSG00000168961	Galectin-9; LGALS9; ortholog	GALECTIN-9 (PTHR11346:SF80)	Cell adhesion molecule(PC00069); signaling molecule(PC00207)
HUMAN|HGNC = 5395|UniProtKB = Q16666	ENSG00000163565	Gamma-interferon-inducible protein 16; IFI16; ortholog	GAMMA-INTERFERON-INDUCIBLE PROTEIN 16 (PTHR12200:SF5)	Transcription factor(PC00218)
HUMAN|HGNC = 5173|UniProtKB = P01112	ENSG00000174775	GTPase HRas; HRAS; ortholog	GTPASE HRAS (PTHR24070:SF385)	Small GTPase(PC00208)
HUMAN|HGNC = 6407|UniProtKB = P01116	ENSG00000133703	GTPase KRas; KRAS; ortholog	GTPASE KRAS (PTHR24070:SF388)	Small GTPase(PC00208)
HUMAN|HGNC = 7989|UniProtKB = P01111	ENSG00000213281	GTPase NRas; NRAS; ortholog	GTPASE NRAS (PTHR24070:SF189)	Small GTPase(PC00208)
HUMAN|HGNC = 5232|UniProtKB = P0DMV8	ENSG00000204389	Heat shock 70 kDa protein 1A; HSPA1A; ortholog	HEAT SHOCK 70 KDA PROTEIN 1A-RELATED (PTHR19375:SF223)	
HUMAN|HGNC = 5233|UniProtKB = P0DMV9	ENSG00000204388	Heat shock 70 kDa protein 1B; HSPA1B; ortholog	HEAT SHOCK 70 KDA PROTEIN 1A-RELATED (PTHR19375:SF223)	
HUMAN|HGNC = 3611|UniProtKB = P30273	ENSG00000158869	High-affinity immunoglobulin epsilon receptor subunit gamma; FCER1G; ortholog	HIGH AFFINITY IMMUNOGLOBULIN EPSILON RECEPTOR SUBUNIT GAMMA (PTHR16803:SF0)	

HUMAN|HGNC = 4983|UniProtKB = P09429	ENSG00000189403	High-mobility group protein B1; HMGB1; ortholog	HIGH MOBILITY GROUP PROTEIN B1 (PTHR13711:SF164)	HMG box transcription factor(PC00024); chromatin/chromatin-binding protein(PC00077); signaling molecule(PC00207)
HUMAN|HGNC = 3373|UniProtKB = Q09472	ENSG00000100393	Histone acetyltransferase p300; EP300; ortholog	HISTONE ACETYLTRANSFERASE P300 (PTHR13808:SF23)	Acetyltransferase(PC00038); chromatin/chromatin-binding protein(PC00077); transcription cofactor(PC00217)
HUMAN|HGNC = 1974|UniProtKB = O15111	ENSG00000213341	Inhibitor of nuclear factor kappa-B kinase subunit alpha; CHUK; ortholog	INHIBITOR OF NUCLEAR FACTOR KAPPA-B KINASE SUBUNIT ALPHA (PTHR22969:SF13)	Non-receptor serine/threonine protein kinase(PC00167)
HUMAN|HGNC = 5960|UniProtKB = O14920	ENSG00000104365	Inhibitor of nuclear factor kappa-B kinase subunit beta; IKBKB; ortholog	INHIBITOR OF NUCLEAR FACTOR KAPPA-B KINASE SUBUNIT BETA (PTHR22969:SF7)	Non-receptor serine/threonine protein kinase(PC00167)
HUMAN|HGNC = 6155|UniProtKB = P05107	ENSG00000160255	Integrin beta-2; ITGB2; ortholog	INTEGRIN BETA-2 (PTHR10082:SF15)	Cell adhesion molecule(PC00069); extracellular matrix glycoprotein(PC00100); receptor(PC00197)
HUMAN|HGNC = 5346|UniProtKB = P32942	ENSG00000076662	Intercellular adhesion molecule 3; ICAM3; ortholog	INTERCELLULAR ADHESION MOLECULE 3 (PTHR13771:SF11)	

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 6116|UniProtKB = P10914	ENSG00000125347	Interferon regulatory factor 1; IRF1; ortholog	INTERFERON REGULATORY FACTOR 1 (PTHR11949:SF3)	Nucleic acid binding(PC00171); winged helix/forkhead transcription factor(PC00246)
HUMAN|HGNC = 6118|UniProtKB = Q14653	ENSG00000126456	Interferon regulatory factor 3; IRF3; ortholog	INTERFERON REGULATORY FACTOR 3 (PTHR11949:SF1)	Nucleic acid binding(PC00171); winged helix/forkhead transcription factor(PC00246)
HUMAN|HGNC = 6122|UniProtKB = Q92985	ENSG00000185507	Interferon regulatory factor 7; IRF7; ortholog	INTERFERON REGULATORY FACTOR 7 (PTHR11949:SF2)	Nucleic acid binding(PC00171); winged helix/forkhead transcription factor(PC00246)
HUMAN|HGNC = 18873|UniProtKB = Q9BYX4	ENSG00000115267	Interferon-induced helicase C domain-containing protein 1; IFIH1; ortholog	INTERFERON-INDUCED HELICASE C DOMAIN-CONTAINING PROTEIN 1 (PTHR14074:SF14)	
HUMAN|HGNC = 6112|UniProtKB = P51617	ENSG00000184216	Interleukin-1 receptor-associated kinase 1; IRAK1; ortholog	INTERLEUKIN-1 RECEPTOR-ASSOCIATED KINASE 1 (PTHR24419:SF1)	
HUMAN|HGNC = 17020|UniProtKB = Q9Y616	ENSG00000090376	Interleukin-1 receptor-associated kinase 3; IRAK3; ortholog	INTERLEUKIN-1 RECEPTOR-ASSOCIATED KINASE 3 (PTHR24419:SF7)	

HUMAN|HGNC = 17967|UniProtKB = Q9NWZ3	ENSG00000198001	Interleukin-1 receptor-associated kinase 4; IRAK4; ortholog	INTERLEUKIN-1 RECEPTOR-ASSOCIATED KINASE 4 (PTHR24419:SF22)	
HUMAN|HGNC = 9472|UniProtKB = Q99538	ENSG00000100600	Legumain; LGMN; ortholog	LEGUMAIN (PTHR12000:SF3)	Cysteine protease(PC00081)
HUMAN|HGNC = 13299|UniProtKB = Q9BXB1	ENSG00000205213	Leucine-rich repeat-containing G-protein-coupled receptor 4; LGR4; ortholog	LEUCINE-RICH REPEAT-CONTAINING G-PROTEIN COUPLED RECEPTOR 4 (PTHR24372:SF67)	Extracellular matrix protein(PC00102); receptor(PC00197)
HUMAN|HGNC = 6887|UniProtKB = P49137	ENSG00000162889	MAP kinase-activated protein kinase 2; MAPKAPK2; ortholog	MAP KINASE-ACTIVATED PROTEIN KINASE 2 (PTHR24349:SF63)	Non-motor microtubule binding protein(PC00166); non-receptor serine/threonine protein kinase(PC00167)
HUMAN|HGNC = 6888|UniProtKB = Q16644	ENSG00000114738	MAP kinase-activated protein kinase 3; MAPKAPK3; ortholog	MAP KINASE-ACTIVATED PROTEIN KINASE 3 (PTHR24349:SF64)	Non-motor microtubule binding protein(PC00166); non-receptor serine/threonine protein kinase(PC00167)
HUMAN|HGNC = 29233|UniProtKB = Q7Z434	ENSG00000088888	Mitochondrial antiviral-signaling protein; MAVS; ortholog	MITOCHONDRIAL ANTIVIRAL-SIGNALING PROTEIN (PTHR21446:SF6)	
HUMAN|HGNC = 6848|UniProtKB = Q13233	ENSG00000095015	Mitogen-activated protein kinase kinase kinase 1; MAP3K1; ortholog	MITOGEN-ACTIVATED PROTEIN KINASE KINASE KINASE 1 (PTHR24361:SF414)	

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 6859|UniProtKB = O43318	ENSG00000135341	Mitogen-activated protein kinase kinase kinase 7; MAP3K7; ortholog	MITOGEN-ACTIVATED PROTEIN KINASE KINASE KINASE 7 (PTHR46716:SF1)	
HUMAN|HGNC = 1628|UniProtKB = P08571	ENSG00000170458	Monocyte differentiation antigen CD14; CD14; ortholog	MONOCYTE DIFFERENTIATION ANTIGEN CD14 (PTHR10630:SF3)	
HUMAN|HGNC = 6819|UniProtKB = Q9UDY8	ENSG00000172175	Mucosa-associated lymphoid tissue lymphoma translocation protein 1; MALT1; ortholog	MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA TRANSLOCATION PROTEIN 1 (PTHR22576:SF29)	Cysteine protease(PC00081)
HUMAN|HGNC = 7562|UniProtKB = Q99836	ENSG00000172936	Myeloid differentiation primary response protein MyD88; MYD88; ortholog	MYELOID DIFFERENTIATION PRIMARY RESPONSE PROTEIN MYD88 (PTHR15079:SF3)	
HUMAN|HGNC = 5961|UniProtKB = Q9Y6K9	ENSG00000269335	NF-kappa-B essential modulator; IKBKG; ortholog	NF-KAPPA-B ESSENTIAL MODULATOR (PTHR31553:SF3)	
HUMAN|HGNC = 7797|UniProtKB = P25963	ENSG00000100906	NF-kappa-B inhibitor alpha; NFKBIA; ortholog	NF-KAPPA-B INHIBITOR ALPHA (PTHR46680:SF1)	

HUMAN|HGNC = 7800|UniProtKB = Q9UBC1	ENSG00000204498	NF-kappa-B inhibitor-like protein 1; NFKBIL1; ortholog	NF-KAPPA-B INHIBITOR-LIKE PROTEIN 1 (PTHR15263:SF1)	
HUMAN|HGNC = 29890|UniProtKB = Q86UT6	ENSG00000160703	NLR family member X1; NLRX1; ortholog	NLR FAMILY MEMBER X1 (PTHR24106:SF152)	Nucleic acid binding(PC00171); serine protease(PC00203); transcription cofactor(PC00217)
HUMAN|HGNC = 7794|UniProtKB = P19838	ENSG00000109320	Nuclear factor NF-kappa-B p105 subunit; NFKB1; ortholog	NUCLEAR FACTOR NF-KAPPA-B P105 SUBUNIT (PTHR24169:SF9)	
HUMAN|HGNC = 7962|UniProtKB = P20393	ENSG00000126368	Nuclear receptor subfamily 1 group D member 1; NR1D1; ortholog	NUCLEAR RECEPTOR SUBFAMILY 1 GROUP D MEMBER 1 (PTHR24082:SF113)	C4 zinc finger nuclear receptor(PC00169); nucleic acid binding(PC00171); receptor(PC00197)
HUMAN|HGNC = 16390|UniProtKB = Q9Y239	ENSG00000106100	Nucleotide-binding oligomerization domain-containing protein 1; NOD1; ortholog	NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN-CONTAINING PROTEIN 1 (PTHR24106:SF18)	Nucleic acid binding(PC00171); serine protease(PC00203); transcription cofactor(PC00217)
HUMAN|HGNC = 5331|UniProtKB = Q9HC29	ENSG00000167207	Nucleotide-binding oligomerization domain-containing protein 2; NOD2; ortholog	NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN-CONTAINING PROTEIN 2 (PTHR24106:SF64)	Nucleic acid binding(PC00171); serine protease(PC00203); transcription cofactor(PC00217)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 7966|UniProtKB = Q13133	ENSG00000025434	Oxysterols receptor LXR-alpha; NR1H3; ortholog	OXYSTEROLS RECEPTOR LXR-ALPHA (PTHR24082:SF259)	C4 zinc finger nuclear receptor(PC00169); nucleic acid binding(PC00171); receptor(PC00197)
HUMAN|HGNC = 19353|UniProtKB = Q96ST3	ENSG00000169375	Paired amphipathic helix protein Sin3a; SIN3A; ortholog	PAIRED AMPHIPATHIC HELIX PROTEIN SIN3A (PTHR12346:SF2)	Chromatin/chromatin-binding protein(PC00077); deacetylase(PC00087); transcription factor(PC00218)
HUMAN|HGNC = 8974|UniProtKB = Q8NEB9	ENSG00000078142	Phosphatidylinositol 3-kinase catalytic subunit type 3; PIK3C3; ortholog	PHOSPHATIDYLINOSITOL 3-KINASE CATALYTIC SUBUNIT TYPE 3 (PTHR10048:SF7)	Kinase(PC00137)
HUMAN|HGNC = 8982|UniProtKB = Q99570	ENSG00000196455	Phosphoinositide 3-kinase regulatory subunit 4; PIK3R4; ortholog	PHOSPHOINOSITIDE 3-KINASE REGULATORY SUBUNIT 4 (PTHR17583:SF0)	
HUMAN|HGNC = 1663|UniProtKB = P16671	ENSG00000135218	Platelet glycoprotein 4; CD36; ortholog	PLATELET GLYCOPROTEIN 4 (PTHR11923:SF12)	Receptor(PC00197)
HUMAN|HGNC = 12463|UniProtKB = P0CG47	ENSG00000170315	Polyubiquitin-B; UBB; ortholog	POLYUBIQUITIN-B (PTHR10666:SF165)	Ribosomal protein(PC00202)
HUMAN|HGNC = 12468|UniProtKB = P0CG48	ENSG00000150991	Polyubiquitin-C; UBC; ortholog	POLYUBIQUITIN-C (PTHR10666:SF277)	Ribosomal protein(PC00202)

