Table SI. Localization of TMEMs in cells.

TMEMs	Assigned organelle/s	Experimental method	(Refs.)
TMEM16F	Plasma membrane	Immunofluorescence	(10)
TMEM16A	Plasma membrane	Immunofluorescence and electrophysiology	(11)
TMEM88	Plasma membrane	Immunofluorescence and immunohistochemistry	(12)
TMEM72	Plasma membrane/ER	Epitope-tagged construct imaging	(13,15,21)
TMEM66/SARAF	ER	Confocal microscopy and co-immunoprecipitation	(67)
TMEM127	Plasma membrane/lysosomes	Confocal microscopy	(17)
TMEM45A	Golgi	Immunohistochemical staining	(25)
TMEM176A/B	Golgi	Retention using selective hooks system fluorescence-based analysis and immunofluorescence	(26,27)
TMEM59	Golgi	Immunocytochemistry	(28)
TMEM173	ER/Golgi	Immunostaining	(29)
TMEM242	Mitochondria	Immunofluorescence	(33)
TMEM65	Mitochondria	Immunostaining	(35)
TMEM63A	Lysosomes	Immunofluorescence	(20)

TMEMs, transmembrane proteins.

Table SII. TMEMs-associated with non-cancerous diseases grouped by shared biological mechanism.

A, Ion channels, transporters and phospholipid scrambling				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM16F	Scott syndrome	TMEM16F was shown to directly mediate phosphatidylserine exposure in cells loaded with Ca^{2+} ionophore, and TMEM16F-deficient cells failed to expose it.	Study type: Expression cloning and *in vitro* functional study (mouse lymphocyte lines) with analysis of cells from a patient with Scott syndrome. Evidence category: Established causal human genetic and functional evidence. Pathogenic variants in patients, defective platelet phospholipid scrambling and biochemical experiments demonstrated a direct disease mechanism.	(51)
TMEM16F	Bleeding disorders	Platelets without TMEM16F were unable to stimulate aminophospholipid externalization; five acidic amino acids of TMEM16F were important for Ca^{2+} binding and PLSCR activity.	Study type: *Ex vivo* study of human platelets, including platelets from patients with Scott syndrome. Evidence category: Established causal human genetic and functional evidence. Patient mutations and defective aminophospholipid externalization support a direct role in Scott syndrome and related bleeding phenotypes; ↑: PLSCR.	(10,52)
TMEM16A	Bowel syndrome	TMEM16A was downregulated in short bowel syndrome model rats with symptoms of dysmotility.	Study type: Animal study (rat model of short bowel syndrome). Evidence category: Animal expression and association evidence. Reduced expression in a rat disease model is associated with intestinal dysmotility; this does not establish TMEM16A as a causal determinant in human short bowel syndrome.	(54)
TMEM16A	Sweat production	Ectodermal tissue-specific deletion of Orai1 or STIM1/STIM2 led to a failure to produce sweat despite normal sweat gland development in mice, owing to the loss of SOCE-dependent TMEM16A activation.	Study type: Animal studies (mouse embryos; ectodermal tissue-specific knockout mice); *in vitro* human sweat gland cells and biopsy samples; individual patient case reports (ORAI1/STIM1 mutations). Evidence category: Strong human genetic and functional evidence. Loss-of-function ORAI1/STIM1 mutations in humans, together with mouse tissue-specific deletion and functional studies, support a direct role in sweat production and thermoregulation.	(55-57)
TMEM16A	Other disease	TMEM16A knockout mice diminished rhythmic smooth muscle contraction of the gastrointestinal tract.	Study type: Animal study (knockout mice) with *in vitro* functional analyses. Evidence category: Strong physiological and preclinical functional evidence. Knockout, localization, electrophysiological and pharmacological studies establish TMEM16A as a calcium-activated chloride-channel component; disease-specific human causality varies by phenotype; ↑: CaCCs.	(53)
TMEM16A	Other disease	TMEM16A antibody inhibited CaCCs of arterial smooth muscle cells.	Study type: *In vitro* study (isolated rat cerebral artery smooth muscle cells). Evidence category: Cellular functional evidence; disease relevance is indirect; ↑: CaCCs	(11)
TMEM16A	Other disease	Transfected TMEM16A-GFP in 293 cells displayed response similar to CaCCs.	Study type: *In vitro* study (murine smooth muscle cells; transfected 293 cells). Evidence category: Expression and heterologous functional evidence; disease relevance is indirect; ↑: CaCCs	(58)
TMEM16A	Other disease	TMEM16A is involved in several diseases including motility disorders, hypertension, cystic fibrosis and various	Study type: Review article. This review is cited only to summarize TMEM16A involvement across multiple disease categories, which no single primary study covers.	(59)

		cancer types, such as gastrointestinal cancer.	Evidence category: Summarized experimental evidence; ↑: CaCCs	
TMEM163	Mucolipidosis type IV	