HUMAN|HGNC = 19102|UniProtKB = O95786	ENSG00000107201	Probable ATP-dependent RNA helicase DDX58; DDX58; ortholog	ATP-DEPENDENT RNA HELICASE DDX58-RELATED (PTHR14074:SF31)	
HUMAN|HGNC = 25942|UniProtKB = Q8IY21	ENSG00000137628	Probable ATP-dependent RNA helicase DDX60; DDX60; ortholog	ATP-DEPENDENT RNA HELICASE DDX60-RELATED (PTHR44533:SF3)	
HUMAN|HGNC = 29517|UniProtKB = Q96C10	ENSG00000108771	Probable ATP-dependent RNA helicase DHX58; DHX58; ortholog	ATP-DEPENDENT RNA HELICASE DHX58-RELATED (PTHR14074:SF7)	
HUMAN|HGNC = 9568|UniProtKB = Q06323	ENSG00000092010	Proteasome activator complex subunit 1; PSME1; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 1 (PTHR10660:SF5)	
HUMAN|HGNC = 9569|UniProtKB = Q9UL46	ENSG00000100911	Proteasome activator complex subunit 2; PSME2; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 2 (PTHR10660:SF6)	
HUMAN|HGNC = 9570|UniProtKB = P61289	ENSG00000131467	Proteasome activator complex subunit 3; PSME3; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 3 (PTHR10660:SF4)	
HUMAN|HGNC = 20635|UniProtKB = Q14997	ENSG00000068878	Proteasome activator complex subunit 4; PSME4; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 4 (PTHR32170:SF3)	
HUMAN|HGNC = 9571|UniProtKB = Q92530	ENSG00000125818	Proteasome inhibitor PI31 subunit; PSMF1; ortholog	PROTEASOME INHIBITOR PI31 SUBUNIT (PTHR13266:SF1)	Protease inhibitor(PC00191)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 9530|UniProtKB = P25786	ENSG00000129084	Proteasome subunit alpha type-1; PSMA1; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-RELATED (PTHR11599:SF12)	Protease(PC00190)
HUMAN|HGNC = 9531|UniProtKB = P25787	ENSG00000106588	Proteasome subunit alpha type-2; PSMA2; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-2 (PTHR11599:SF16)	Protease(PC00190)
HUMAN|HGNC = 9532|UniProtKB = P25788	ENSG00000100567	Proteasome subunit alpha type-3; PSMA3; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-3 (PTHR11599:SF10)	Protease(PC00190)
HUMAN|HGNC = 9533|UniProtKB = P25789	ENSG00000041357	Proteasome subunit alpha type-4; PSMA4; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-4 (PTHR11599:SF13)	Protease(PC00190)
HUMAN|HGNC = 9534|UniProtKB = P28066	ENSG00000143106	Proteasome subunit alpha type-5; PSMA5; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-5 (PTHR11599:SF14)	Protease(PC00190)
HUMAN|HGNC = 9535|UniProtKB = P60900	ENSG00000100902	Proteasome subunit alpha type-6; PSMA6; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-6 (PTHR11599:SF11)	Protease(PC00190)
HUMAN|HGNC = 9536|UniProtKB = O14818	ENSG00000101182	Proteasome subunit alpha type-7; PSMA7; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-7 (PTHR11599:SF40)	Protease(PC00190)
HUMAN|HGNC = 9537|UniProtKB = P20618	ENSG00000008018	Proteasome subunit beta type-1; PSMB1; ortholog	PROTEASOME SUBUNIT BETA TYPE-1 (PTHR11599:SF59)	Protease(PC00190)

HUMAN|HGNC = 9538|UniProtKB = P40306	ENSG00000205220	Proteasome subunit beta type-10; PSMB10; ortholog	PROTEASOME SUBUNIT BETA TYPE-10 (PTHR11599:SF41)	Protease(PC00190)
HUMAN|HGNC = 9539|UniProtKB = P49721	ENSG00000126067	Proteasome subunit beta type-2; PSMB2; ortholog	PROTEASOME SUBUNIT BETA TYPE-2 (PTHR11599:SF6)	Protease(PC00190)
HUMAN|HGNC = 9540|UniProtKB = P49720	ENSG00000277791	Proteasome subunit beta type-3; PSMB3; ortholog	PROTEASOME SUBUNIT BETA TYPE-3 (PTHR11599:SF62)	Protease(PC00190)
HUMAN|HGNC = 9541|UniProtKB = P28070	ENSG00000159377	Proteasome subunit beta type-4; PSMB4; ortholog	PROTEASOME SUBUNIT BETA TYPE-4 (PTHR11599:SF5)	Protease(PC00190)
HUMAN|HGNC = 9543|UniProtKB = P28072	ENSG00000142507	Proteasome subunit beta type-6; PSMB6; ortholog	PROTEASOME SUBUNIT BETA TYPE-6 (PTHR11599:SF46)	Protease(PC00190)
HUMAN|HGNC = 9544|UniProtKB = Q99436	ENSG00000136930	Proteasome subunit beta type-7; PSMB7; ortholog	PROTEASOME SUBUNIT BETA TYPE-7 (PTHR11599:SF42)	Protease(PC00190)
HUMAN|HGNC = 9545|UniProtKB = P28062	ENSG00000204264	Proteasome subunit beta type-8; PSMB8; ortholog	PROTEASOME SUBUNIT BETA TYPE-8 (PTHR11599:SF53)	Protease(PC00190)
HUMAN|HGNC = 9546|UniProtKB = P28065	ENSG00000240065	Proteasome subunit beta type-9; PSMB9; ortholog	PROTEASOME SUBUNIT BETA TYPE-9 (PTHR11599:SF50)	Protease(PC00190)
HUMAN|HGNC = 11968|UniProtKB = Q9BT09	ENSG00000137161	Protein canopy homolog 3; CNPY3; ortholog	PROTEIN CANOPY HOMOLOG 3 (PTHR15382:SF2)	

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Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 9399|UniProtKB = Q05655	ENSG00000163932	Protein kinase C delta type; PRKCD; ortholog	PROTEIN KINASE C DELTA TYPE (PTHR24356:SF322)	Annexin(PC00050); calmodulin(PC00061); non-receptor serine/threonine protein kinase(PC00167); transfer/carrier protein(PC00219)
HUMAN|HGNC = 9401|UniProtKB = Q02156	ENSG00000171132	Protein kinase C epsilon type; PRKCE; ortholog	PROTEIN KINASE C EPSILON TYPE (PTHR24356:SF159)	Annexin(PC00050); calmodulin(PC00061); non-receptor serine/threonine protein kinase(PC00167); transfer/carrier protein(PC00219)
HUMAN|HGNC = 24489|UniProtKB = Q8ND56	ENSG00000257103	Protein LSM14 homolog A; LSM14A; ortholog	PROTEIN LSM14 HOMOLOG A (PTHR13586:SF2)	RNA-binding protein(PC00031)
HUMAN|HGNC = 13481|UniProtKB = Q9H1C4	ENSG00000110057	Protein unc-93 homolog B1; UNC93B1; ortholog	PROTEIN UNC-93 HOMOLOG B1 (PTHR46744:SF1)	
HUMAN|HGNC = 11283|UniProtKB = P12931	ENSG00000197122	Proto-oncogene tyrosine-protein kinase Src; SRC; ortholog	PROTO-ONCOGENE TYROSINE-PROTEIN KINASE SRC (PTHR24418:SF53)	
HUMAN|HGNC = 14957|UniProtKB = Q14671	ENSG00000134644	Pumilio homolog 1; PUM1; ortholog	PUMILIO HOMOLOG 1 (PTHR12537:SF1)	mRNA processing factor(PC00147); translation factor(PC00223)

HUMAN|HGNC = 14958|UniProtKB = Q8TB72	ENSG00000055917	Pumilio homolog 2; PUM2; ortholog	PUMILIO HOMOLOG 2 (PTHR12537:SF52)	mRNA processing factor(PC00147); translation factor(PC00223)
HUMAN|HGNC = 30908|UniProtKB = Q8WXG1	ENSG00000134321	Radical S-adenosylmethionine domain-containing protein 2; RSAD2; ortholog	RADICAL S-ADENOSYL METHIONINE DOMAIN-CONTAINING PROTEIN 2 (PTHR21339:SF0)	
HUMAN|HGNC = 9829|UniProtKB = P04049	ENSG00000132155	RAF proto-oncogene serine/threonine-protein kinase; RAF1; ortholog	RAF PROTO-ONCOGENE SERINE/THREONINE-PROTEIN KINASE (PTHR44329:SF22)	
HUMAN|HGNC = 30278|UniProtKB = Q14699	ENSG00000131378	Raftlin; RFTN1; ortholog	RAFTLIN (PTHR17601:SF3)	
HUMAN|HGNC = 10019|UniProtKB = Q13546	ENSG00000137275	Receptor-interacting serine/threonine-protein kinase 1; RIPK1; ortholog	RECEPTOR-INTERACTING SERINE/THREONINE-PROTEIN KINASE 1 (PTHR44329:SF6)	
HUMAN|HGNC = 10432|UniProtKB = P51812	ENSG00000177189	Ribosomal protein S6 kinase alpha-3; RPS6KA3; ortholog	RIBOSOMAL PROTEIN S6 KINASE ALPHA-3 (PTHR24351:SF58)	
HUMAN|HGNC = 10434|UniProtKB = O75582	ENSG00000100784	Ribosomal protein S6 kinase alpha-5; RPS6KA5; ortholog	RIBOSOMAL PROTEIN S6 KINASE ALPHA-5 (PTHR24351:SF115)	
HUMAN|HGNC = 19000|UniProtKB = Q6AZY7	ENSG00000168077	Scavenger receptor class A member 3; SCARA3; ortholog	SCAVENGER RECEPTOR CLASS A MEMBER 3 (PTHR24020:SF10)	Receptor(PC00197)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 10698|UniProtKB = Q92503	ENSG00000129657	SEC14-like protein 1; SEC14L1; ortholog	SEC14-LIKE PROTEIN 1 (PTHR23324:SF51)	
HUMAN|HGNC = 8590|UniProtKB = Q13153	ENSG00000149269	Serine/threonine-protein kinase PAK 1; PAK1; ortholog	SERINE/THREONINE-PROTEIN KINASE PAK 1 (PTHR24361:SF232)	
HUMAN|HGNC = 8591|UniProtKB = Q13177	ENSG00000180370	Serine/threonine-protein kinase PAK 2; PAK2; ortholog	SERINE/THREONINE-PROTEIN KINASE PAK 2 (PTHR24361:SF281)	
HUMAN|HGNC = 8592|UniProtKB = O75914	ENSG00000077264	Serine/threonine-protein kinase PAK 3; PAK3; ortholog	SERINE/THREONINE-PROTEIN KINASE PAK 3 (PTHR24361:SF250)	
HUMAN|HGNC = 11584|UniProtKB = Q9UHD2	ENSG00000183735	Serine/threonine-protein kinase TBK1; TBK1; ortholog	SERINE/THREONINE-PROTEIN KINASE TBK1 (PTHR22969:SF14)	Non-receptor serine/threonine protein kinase(PC00167)
HUMAN|HGNC = 10899|UniProtKB = P63208	ENSG00000113558	S-phase kinase-associated protein 1; SKP1; ortholog	S-PHASE KINASE-ASSOCIATED PROTEIN 1 (PTHR11165:SF24)	
HUMAN|HGNC = 17074|UniProtKB = Q6SZW1	ENSG00000004139	Sterile alpha and TIR motif-containing protein 1; SARM1; ortholog	STERILE ALPHA AND TIR MOTIF-CONTAINING PROTEIN 1 (PTHR22998:SF1)	
HUMAN|HGNC = 27962|UniProtKB = Q86WV6	ENSG00000184584	Stimulator of interferon genes protein; TMEM173; ortholog	STIMULATOR OF INTERFERON GENES PROTEIN (PTHR34339:SF1)	

HUMAN|HGNC = 11858|UniProtKB = O43657	ENSG00000000003	Tetraspanin-6; TSPAN6; ortholog	TETRASPANIN-6 (PTHR19282:SF169)	
HUMAN|HGNC = 18157|UniProtKB = Q15750	ENSG00000100324	TGF-beta-activated kinase 1 and MAP3K7-binding protein 1; TAB1; ortholog	TGF-BETA-ACTIVATED KINASE 1 AND MAP3K7-BINDING PROTEIN 1 (PTHR13832:SF533)	Kinase inhibitor(PC00139); protein phosphatase(PC00195)
HUMAN|HGNC = 17075|UniProtKB = Q9NYJ8	ENSG00000055208	TGF-beta-activated kinase 1 and MAP3K7-binding protein 2; TAB2; ortholog	TGF-BETA-ACTIVATED KINASE 1 AND MAP3K7-BINDING PROTEIN 2 (PTHR46253:SF2)	
HUMAN|HGNC = 30681|UniProtKB = Q8N5C8	ENSG00000157625	TGF-beta-activated kinase 1 and MAP3K7-binding protein 3; TAB3; ortholog	TGF-BETA-ACTIVATED KINASE 1 AND MAP3K7-BINDING PROTEIN 3 (PTHR46253:SF3)	
HUMAN|HGNC = 18348|UniProtKB = Q8IUC6	ENSG00000127666	TIR domain-containing adapter molecule 1; TICAM1; ortholog	TIR DOMAIN-CONTAINING ADAPTER MOLECULE 1 (PTHR47230:SF1)	
HUMAN|HGNC = 12033|UniProtKB = Q13114	ENSG00000131323	TNF receptor-associated factor 3; TRAF3; ortholog	TNF RECEPTOR-ASSOCIATED FACTOR 3 (PTHR10131:SF76)	Signaling molecule(PC00207)
HUMAN|HGNC = 16903|UniProtKB = Q15025	ENSG00000145901	TNFAIP3-interacting protein 1; TNIP1; ortholog	TNFAIP3-INTERACTING PROTEIN 1 (PTHR31882:SF3)	

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 19118|UniProtKB = Q8NFZ5	ENSG00000168884	TNFAIP3-interacting protein 2; TNIP2; ortholog	TNFAIP3-INTERACTING PROTEIN 2 (PTHR31882:SF6)	
HUMAN|HGNC = 11850|UniProtKB = O00206	ENSG00000136869	Toll-like receptor 4; TLR4; ortholog	TOLL-LIKE RECEPTOR 4 (PTHR24365:SF521)	
HUMAN|HGNC = 11851|UniProtKB = O60602	ENSG00000187554	Toll-like receptor 5; TLR5; ortholog	TOLL-LIKE RECEPTOR 5 (PTHR24365:SF525)	
HUMAN|HGNC = 11562|UniProtKB = Q92844	ENSG00000136560	TRAF family member-associated NF-kappa-B activator; TANK; ortholog	TRAF FAMILY MEMBER-ASSOCIATED NF-KAPPA-B ACTIVATOR (PTHR15249:SF0)	
HUMAN|HGNC = 9955|UniProtKB = Q04206	ENSG00000173039	Transcription factor p65; RELA; ortholog	TRANSCRIPTION FACTOR P65 (PTHR24169:SF1)	P53-like transcription factor(PC00253); Rel homology transcription factor(PC00252); nucleic acid binding(PC00171)
HUMAN|HGNC = 9956|UniProtKB = Q01201	ENSG00000104856	Transcription factor RelB; RELB; ortholog	TRANSCRIPTION FACTOR RELB (PTHR24169:SF18)	P53-like transcription factor(PC00253); Rel homology transcription factor(PC00252); nucleic acid binding(PC00171)
HUMAN|HGNC = 24552|UniProtKB = Q3LXA3	ENSG00000149476	Triokinase/FMN cyclase; TKFC; ortholog	TRIOKINASE/FMN CYCLASE (PTHR28629:SF4)	
HUMAN|HGNC = 16276|UniProtKB = Q9C035	ENSG00000132256	Tripartite motif-containing protein 5; TRIM5; ortholog	TRIPARTITE MOTIF-CONTAINING PROTEIN 5 (PTHR24103:SF426)	

HUMAN|HGNC = 11896|UniProtKB = P21580	ENSG00000118503	Tumor necrosis factor alpha-induced protein 3; TNFAIP3; ortholog	TUMOR NECROSIS FACTOR ALPHA-INDUCED PROTEIN 3 (PTHR13367:SF3)	DNA-binding protein(PC00009); cysteine protease(PC00081)
HUMAN|HGNC = 4037|UniProtKB = P06241	ENSG00000010810	Tyrosine-protein kinase Fyn; FYN; ortholog	TYROSINE-PROTEIN KINASE FYN (PTHR24418:SF44)	
HUMAN|HGNC = 6735|UniProtKB = P07948	ENSG00000254087	Tyrosine-protein kinase Lyn; LYN; ortholog	TYROSINE-PROTEIN KINASE LYN (PTHR24418:SF42)	
HUMAN|HGNC = 12446|UniProtKB = Q06418	ENSG00000092445	Tyrosine-protein kinase receptor TYRO3; TYRO3; ortholog	TYROSINE-PROTEIN KINASE RECEPTOR TYRO3 (PTHR24416:SF517)	
HUMAN|HGNC = 12508|UniProtKB = Q9UMX0	ENSG00000135018	Ubiquilin-1; UBQLN1; ortholog	UBIQUILIN-1 (PTHR10677:SF16)	
HUMAN|HGNC = 2584|UniProtKB = Q9NQC7	ENSG00000083799	Ubiquitin carboxyl-terminal hydrolase CYLD; CYLD; ortholog	UBIQUITIN CARBOXYL-TERMINAL HYDROLASE CYLD (PTHR11830:SF15)	Cysteine protease(PC00081); ribosomal protein(PC00202)
HUMAN|HGNC = 25118|UniProtKB = Q96BN8	ENSG00000154124	Ubiquitin thioesterase otulin; OTULIN; ortholog	UBIQUITIN THIOESTERASE OTULIN (PTHR33662:SF2)	
HUMAN|HGNC = 10417|UniProtKB = P62979	ENSG00000143947	Ubiquitin-40S ribosomal protein S27a; RPS27A; ortholog	UBIQUITIN-40S RIBOSOMAL PROTEIN S27A (PTHR10666:SF258)	Ribosomal protein(PC00202)

(continued)

Table 1 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	**Panther protein class**
HUMAN|HGNC = 12458|UniProtKB = P62987	ENSG00000221983	Ubiquitin-60S ribosomal protein L40; UBA52; ortholog	UBIQUITIN-60S RIBOSOMAL PROTEIN L40 (PTHR10666:SF268)	Ribosomal protein(PC00202)
HUMAN|HGNC = 12475|UniProtKB = P62837	ENSG00000131508	Ubiquitin-conjugating enzyme E2 D2; UBE2D2; ortholog	UBIQUITIN-CONJUGATING ENZYME E2 D2 (PTHR24068:SF40)	Ligase(PC00142)
HUMAN|HGNC = 12476|UniProtKB = P61077	ENSG00000109332	Ubiquitin-conjugating enzyme E2 D3; UBE2D3; ortholog	UBIQUITIN-CONJUGATING ENZYME E2 D3 (PTHR24068:SF48)	Ligase(PC00142)
HUMAN|HGNC = 12492|UniProtKB = P61088	ENSG00000177889	Ubiquitin-conjugating enzyme E2 N; UBE2N; ortholog	UBIQUITIN-CONJUGATING ENZYME E2 N (PTHR24068:SF152)	
HUMAN|HGNC = 12494|UniProtKB = Q13404	ENSG00000244687	Ubiquitin-conjugating enzyme E2 variant 1; UBE2V1; ortholog	HCG2044781-RELATED (PTHR24068:SF169)	
HUMAN|HGNC = 20451|UniProtKB = Q8IWB7	ENSG00000085449	WD repeat and FYVE domain-containing protein 1; WDFY1; ortholog	WD REPEAT AND FYVE DOMAIN-CONTAINING PROTEIN 1 (PTHR46189:SF2)	

Table 2 List of known molecules involved in antigen processing and presentation expressed by the human BNB transcriptome in health that may be relevant in physiological cross-talk between the systemic immune compartment and peripheral nerve endoneurium and in peripheral nerve autoimmune disorders

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 9553|UniProtKB = P62333	ENSG00000100519	26S protease regulatory subunit 10B; PSMC6; ortholog	26S PROTEASE REGULATORY SUBUNIT 10B (PTHR23073:SF31)	Hydrolase(PC00121)
HUMAN|HGNC = 9547|UniProtKB = P62191	ENSG00000100764	26S protease regulatory subunit 4; PSMC1; ortholog	26S PROTEASE REGULATORY SUBUNIT 4 (PTHR23073:SF24)	Hydrolase(PC00121)
HUMAN|HGNC = 9549|UniProtKB = P17980	ENSG00000165916	26S protease regulatory subunit 6A; PSMC3; ortholog	26S PROTEASE REGULATORY SUBUNIT 6A (PTHR23073:SF7)	Hydrolase(PC00121)
HUMAN|HGNC = 9551|UniProtKB = P43686	ENSG00000013275	26S protease regulatory subunit 6B; PSMC4; ortholog	26S PROTEASE REGULATORY SUBUNIT 6B (PTHR23073:SF8)	Hydrolase(PC00121)
HUMAN|HGNC = 9548|UniProtKB = P35998	ENSG00000161057	26S protease regulatory subunit 7; PSMC2; ortholog	26S PROTEASE REGULATORY SUBUNIT 7 (PTHR23073:SF13)	Hydrolase(PC00121)
HUMAN|HGNC = 9552|UniProtKB = P62195	ENSG00000087191	26S protease regulatory subunit 8; PSMC5; ortholog	26S PROTEASE REGULATORY SUBUNIT 8 (PTHR23073:SF12)	Hydrolase(PC00121)
HUMAN|HGNC = 9554|UniProtKB = Q99460	ENSG00000173692	26S proteasome non-ATPase regulatory subunit 1; PSMD1; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 1 (PTHR10943:SF2)	Enzyme modulator(PC00095)

(continued)

Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 9555|UniProtKB = O75832	ENSG00000101843	26S proteasome non-ATPase regulatory subunit 10; PSMD10; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 10 (PTHR24126:SF24)	
HUMAN|HGNC = 9556|UniProtKB = O00231	ENSG00000108671	26S proteasome non-ATPase regulatory subunit 11; PSMD11; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 11 (PTHR10678:SF2)	
HUMAN|HGNC = 9557|UniProtKB = O00232	ENSG00000197170	26S proteasome non-ATPase regulatory subunit 12; PSMD12; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 12 (PTHR10855:SF1)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9558|UniProtKB = Q9UNM6	ENSG00000185627	26S proteasome non-ATPase regulatory subunit 13; PSMD13; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 13 (PTHR10539:SF0)	Enzyme modulator(PC00095)
HUMAN|HGNC = 16889|UniProtKB = O00487	ENSG00000115233	26S proteasome non-ATPase regulatory subunit 14; PSMD14; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 14 (PTHR10410:SF5)	Metalloprotease(PC00153); transcription factor(PC00218)

HUMAN|HGNC = 9559|UniProtKB = Q13200	ENSG00000175166	26S proteasome non-ATPase regulatory subunit 2; PSMD2; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 2 (PTHR10943:SF1)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9560|UniProtKB = O43242	ENSG00000108344	26S proteasome non-ATPase regulatory subunit 3; PSMD3; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 3 (PTHR10758:SF2)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9561|UniProtKB = P55036	ENSG00000159352	26S proteasome non-ATPase regulatory subunit 4; PSMD4; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 4 (PTHR10223:SF0)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9563|UniProtKB = Q16401	ENSG00000095261	26S proteasome non-ATPase regulatory subunit 5; PSMD5; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 5 (PTHR13554:SF10)	
HUMAN|HGNC = 9564|UniProtKB = Q15008	ENSG00000163636	26S proteasome non-ATPase regulatory subunit 6; PSMD6; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 6 (PTHR14145:SF1)	
HUMAN|HGNC = 9565|UniProtKB = P51665	ENSG00000103035	26S proteasome non-ATPase regulatory subunit 7; PSMD7; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 7 (PTHR10540:SF7)	Metalloprotease(PC00153)

(continued)

Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 9566|UniProtKB = P48556	ENSG00000099341	26S proteasome non-ATPase regulatory subunit 8; PSMD8; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 8 (PTHR12387:SF0)	Enzyme modulator(PC00095)
HUMAN|HGNC = 9567|UniProtKB = O00233	ENSG00000110801	26S proteasome non-ATPase regulatory subunit 9; PSMD9; ortholog	26S PROTEASOME NON-ATPASE REGULATORY SUBUNIT 9 (PTHR12651:SF1)	Enzyme modulator(PC00095)
HUMAN|HGNC = 652|UniProtKB = P84077	ENSG00000143761	ADP-ribosylation factor 1; ARF1; ortholog	ADP-RIBOSYLATION FACTOR 1 (PTHR11711:SF308)	
HUMAN|HGNC = 167|UniProtKB = P61163	ENSG00000138107	Alpha-centractin; ACTR1A; ortholog	ALPHA-CENTRACTIN (PTHR11937:SF370)	Actin and actin-related protein(PC00039)
HUMAN|HGNC = 2707|UniProtKB = P12821	ENSG00000159640	Angiotensin-converting enzyme; ACE; ortholog	ANGIOTENSIN-CONVERTING ENZYME (PTHR10514:SF25)	Metalloprotease(PC00153)
HUMAN|HGNC = 43|UniProtKB = Q03518	ENSG00000168394	Antigen peptide transporter 1; TAP1; ortholog	ANTIGEN PEPTIDE TRANSPORTER 1 (PTHR24221:SF249)	Cysteine protease(PC00081); serine protease(PC00203)
HUMAN|HGNC = 44|UniProtKB = Q03519	ENSG00000204267	Antigen peptide transporter 2; TAP2; ortholog	ANTIGEN PEPTIDE TRANSPORTER 2 (PTHR24221:SF428)	Cysteine protease(PC00081); serine protease(PC00203)
HUMAN|HGNC = 554|UniProtKB = Q10567	ENSG00000100280	AP-1 complex subunit beta-1; AP1B1; ortholog	AP-1 COMPLEX SUBUNIT BETA-1 (PTHR11134:SF3)	Membrane traffic protein(PC00150)
HUMAN|HGNC = 555|UniProtKB = O43747	ENSG00000166747	AP-1 complex subunit gamma-1; AP1G1; ortholog	AP-1 COMPLEX SUBUNIT GAMMA-1 (PTHR22780:SF26)	Transmembrane receptor regulatory/adaptor protein(PC00226)

HUMAN|HGNC = 13667|UniProtKB = Q9BXS5	ENSG00000072958	AP-1 complex subunit mu-1; AP1M1; ortholog	AP-1 COMPLEX SUBUNIT MU-1 (PTHR10529:SF257)	Extracellular matrix glycoprotein(PC00100); receptor(PC00197)
HUMAN|HGNC = 560|UniProtKB = P56377	ENSG00000182287	AP-1 complex subunit sigma-2; AP1S2; ortholog	AP-1 COMPLEX SUBUNIT SIGMA-2 (PTHR11753:SF19)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 18971|UniProtKB = Q96PC3	ENSG00000152056	AP-1 complex subunit sigma-3; AP1S3; ortholog	AP-1 COMPLEX SUBUNIT SIGMA-3 (PTHR11753:SF18)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 561|UniProtKB = O95782	ENSG00000196961	AP-2 complex subunit alpha-1; AP2A1; ortholog	AP-2 COMPLEX SUBUNIT ALPHA-1 (PTHR22780:SF4)	Transmembrane receptor regulatory/adaptor protein(PC00226)
HUMAN|HGNC = 562|UniProtKB = O94973	ENSG00000183020	AP-2 complex subunit alpha-2; AP2A2; ortholog	AP-2 COMPLEX SUBUNIT ALPHA-2 (PTHR22780:SF30)	Transmembrane receptor regulatory/adaptor protein(PC00226)
HUMAN|HGNC = 563|UniProtKB = P63010	ENSG00000006125	AP-2 complex subunit beta; AP2B1; ortholog	AP-2 COMPLEX SUBUNIT BETA (PTHR11134:SF9)	Membrane traffic protein(PC00150)
HUMAN|HGNC = 564|UniProtKB = Q96CW1	ENSG00000161203	AP-2 complex subunit mu; AP2M1; ortholog	AP-2 COMPLEX SUBUNIT MU (PTHR10529:SF236)	Extracellular matrix glycoprotein(PC00100); receptor(PC00197)
HUMAN|HGNC = 565|UniProtKB = P53680	ENSG00000042753	AP-2 complex subunit sigma; AP2S1; ortholog	AP-2 COMPLEX SUBUNIT SIGMA (PTHR11753:SF6)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 566|UniProtKB = O00203	ENSG00000132842	AP-3 complex subunit beta-1; AP3B1; ortholog	AP-3 COMPLEX SUBUNIT BETA-1 (PTHR11134:SF10)	Membrane traffic protein(PC00150)

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Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 568|UniProtKB = O14617	ENSG00000065000	AP-3 complex subunit delta-1; AP3D1; ortholog	AP-3 COMPLEX SUBUNIT DELTA-1 (PTHR22781:SF12)	Transporter(PC00227)
HUMAN|HGNC = 16608|UniProtKB = Q9ULZ3	ENSG00000103490	Apoptosis-associated speck-like protein containing a CARD; PYCARD; ortholog	APOPTOSIS-ASSOCIATED SPECK-LIKE PROTEIN CONTAINING A CARD (PTHR10454:SF203)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 50|UniProtKB = Q9NP78	ENSG00000150967	ATP-binding cassette subfamily B member 9; ABCB9; ortholog	ATP-BINDING CASSETTE SUB-FAMILY B MEMBER 9 (PTHR24221:SF242)	Cysteine protease(PC00081); serine protease(PC00203)
HUMAN|HGNC = 16695|UniProtKB = P51572	ENSG00000185825	B-cell receptor-associated protein 31; BCAP31; ortholog	B-CELL RECEPTOR-ASSOCIATED PROTEIN 31 (PTHR12701:SF15)	Membrane traffic protein(PC00150); transporter(PC00227)
HUMAN|HGNC = 914|UniProtKB = P61769	ENSG00000166710	Beta-2-microglobulin; B2M; ortholog	BETA-2-MICROGLOBULIN (PTHR19944:SF62)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 168|UniProtKB = P42025	ENSG00000115073	Beta-centractin; ACTR1B; ortholog	BETA-CENTRACTIN (PTHR11937:SF195)	Actin and actin-related protein(PC00039)
HUMAN|HGNC = 1473|UniProtKB = P27824	ENSG00000127022	Calnexin; CANX; ortholog	CALNEXIN (PTHR11073:SF11)	Calcium-binding protein(PC00060); chaperone(PC00072)
HUMAN|HGNC = 1455|UniProtKB = P27797	ENSG00000179218	Calreticulin; CALR; ortholog	CALRETICULIN (PTHR11073:SF16)	Calcium-binding protein(PC00060)
HUMAN|HGNC = 2529|UniProtKB = P07339	ENSG00000117984	Cathepsin D; CTSD; ortholog	CATHEPSIN D (PTHR13683:SF230)	Aspartic protease(PC00053)

HUMAN|HGNC = 2531|UniProtKB = Q9UBX1	ENSG00000174080	Cathepsin F; CTSF; ortholog	CATHEPSIN F (PTHR12411:SF444)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 2537|UniProtKB = P07711	ENSG00000135047	Cathepsin L1; CTSL; ortholog	CATHEPSIN L1 (PTHR12411:SF411)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 2545|UniProtKB = P25774	ENSG00000163131	Cathepsin S; CTSS; ortholog	CATHEPSIN S (PTHR12411:SF525)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 2092|UniProtKB = Q00610	ENSG00000141367	Clathrin heavy chain 1; CLTC; ortholog	CLATHRIN HEAVY CHAIN 1 (PTHR10292:SF7)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 2090|UniProtKB = P09496	ENSG00000122705	Clathrin light chain A; CLTA; ortholog	CLATHRIN LIGHT CHAIN A (PTHR10639:SF1)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 2577|UniProtKB = P13498	ENSG00000051523	Cytochrome b-245 light chain; CYBA; ortholog	CYTOCHROME B-245 LIGHT CHAIN (PTHR15168:SF0)	
HUMAN|HGNC = 2961|UniProtKB = Q14204	ENSG00000197102	Cytoplasmic dynein 1 heavy chain 1; DYNC1H1; ortholog	CYTOPLASMIC DYNEIN 1 HEAVY CHAIN 1 (PTHR10676:SF314)	Hydrolase(PC00121); microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 2963|UniProtKB = O14576	ENSG00000158560	Cytoplasmic dynein 1 intermediate chain 1; DYNC1I1; ortholog	CYTOPLASMIC DYNEIN 1 INTERMEDIATE CHAIN 1 (PTHR12442:SF34)	Microtubule family cytoskeletal protein(PC00157)
HUMAN|HGNC = 2964|UniProtKB = Q13409	ENSG00000077380	Cytoplasmic dynein 1 intermediate chain 2; DYNC1I2; ortholog	CYTOPLASMIC DYNEIN 1 INTERMEDIATE CHAIN 2 (PTHR12442:SF37)	Microtubule family cytoskeletal protein(PC00157)

(continued)

Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 2966|UniProtKB = O43237	ENSG00000135720	Cytoplasmic dynein 1 light intermediate chain 2; DYNC1LI2; ortholog	CYTOPLASMIC DYNEIN 1 LIGHT INTERMEDIATE CHAIN 2 (PTHR12688:SF1)	Enzyme modulator(PC00095); microtubule family cytoskeletal protein(PC00157)
HUMAN|HGNC = 2962|UniProtKB = Q8NCM8	ENSG00000187240	Cytoplasmic dynein 2 heavy chain 1; DYNC2H1; ortholog	CYTOPLASMIC DYNEIN 2 HEAVY CHAIN 1 (PTHR10676:SF352)	Hydrolase(PC00121); microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 24595|UniProtKB = Q8TCX1	ENSG00000138036	Cytoplasmic dynein 2 light intermediate chain 1; DYNC2LI1; ortholog	CYTOPLASMIC DYNEIN 2 LIGHT INTERMEDIATE CHAIN 1 (PTHR13236:SF0)	Microtubule family cytoskeletal protein(PC00157)
HUMAN|HGNC = 2711|UniProtKB = Q14203	ENSG00000204843	Dynactin subunit 1; DCTN1; ortholog	DYNACTIN SUBUNIT 1 (PTHR18916:SF40)	Non-motor microtubule-binding protein(PC00166)
HUMAN|HGNC = 2712|UniProtKB = Q13561	ENSG00000175203	Dynactin subunit 2; DCTN2; ortholog	DYNACTIN SUBUNIT 2 (PTHR15346:SF0)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 2713|UniProtKB = O75935	ENSG00000137100	Dynactin subunit 3; DCTN3; ortholog	DYNACTIN SUBUNIT 3 (PTHR28360:SF1)	
HUMAN|HGNC = 15518|UniProtKB = Q9UJW0	ENSG00000132912	Dynactin subunit 4; DCTN4; ortholog	DYNACTIN SUBUNIT 4 (PTHR13034:SF2)	
HUMAN|HGNC = 24594|UniProtKB = Q9BTE1	ENSG00000166847	Dynactin subunit 5; DCTN5; ortholog	DYNACTIN SUBUNIT 5 (PTHR46126:SF1)	
HUMAN|HGNC = 2974|UniProtKB = P50570	ENSG00000079805	Dynamin-2; DNM2; ortholog	DYNAMIN-2 (PTHR11566:SF23)	Hydrolase(PC00121); microtubule family cytoskeletal protein(PC00157); small GTPase(PC00208)

HUMAN|HGNC = 15476|UniProtKB = P63167	ENSG00000088986	Dynein light chain 1, cytoplasmic; DYNLL1; ortholog	DYNEIN LIGHT CHAIN 1, CYTOPLASMIC (PTHR11886:SF52)	Enzyme modulator(PC00095); microtubule family cytoskeletal protein(PC00157)
HUMAN|HGNC = 24596|UniProtKB = Q96FJ2	ENSG00000264364	Dynein light chain 2, cytoplasmic; DYNLL2; ortholog	DYNEIN LIGHT CHAIN 2, CYTOPLASMIC (PTHR11886:SF35)	Enzyme modulator(PC00095); microtubule family cytoskeletal protein(PC00157)
HUMAN|HGNC = 26077|UniProtKB = Q8TCQ1	ENSG00000145416	E3 ubiquitin-protein ligase MARCH1; MARCH1; ortholog	E3 UBIQUITIN-PROTEIN LIGASE MARCH1 (PTHR45981:SF1)	
HUMAN|HGNC = 18173|UniProtKB = Q9NZ08	ENSG00000164307	Endoplasmic reticulum aminopeptidase 1; ERAP1; ortholog	ENDOPLASMIC RETICULUM AMINOPEPTIDASE 1 (PTHR11533:SF156)	Metalloprotease(PC00153)
HUMAN|HGNC = 29499|UniProtKB = Q6P179	ENSG00000164308	Endoplasmic reticulum aminopeptidase 2; ERAP2; ortholog	ENDOPLASMIC RETICULUM AMINOPEPTIDASE 2 (PTHR11533:SF239)	Metalloprotease(PC00153)
HUMAN|HGNC = 5398|UniProtKB = P13284	ENSG00000216490	Gamma-interferon-inducible lysosomal thiol reductase; IFI30; ortholog	GAMMA-INTERFERON-INDUCIBLE LYSOSOMAL THIOL REDUCTASE (PTHR13234:SF8)	Reductase(PC00198)

(continued)

Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 10535|UniProtKB = Q9Y6B6	ENSG00000152700	GTP-binding protein SAR1b; SAR1B; ortholog	GTP-BINDING PROTEIN SAR1B (PTHR45684:SF2)	
HUMAN|HGNC = 4886|UniProtKB = Q30201	ENSG00000010704	Hereditary hemochromatosis protein; HFE; ortholog	HEREDITARY HEMOCHROMATOSIS PROTEIN (PTHR16675:SF172)	
HUMAN|HGNC = 3611|UniProtKB = P30273	ENSG00000158869	High-affinity immunoglobulin epsilon receptor subunit gamma; FCER1G; ortholog	HIGH AFFINITY IMMUNOGLOBULIN EPSILON RECEPTOR SUBUNIT GAMMA (PTHR16803:SF0)	
HUMAN|HGNC = 4963|UniProtKB = P30511	ENSG00000204642	HLA class I histocompatibility antigen, alpha chain F; HLA-F; ortholog	HLA CLASS I HISTOCOMPATIBILITY ANTIGEN, ALPHA CHAIN F (PTHR16675:SF187)	
HUMAN|HGNC = 4932|UniProtKB = Q31612	ENSG00000234745	HLA class I histocompatibility antigen, B-73 alpha chain; HLA-B; ortholog	HLA CLASS I HISTOCOMPATIBILITY ANTIGEN, B-73 ALPHA CHAIN (PTHR16675:SF248)	
HUMAN|HGNC = 1697|UniProtKB = P04233	ENSG00000019582	HLA class II histocompatibility antigen gamma chain; CD74; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN GAMMA CHAIN (PTHR14093:SF17)	Protease inhibitor(PC00191)

HUMAN|HGNC = 4934|UniProtKB = P28067	ENSG00000204257	HLA class II histocompatibility antigen, DM alpha chain; HLA-DMA; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DM ALPHA CHAIN (PTHR19944:SF50)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 4935|UniProtKB = P28068	ENSG00000242574	HLA class II histocompatibility antigen, DM beta chain; HLA-DMB; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DM BETA CHAIN (PTHR19944:SF65)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 4938|UniProtKB = P20036	ENSG00000231389	HLA class II histocompatibility antigen, DP alpha 1 chain; HLA-DPA1; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DP ALPHA 1 CHAIN (PTHR19944:SF64)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 4940|UniProtKB = P04440	ENSG00000223865	HLA class II histocompatibility antigen, DP beta 1 chain; HLA-DPB1; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DP BETA 1 CHAIN (PTHR19944:SF46)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 4942|UniProtKB = P01909	ENSG00000196735	HLA class II histocompatibility antigen, DQ alpha 1 chain; HLA-DQA1; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DQ ALPHA 1 CHAIN (PTHR19944:SF59)	Major histocompatibility complex antigen(PC00149)

(continued)

Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 4947|UniProtKB = P01903	ENSG00000204287	HLA class II histocompatibility antigen, DR alpha chain; HLA-DRA; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DR ALPHA CHAIN (PTHR19944:SF63)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 4953|UniProtKB = Q30154	ENSG00000198502	HLA class II histocompatibility antigen, DR beta 5 chain; HLA-DRB5; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DR BETA 4 CHAIN-RELATED (PTHR19944:SF56)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 4948|UniProtKB = P01911	ENSG00000196126	HLA class II histocompatibility antigen, DRB1-15 beta chain; HLA-DRB1; ortholog	HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DR BETA 4 CHAIN-RELATED (PTHR19944:SF56)	Major histocompatibility complex antigen(PC00149)
HUMAN|HGNC = 3621|UniProtKB = P55899	ENSG00000104870	IgG receptor FcRn large subunit p51; FCGRT; ortholog	IGG RECEPTOR FCRN LARGE SUBUNIT P51 (PTHR16675:SF3)	
HUMAN|HGNC = 6150|UniProtKB = P06756	ENSG00000138448	Integrin alpha-V; ITGAV; ortholog	INTEGRIN ALPHA-V (PTHR23220:SF4)	
HUMAN|HGNC = 6160|UniProtKB = P18084	ENSG00000082781	Integrin beta-5; ITGB5; ortholog	INTEGRIN BETA-5 (PTHR10082:SF26)	Cell adhesion molecule(PC00069); extracellular matrix glycoprotein(PC00100); receptor(PC00197)

HUMAN|HGNC = 5344|UniProtKB = P05362	ENSG00000090339	Intercellular adhesion molecule 1; ICAM1; ortholog	INTERCELLULAR ADHESION MOLECULE 1 (PTHR13771:SF9)	
HUMAN|HGNC = 6323|UniProtKB = Q12840	ENSG00000155980	Kinesin heavy chain isoform 5A; KIF5A; ortholog	KINESIN HEAVY CHAIN ISOFORM 5A (PTHR24115:SF317)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6387|UniProtKB = Q07866	ENSG00000126214	Kinesin light chain 1; KLC1; ortholog	KINESIN LIGHT CHAIN 1 (PTHR45783:SF7)	
HUMAN|HGNC = 20716|UniProtKB = Q9H0B6	ENSG00000174996	Kinesin light chain 2; KLC2; ortholog	KINESIN LIGHT CHAIN 2 (PTHR45783:SF2)	
HUMAN|HGNC = 17060|UniProtKB = Q92845	ENSG00000075945	Kinesin-associated protein 3; KIFAP3; ortholog	KINESIN-ASSOCIATED PROTEIN 3 (PTHR15605:SF2)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6388|UniProtKB = P52732	ENSG00000138160	Kinesin-like protein KIF11; KIF11; ortholog	KINESIN-LIKE PROTEIN KIF11 (PTHR24115:SF105)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6391|UniProtKB = Q14807	ENSG00000079616	Kinesin-like protein KIF22; KIF22; ortholog	KINESIN-LIKE PROTEIN KIF22 (PTHR24115:SF462)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6392|UniProtKB = Q02241	ENSG00000137807	Kinesin-like protein KIF23; KIF23; ortholog	KINESIN-LIKE PROTEIN KIF23 (PTHR24115:SF467)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 20226|UniProtKB = Q9ULI4	ENSG00000066735	Kinesin-like protein KIF26A; KIF26A; ortholog	KINESIN-LIKE PROTEIN KIF26A (PTHR24115:SF407)	Microtubule-binding motor protein(PC00156)

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Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 6318|UniProtKB = O00139	ENSG00000068796	Kinesin-like protein KIF2A; KIF2A; ortholog	KINESIN-LIKE PROTEIN KIF2A (PTHR24115:SF486)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6319|UniProtKB = Q9Y496	ENSG00000131437	Kinesin-like protein KIF3A; KIF3A; ortholog	KINESIN-LIKE PROTEIN KIF3A (PTHR24115:SF472)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6320|UniProtKB = O15066	ENSG00000101350	Kinesin-like protein KIF3B; KIF3B; ortholog	KINESIN-LIKE PROTEIN KIF3B (PTHR24115:SF744)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 6321|UniProtKB = O14782	ENSG00000084731	Kinesin-like protein KIF3C; KIF3C; ortholog	KINESIN-LIKE PROTEIN KIF3C (PTHR24115:SF734)	Microtubule-binding motor protein(PC00156)
HUMAN|HGNC = 9472|UniProtKB = Q99538	ENSG00000100600	Legumain; LGMN; ortholog	LEGUMAIN (PTHR12000:SF3)	Cysteine protease(PC00081)
HUMAN|HGNC = 6656|UniProtKB = Q9UIQ6	ENSG00000113441	Leucyl-cystinyl aminopeptidase; LNPEP; ortholog	LEUCYL-CYSTINYL AMINOPEPTIDASE (PTHR11533:SF42)	Metalloprotease(PC00153)
HUMAN|HGNC = 4975|UniProtKB = Q95460	ENSG00000153029	Major histocompatibility complex class I-related gene protein; MR1; ortholog	MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I-RELATED GENE PROTEIN (PTHR16675:SF241)	
HUMAN|HGNC = 40|UniProtKB = P08183	ENSG00000085563	Multidrug resistance protein 1; ABCB1; ortholog	MULTIDRUG RESISTANCE PROTEIN 1 (PTHR24221:SF251)	Cysteine protease(PC00081); serine protease(PC00203)

HUMAN|HGNC = 10907|UniProtKB = P49279	ENSG00000018280	Natural resistance-associated macrophage protein 1; SLC11A1; ortholog	NATURAL RESISTANCE-ASSOCIATED MACROPHAGE PROTEIN 1 (PTHR11706:SF52)	Cation transporter(PC00068)
HUMAN|HGNC = 7660|UniProtKB = P14598	ENSG00000158517	Neutrophil cytosol factor 1; NCF1; ortholog	NEUTROPHIL CYTOSOL FACTOR 1-RELATED (PTHR15706:SF6)	
HUMAN|HGNC = 7661|UniProtKB = P19878	ENSG00000116701	Neutrophil cytosol factor 2; NCF2; ortholog	NEUTROPHIL CYTOSOL FACTOR 2 (PTHR15175:SF3)	Oxidase(PC00175)
HUMAN|HGNC = 16390|UniProtKB = Q9Y239	ENSG00000106100	Nucleotide-binding oligomerization domain-containing protein 1; NOD1; ortholog	NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN-CONTAINING PROTEIN 1 (PTHR24106:SF18)	Nucleic acid binding(PC00171); serine protease(PC00203); transcription cofactor(PC00217)
HUMAN|HGNC = 5331|UniProtKB = Q9HC29	ENSG00000167207	Nucleotide-binding oligomerization domain-containing protein 2; NOD2; ortholog	NUCLEOTIDE-BINDING OLIGOMERIZATION DOMAIN-CONTAINING PROTEIN 2 (PTHR24106:SF64)	Nucleic acid binding(PC00171); serine protease(PC00203); transcription cofactor(PC00217)
HUMAN|HGNC = 16398|UniProtKB = Q9BXW6	ENSG00000141447	Oxysterol-binding protein-related protein 1; OSBPL1A; ortholog	OXYSTEROL-BINDING PROTEIN-RELATED PROTEIN 1 (PTHR10972:SF53)	

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Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 1663|UniProtKB = P16671	ENSG00000135218	Platelet glycoprotein 4; CD36; ortholog	PLATELET GLYCOPROTEIN 4 (PTHR11923:SF12)	Receptor(PC00197)
HUMAN|HGNC = 2535|UniProtKB = P09668	ENSG00000103811	Pro-cathepsin H; CTSH; ortholog	PRO-CATHEPSIN H (PTHR12411:SF572)	Cysteine protease(PC00081); protease inhibitor(PC00191)
HUMAN|HGNC = 9568|UniProtKB = Q06323	ENSG00000092010	Proteasome activator complex subunit 1; PSME1; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 1 (PTHR10660:SF5)	
HUMAN|HGNC = 9569|UniProtKB = Q9UL46	ENSG00000100911	Proteasome activator complex subunit 2; PSME2; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 2 (PTHR10660:SF6)	
HUMAN|HGNC = 9570|UniProtKB = P61289	ENSG00000131467	Proteasome activator complex subunit 3; PSME3; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 3 (PTHR10660:SF4)	
HUMAN|HGNC = 20635|UniProtKB = Q14997	ENSG00000068878	Proteasome activator complex subunit 4; PSME4; ortholog	PROTEASOME ACTIVATOR COMPLEX SUBUNIT 4 (PTHR32170:SF3)	
HUMAN|HGNC = 9571|UniProtKB = Q92530	ENSG00000125818	Proteasome inhibitor PI31 subunit; PSMF1; ortholog	PROTEASOME INHIBITOR PI31 SUBUNIT (PTHR13266:SF1)	Protease inhibitor(PC00191)
HUMAN|HGNC = 9530|UniProtKB = P25786	ENSG00000129084	Proteasome subunit alpha type-1; PSMA1; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-RELATED (PTHR11599:SF12)	Protease(PC00190)

HUMAN|HGNC = 9531|UniProtKB = P25787	ENSG00000106588	Proteasome subunit alpha type-2; PSMA2; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-2 (PTHR11599:SF16)	Protease(PC00190)
HUMAN|HGNC = 9532|UniProtKB = P25788	ENSG00000100567	Proteasome subunit alpha type-3; PSMA3; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-3 (PTHR11599:SF10)	Protease(PC00190)
HUMAN|HGNC = 9533|UniProtKB = P25789	ENSG00000041357	Proteasome subunit alpha type-4; PSMA4; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-4 (PTHR11599:SF13)	Protease(PC00190)
HUMAN|HGNC = 9534|UniProtKB = P28066	ENSG00000143106	Proteasome subunit alpha type-5; PSMA5; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-5 (PTHR11599:SF14)	Protease(PC00190)
HUMAN|HGNC = 9535|UniProtKB = P60900	ENSG00000100902	Proteasome subunit alpha type-6; PSMA6; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-6 (PTHR11599:SF11)	Protease(PC00190)
HUMAN|HGNC = 9536|UniProtKB = O14818	ENSG00000101182	Proteasome subunit alpha type-7; PSMA7; ortholog	PROTEASOME SUBUNIT ALPHA TYPE-7 (PTHR11599:SF40)	Protease(PC00190)
HUMAN|HGNC = 9537|UniProtKB = P20618	ENSG00000008018	Proteasome subunit beta type-1; PSMB1; ortholog	PROTEASOME SUBUNIT BETA TYPE-1 (PTHR11599:SF59)	Protease(PC00190)
HUMAN|HGNC = 9538|UniProtKB = P40306	ENSG00000205220	Proteasome subunit beta type-10; PSMB10; ortholog	PROTEASOME SUBUNIT BETA TYPE-10 (PTHR11599:SF41)	Protease(PC00190)
HUMAN|HGNC = 9539|UniProtKB = P49721	ENSG00000126067	Proteasome subunit beta type-2; PSMB2; ortholog	PROTEASOME SUBUNIT BETA TYPE-2 (PTHR11599:SF6)	Protease(PC00190)

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Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 9540|UniProtKB = P49720	ENSG00000277791	Proteasome subunit beta type-3; PSMB3; ortholog	PROTEASOME SUBUNIT BETA TYPE-3 (PTHR11599:SF62)	Protease(PC00190)
HUMAN|HGNC = 9541|UniProtKB = P28070	ENSG00000159377	Proteasome subunit beta type-4; PSMB4; ortholog	PROTEASOME SUBUNIT BETA TYPE-4 (PTHR11599:SF5)	Protease(PC00190)
HUMAN|HGNC = 9543|UniProtKB = P28072	ENSG00000142507	Proteasome subunit beta type-6; PSMB6; ortholog	PROTEASOME SUBUNIT BETA TYPE-6 (PTHR11599:SF46)	Protease(PC00190)
HUMAN|HGNC = 9544|UniProtKB = Q99436	ENSG00000136930	Proteasome subunit beta type-7; PSMB7; ortholog	PROTEASOME SUBUNIT BETA TYPE-7 (PTHR11599:SF42)	Protease(PC00190)
HUMAN|HGNC = 9545|UniProtKB = P28062	ENSG00000204264	Proteasome subunit beta type-8; PSMB8; ortholog	PROTEASOME SUBUNIT BETA TYPE-8 (PTHR11599:SF53)	Protease(PC00190)
HUMAN|HGNC = 9546|UniProtKB = P28065	ENSG00000240065	Proteasome subunit beta type-9; PSMB9; ortholog	PROTEASOME SUBUNIT BETA TYPE-9 (PTHR11599:SF50)	Protease(PC00190)
HUMAN|HGNC = 4606|UniProtKB = P30101	ENSG00000167004	Protein disulfide-isomerase A3; PDIA3; ortholog	PROTEIN DISULFIDE-ISOMERASE A3 (PTHR18929:SF191)	
HUMAN|HGNC = 10697|UniProtKB = P55735	ENSG00000157020	Protein SEC13 homolog; SEC13; ortholog	PROTEIN SEC13 HOMOLOG (PTHR11024:SF2)	Membrane trafficking regulatory protein(PC00151)
HUMAN|HGNC = 10701|UniProtKB = Q15436	ENSG00000100934	Protein transport protein Sec23A; SEC23A; ortholog	PROTEIN TRANSPORT PROTEIN SEC23A (PTHR11141:SF7)	G-protein modulator(PC00022)

HUMAN|HGNC = 10703|UniProtKB = O95486	ENSG00000113615	Protein transport protein Sec24A; SEC24A; ortholog	PROTEIN TRANSPORT PROTEIN SEC24A (PTHR13803:SF1)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 10704|UniProtKB = O95487	ENSG00000138802	Protein transport protein Sec24B; SEC24B; ortholog	PROTEIN TRANSPORT PROTEIN SEC24B (PTHR13803:SF4)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 10705|UniProtKB = P53992	ENSG00000176986	Protein transport protein Sec24C; SEC24C; ortholog	PROTEIN TRANSPORT PROTEIN SEC24C (PTHR13803:SF5)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 10706|UniProtKB = O94855	ENSG00000150961	Protein transport protein Sec24D; SEC24D; ortholog	PROTEIN TRANSPORT PROTEIN SEC24D (PTHR13803:SF6)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 17052|UniProtKB = O94979	ENSG00000138674	Protein transport protein Sec31A; SEC31A; ortholog	PROTEIN TRANSPORT PROTEIN SEC31A (PTHR13923:SF23)	Vesicle coat protein(PC00235)
HUMAN|HGNC = 30266|UniProtKB = Q96NA2	ENSG00000167705	Rab-interacting lysosomal protein; RILP; ortholog	RAB-INTERACTING LYSOSOMAL PROTEIN (PTHR21502:SF7)	Nucleic acid binding(PC00171)
HUMAN|HGNC = 30278|UniProtKB = Q14699	ENSG00000131378	Raftlin; RFTN1; ortholog	RAFTLIN (PTHR17601:SF3)	
HUMAN|HGNC = 9759|UniProtKB = P61026	ENSG00000084733	Ras-related protein Rab-10; RAB10; ortholog	RAS-RELATED PROTEIN RAB-10 (PTHR24073:SF483)	
HUMAN|HGNC = 9766|UniProtKB = P51159	ENSG00000069974	Ras-related protein Rab-27A; RAB27A; ortholog	RAS-RELATED PROTEIN RAB-27A (PTHR24073:SF511)	

(continued)

Table 2 (continued)

Gene ID	Mapped IDs	Gene name/gene symbol	Panther family/subfamily	Panther protein class
HUMAN|HGNC = 9772|UniProtKB = Q13637	ENSG00000118508	Ras-related protein Rab-32; RAB32; ortholog	RAS-RELATED PROTEIN RAB-32 (PTHR24073:SF862)	
HUMAN|HGNC = 16519|UniProtKB = Q9BZG1	ENSG00000109113	Ras-related protein Rab-34; RAB34; ortholog	RAS-RELATED PROTEIN RAB-34 (PTHR24073:SF468)	
HUMAN|HGNC = 9774|UniProtKB = Q15286	ENSG00000111737	Ras-related protein Rab-35; RAB35; ortholog	RAS-RELATED PROTEIN RAB-35 (PTHR24073:SF933)	
HUMAN|HGNC = 9778|UniProtKB = P20337	ENSG00000169213	Ras-related protein Rab-3B; RAB3B; ortholog	RAS-RELATED PROTEIN RAB-3B (PTHR24073:SF396)	
HUMAN|HGNC = 9781|UniProtKB = P20338	ENSG00000168118	Ras-related protein Rab-4A; RAB4A; ortholog	RAS-RELATED PROTEIN RAB-4A (PTHR24073:SF450)	
HUMAN|HGNC = 9784|UniProtKB = P61020	ENSG00000111540	Ras-related protein Rab-5B; RAB5B; ortholog	RAS-RELATED PROTEIN RAB-5B (PTHR24073:SF555)	
HUMAN|HGNC = 9786|UniProtKB = P20340	ENSG00000175582	Ras-related protein Rab-6A; RAB6A; ortholog	RAS-RELATED PROTEIN RAB-6A (PTHR24073:SF421)	
HUMAN|HGNC = 9788|UniProtKB = P51149	ENSG00000075785	Ras-related protein Rab-7a; RAB7A; ortholog	RAS-RELATED PROTEIN RAB-7A (PTHR24073:SF556)	
HUMAN|HGNC = 30273|UniProtKB = Q92930	ENSG00000166128	Ras-related protein Rab-8B; RAB8B; ortholog	RAS-RELATED PROTEIN RAB-8B (PTHR24073:SF22)	

HUMAN|HGNC = 11276|UniProtKB = O15020	ENSG00000173898	Spectrin beta chain, non-erythrocytic 2; SPTBN2; ortholog	SPECTRIN BETA CHAIN, NON-ERYTHROCYTIC 2 (PTHR11915:SF325)	
HUMAN|HGNC = 11566|UniProtKB = O15533	ENSG00000231925	Tapasin; TAPBP; ortholog	TAPASIN (PTHR23411:SF5)	Immunoglobulin receptor superfamily(PC00124)
HUMAN|HGNC = 30683|UniProtKB = Q9BX59	ENSG00000139192	Tapasin-related protein; TAPBPL; ortholog	TAPASIN-RELATED PROTEIN (PTHR23411:SF7)	Immunoglobulin receptor superfamily(PC00124)
HUMAN|HGNC = 11785|UniProtKB = P07996	ENSG00000137801	Thrombospondin-1; THBS1; ortholog	THROMBOSPONDIN-1 (PTHR10199:SF78)	
HUMAN|HGNC = 9956|UniProtKB = Q01201	ENSG00000104856	Transcription factor RelB; RELB; ortholog	TRANSCRIPTION FACTOR RELB (PTHR24169:SF18)	P53-like transcription factor(PC00253); Rel homology transcription factor(PC00252); nucleic acid binding(PC00171)
HUMAN|HGNC = 12731|UniProtKB = P42768	ENSG00000015285	Wiskott-Aldrich syndrome protein; WAS; ortholog	WISKOTT-ALDRICH SYNDROME PROTEIN (PTHR23202:SF35)	Actin family cytoskeletal protein(PC00041)
HUMAN|HGNC = 910|UniProtKB = P25311	ENSG00000160862	Zinc-alpha-2-glycoprotein; AZGP1; ortholog	ZINC-ALPHA-2-GLYCOPROTEIN (PTHR16675:SF198)	

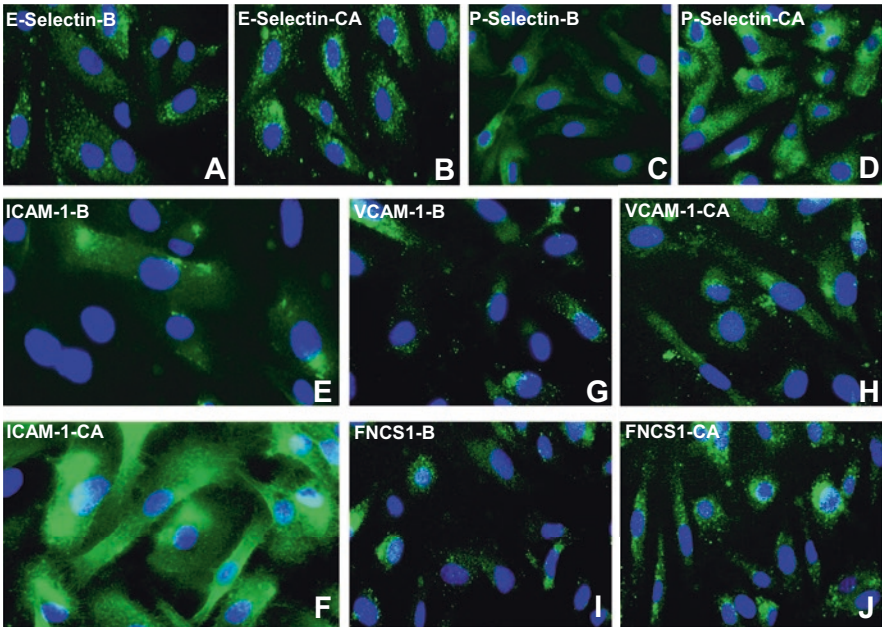

Fig. 4 Composite indirect fluorescent digital photomicrographs showing cellular adhesion molecule expression by confluent primary human endoneurial endothelial cells under basal and physiological cytokine-activated states in vitro (B indicates expression under basal culture conditions; CA indicates expression following cytokine activation with 10 U/mL TNF-α and 20 U/mL IFN-γ for 24 hours) A, C, E, G and I indicate cellular adhesion molecule expression under basal cultures conditions, while B, D, F, H and J indicate upregulated expression following physiological cytokine stimulus in vitro

Structural and Functional Changes at the BNB Associated with Autoimmune Disorders

Increased permeability of or leukocyte trafficking at the human BNB, commonly cited as "BNB breakdown," has been pathologically associated with peripheral nerve autoimmune disorders, with a paper reporting downregulation of BNB tight junction protein claudin-5 and translocation of ZO-1 by immunohistochemistry in sural nerve biopsies of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), without change in occludin expression [21]. It is important to recognize that claudin-5 was also expressed on epineurial macrovessels that do not form the restrictive tight junctions [21], as well as immature endoneurial microvessels during development [23], calling to question its role in mediating restrictive junction barrier function in human peripheral nerves. Importantly, this commonly held viewpoint implies that the human BNB is relatively passive during autoimmune disorders affecting peripheral nerves.

Recent data demonstrating the complexity of the restrictive junction components and possible redundancy of tight junction-forming molecules involved in the human BNB [22] suggest that downregulation of a single tight junction-forming molecule or reduction in TEER or increase in solute permeability demonstrated in vitro following administration of sera from GBS or CIDP patients [56–58] may be an insufficient structural or functional change at the human BNB in vivo during autoimmune disorders. In support of this, physiological cytokine stimulus of confluent primary human endoneurial endothelial cells grown on transwell inserts with TNF-α and IFN-γ over a 100-fold range did not alter TEER in vitro [55]. Ultrastructural examination of endoneurial microvessels within the inflammatory milieu from patients with GBS and CIDP demonstrates intact electron-dense intercellular tight junctions, with similar electron-dense contacts between infiltrating leukocytes and endothelial cells (Fig. 5) [59, 60]. These observations should provide the impetus for further studies to better understand biologically relevant structural and functional alterations at the human BNB during peripheral nerve autoimmune disorders relative to healthy nerves.

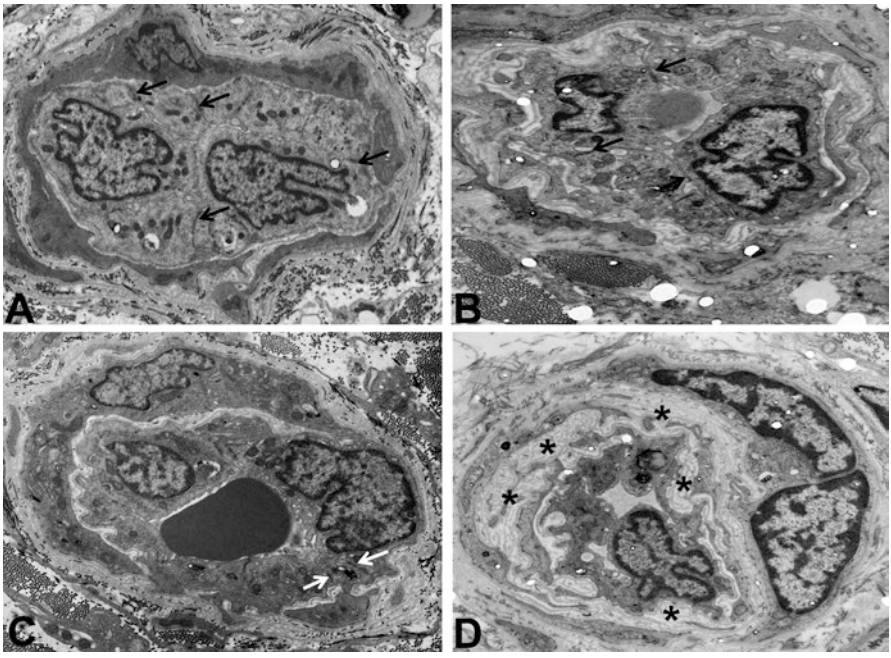

Fig. 5 Composite digital electron ultramicrographs demonstrating intact electron-dense intercellular tight junctions (solid black arrows) between endoneurial endothelial cells within the inflammatory milieu in a GBS (**a**) and CIDP (**b**) patient sural nerve biopsy, with electron-dense intercellular contacts observed between infiltrating leukocytes and endothelial cells (**c**, white arrows) and endoneurial microvessel basement membrane duplication (**d**, black asterisk)

Endoneurial microvessel basement membrane thickening/duplication (Fig. 5d) has been described in association with CIDP and peripheral nerve vasculitis (which typically affects epineurial arteries or arterioles and rarely involves endoneurial capillary-like vessels with resultant endoneurial ischemia) [60–62]. The functional implications of the basement membrane alterations are undetermined; however, this may reflect an adaptive or maladaptive response to chronic and persistent endothelial cell/pericyte pro-inflammatory cytokine exposure or hypoxia/ischemia as a compensatory or reactive means of maintaining BNB functional integrity.

BNB Endothelial-Leukocyte Interactions in Immune-Mediated Neuropathies

While it is unresolved whether systemic immune system activation (e.g., by infections, minor surgery or trauma) with primary attack of peripheral nerves and nerve roots (through the process of "molecular mimicry") [63, 64] or endogenous activation of the innate immune system in peripheral nerves (e.g., by viruses) [65] with secondary selective adaptive immune system activation in genetically susceptible individuals is responsible for tissue-specific autoimmunity, or whether suspected circulating polyclonal anti-myelin protein, anti-axonal nodal protein, and anti-ganglioside or anti-glycolipid autoantibodies can cross the human BNB in vivo, a pathologic hallmark of autoimmune neuropathies is the infiltration of subpopulations of hematogenous leukocytes in peripheral nerves and nerve roots, commonly demonstrated in situ on patient nerve biopsies [61].

In GBS and CIDP, leukocyte infiltration is associated with demyelination, axonal degeneration, or both. In peripheral nerve vasculitis, leukocyte infiltration is associated with vascular wall infiltration, transmural vasonecrosis, and endoneurial ischemia. In HIV-associated distal sensory polyneuropathy (DSP), although not considered an autoimmune neuropathy, clusters of leukocytes are also seen within the endoneurium, associated with axonal loss. Since endoneurial microvessels that form the BNB provide the main route of entry for hematogenous leukocytes from circulation into the endoneurium, leukocyte-endothelial cell interactions are important in the pathogenesis of peripheral nerve autoimmune disorders. In support of this, hematogenous leukocytes interacting with the endoneurial microvessels that form the BNB have been observed in untreated patients with GBS, CIDP, and HIV-DSP in situ (Fig. 6).

Using a flow-dependent leukocyte-BNB trafficking model in vitro, untreated GBS, CIDP, and HIV-DSP patient peripheral blood mononuclear leukocytes (PBMLs) firmly adhere to the surface of confluent primary endoneurial endothelial cells and undergo paracellular transmigration at higher rates that normal healthy donor PBMLs in vitro [53, 55], supporting the notion that leukocyte trafficking at the BNB is pathogenically relevant to autoimmune peripheral neuropathies and potentially HIV-DSP.

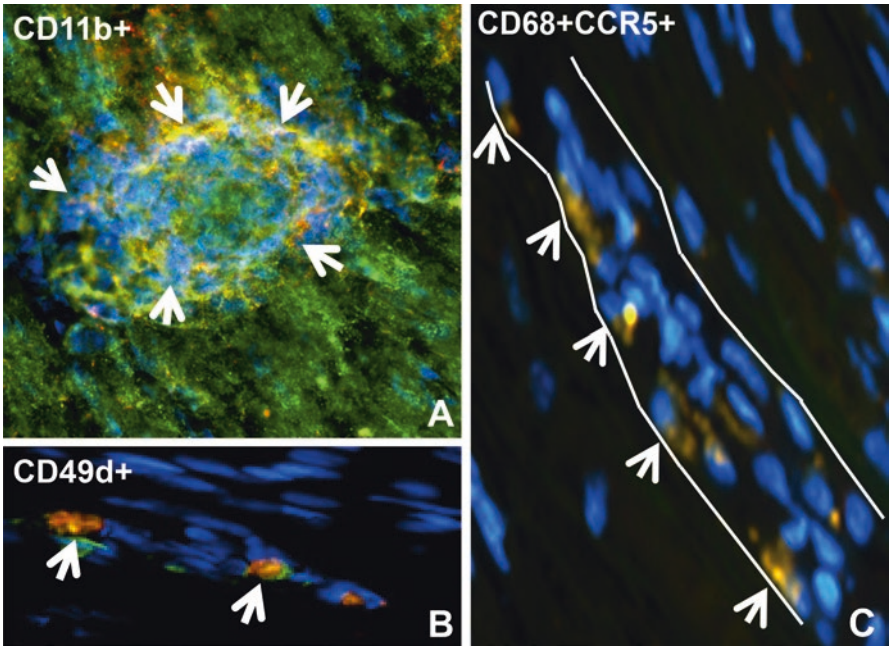

Fig. 6 Composite digital indirect fluorescent photomicrographs showing interaction between hematogenous leukocytes and endoneurial microvessels in GBS (**a**; CD11b+), CIDP (**b**; CD49d+), and HIV-DSP (**c**; CD68+ CCR5+) patient sural nerve biopsies (yellow cells shown with white arrows). S100β+ myelinating Schwann cells associated with axons (green) are also depicted in **a**. The outline of an endoneurial microvessel in longitudinal section is shown with the white lines in **c**

Subpopulation Leukocyte Infiltration in Immune-Mediated Neuropathies

The major challenges in definitively ascertaining the phenotypic characteristics of infiltrating leukocytes in autoimmune neuropathies include disease heterogeneity, the scarcity of pathologic patient biopsies for large-scale comparative analyses, the frequent analysis of sural nerves that may be partially involved in the disease process but practically safer to biopsy in patients rather than clinically and electrophysiologically affected motor nerves, the paucity or multifocal nature of inflammatory infiltrates reducing the likelihood of detecting pathogenic leukocytes in small specimens, and the selection and ascertainment biases intrinsic to immunohistochemistry studies.

The expression of HLA class II molecules, interleukin 1-beta (IL-1β), IFN-γ, TNF-α, CCL2, CXCL10, and ICAM-1 on endoneurial endothelial cells has been described in peripheral nerve biopsies of GBS patients. Similarly, HLA-DR, interleukin-2 (IL-2), IFN-γ, TNF-α, CXCL10, and ICAM-1 have also been expressed at the human BNB in situ in CIDP patient nerve biopsies at higher levels compared to

control nerves, supporting the notion that local activation of the adaptive immune response at the BNB may be pathogenically significant in GBS and CIDP [66–76]. In a single study, chemokine receptors CCR1 and CCR5 were demonstrated on endoneurial macrophages with CCR2, CCR4, and CXCR3 expressed on infiltrating T lymphocytes in GBS and CIDP patient sural nerve biopsies [76]. Another study demonstrated increased numbers of CCR2+ mononuclear cells in GBS patient nerve biopsies [69].

Guided by in vitro observations implying a role for leukocyte integrin CD11b (also known as α_M-integrin or Mac-1)-ICAM-1 interactions in mediating pathogenic leukocyte trafficking at the human BNB under hydrodynamic forces mimicking in vivo capillary flow rates [55], expression of clusters of infiltrated CD11b+ leukocytes interacting with endoneurial endothelial cells that accumulate within untreated GBS patient sural nerve biopsy endoneurium has been shown (Fig. 7) [59]. Similarly, CD49d+ (also known as α_4-integrin or very late antigen-4) mononuclear leukocytes in CIDP patient sural nerve biopsy endoneurium [53] and CCR5+ and CD11d+ (also known as α_D-integrin) mononuclear leukocytes in untreated HIV-DSP patient sural nerve biopsies have been demonstrated (Fig. 6), consistent with a prior report indicating a predominance of CCR5-dependent and macrophage tropic HIV-1 virus based on sequence analysis and evaluation of infectious recombinant viruses containing peripheral nerve-derived C2V3 sequences in autopsied sural and peroneal nerves in decedent HIV+ individuals [77].

Peripheral nerve vasculitis is typically associated with leukocyte infiltration of epineurial macrovascular endothelium walls, rather than direct involvement with endoneurial microvessels that form the BNB. However, strong expression of HLA class I and class II molecules on affected vascular endothelial cells has been described, typically associated with prominent CD4+ and fewer CD8+ T lymphocytes and CD68+ macrophages. CD22+ B lymphocytes and CD16+ natural killer cells are less commonly observed in vasculitic neuropathy than T lymphocytes and macrophages. T lymphocyte infiltrates in vasculitic neuropathy are heterogeneous based on T-cell receptor Vβ utilization, similar to descriptions in CIDP, supporting the polyclonal nature of these conditions [74, 75, 78–81].

Expression of CD58 (also known as lymphocyte function-associated antigen-3; a cell adhesion molecule typically expressed on antigen-presenting cells such as macrophages and binds to CD2 on T lymphocytes) and CD86 (a protein expressed on antigen-presenting cells that provides costimulatory signals necessary for T-cell activation and survival) on affected vascular endothelial cells have also been described, with the former also expressed by Schwann cells [75]. Variable focal expression of hypoxia-inducing factors (HIFs), HIF-1α, HIF-1β, and HIF-2α, as well as VEGF, VEGFR, and erythropoietin receptor was seen on endoneurial microvessels in a small percentage of nerve biopsies from patients with vasculitic neuropathy at higher rates than control sural nerve biopsies [82, 83].

Recent work elucidating the normal adult BNB transcriptome provides molecular targets putatively involved in cross-talk between the innate (Table 1) and adaptive (Table 2) immune responses in peripheral nerves. Validation of these proposed molecules and their associated signaling networks, as well as future single cell tran-

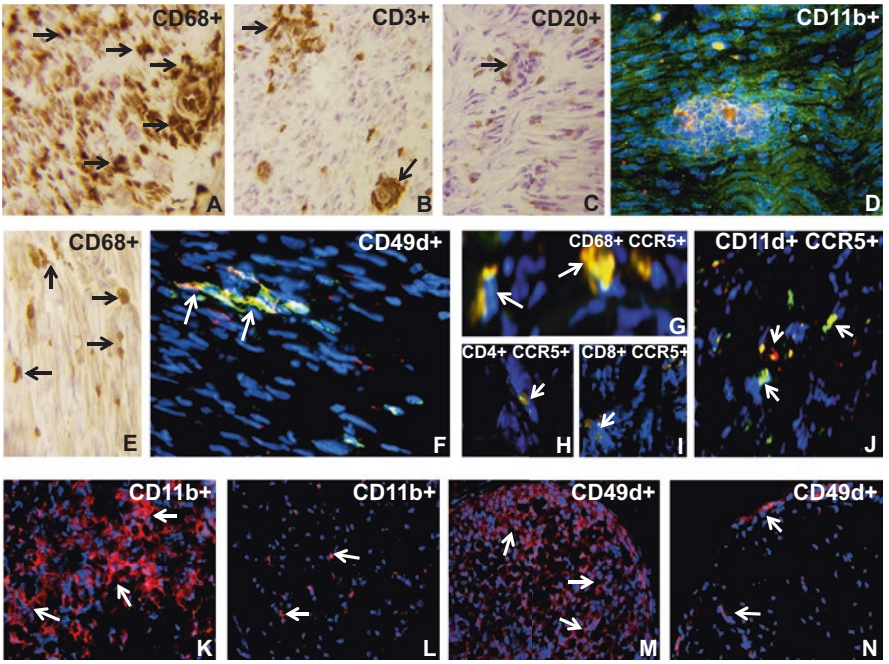

Fig. 7 Composite digital indirect fluorescent photomicrographs depicting subpopulations of hematogenous leukocytes that have infiltrated into sural nerve endoneurium in untreated GBS (**a**–**d**)-, CIDP (**e**, **f**)-, and HIV-DSP (**g**–**j**)-affected patients, the sciatic nerves of representative murine GBS (**k**, **l**) and CIDP (**m**, **n**) animal models, and the effect of targeted molecular inhibition in the mouse models. Clusters of infiltrated monocytes/macrophages (**a**), T lymphocytes (**b**), B lymphocytes (**c**), and CD11b+ leukocytes in a region of demyelination (**d**; green depicts S100β+ myelinating Schwann cells associated with axons) are shown in GBS patients, and clusters of infiltrated monocytes/macrophages (**e**) and CD49d+ leukocytes (**f**) are shown in CIDP patients, with CCR5+ monocytes/macrophages (**g**), CD4+ T lymphocytes (**h**), CD8+ T lymphocytes (**i**), and CD11d+ leukocytes (**j**) shown in HIV-DSP patients. The sciatic nerve of an untreated severe EAN-affected mouse shows intense endoneurial infiltrates of CD11b+ leukocytes (**k**) with a significant reduction in infiltrates seen in another mouse treated with a function-neutralizing rat anti-mouse CD11b monoclonal antibody (**l**). The sciatic nerve of an untreated SAPP-affected mouse shows intense CD45+ leukocyte infiltrates (**m**) that are significantly reduced in another mouse treated with a fibronectin-connecting segment 1 peptide (**n**) early in the disease course. Examples of infiltrated leukocytes are depicted with either black or white arrows in the photomicrographs

scriptomics and proteomics studies, could provide avenues to more comprehensively elucidate molecular changes at the human BNB in situ and characterize the different infiltrated leukocyte subpopulations associated with specific peripheral nerve autoimmune disorders required to better understand the pathogenesis of these conditions and also understand how HIV-infected leukocytes could gain access into peripheral nerves. The ultimate goal is to devise targeted efficacious molecular therapies for autoimmune neuropathies and prevent the development of consequential chronic neuropathic pain.

Animal Models and Targeted Inhibition of Pathogenic Leukocyte Trafficking

Despite the limitations of autoimmune neuropathy animal models and species differences in BNB function and the inflammatory cascade [84, 85], experimental observations made in representative animal models guided by data derived from human in situ leukocyte-BNB interactions in autoimmune neuropathies could provide further insights into the pathogenesis of these disorders and the adaptive or pathological changes that occur at the BNB during autoimmunity. Animal models could also aid dissect the mechanisms by which the systemic immune system engages with peripheral nerves and nerve roots during normal physiologic states and the earliest signaling pathways associated with tissue-specific autoimmune disorders.

Experimental autoimmune neuritis (EAN, an established model of GBS) in the Lewis rat implicated important roles of CD11a (also known as α_L-integrin or lymphocyte function-associated antigen-1) in disease induction [86] and CCL3 and partially CCL2 in pathogenic leukocyte trafficking [87]. Pharmacologic blockade and germline gene knockout of CCR2 (expressed by monocytes/macrophages and a subset of T lymphocytes which most commonly binds to CCL2) ameliorated disease in a severe murine EAN model associated with markedly attenuated leukocyte trafficking into the sciatic nerves [9], while germline CCR5 knockout did not modulate disease in a less severe murine EAN model associated with compensatory increase in sciatic nerve CCL4 and CXCL10 expression [88]. Integrin blockade with a depleting function-neutralizing rat anti-mouse CD11b monoclonal antibody administered after clinically discernible disease onset was efficacious in the severe murine EAN model (Fig. 7) [59], providing further insight into the molecular determinants of pathogenic leukocyte trafficking in acute autoimmune neuropathies in vivo.

Chronic relapsing EAN animal models have been employed to understand CIDP pathogenesis; however, these models are generally limited by variable disease onset and severity. A severe murine chronic demyelinating neuritis model has been established in the autoimmune disease-susceptible CD86 (also known as B7-2)-deficient non-obese diabetic mouse strain, known as spontaneous autoimmune peripheral polyneuropathy (SAPP) that recapitulates features of severe CIDP [89, 90]. In this model associated with a cell and humoral autoimmune response to myelin protein zero [91], peptide blockade of fibronectin connecting segment 1 (which serves as an endothelial counterligand for CD49d or α_4-integrin) ameliorated disease to a similar magnitude as functional neutralizing rat anti-mouse monoclonal CD49d and VCAM-1 antibodies, associated with reduced leukocyte infiltration into the sciatic nerves (Fig. 7) [53], providing further insight into the molecular determinants of pathogenic leukocyte trafficking in chronic autoimmune neuropathies in vivo.

Future Directions

The human BNB, formed by endoneurial microvascular endothelial cells, is a critical interface hypothetically essential to the cross-talk between components of the systemic immune system and peripheral nerves and nerve roots in health during normal immune surveillance and in disease states that manifest as autoimmune neuropathies. The molecular determinants and signaling pathways responsible for hematogenous leukocyte interaction with and trafficking across the human BNB in health and disease are incompletely understood, with advances being made using a near-physiological flow-dependent leukocyte-endothelial cell trafficking model and animal models of peripheral nerve autoimmune disorders, critically supported by observational in situ data obtained from human peripheral nerve biopsies. Applying bioinformatics analyses to transcriptomic and proteomic data derived from normal and pathologic peripheral nerves at the batch or single cell level to establish biologically relevant networks/signaling pathways could accelerate our knowledge of the essential structural and functional characteristics of the human BNB in health, alterations, or adaptations in autoimmune disorders and aid discover molecular targets for disease-specific therapeutic modulation in this group of disorders that takes into account the unique biology of the BNB and the peripheral nervous system.

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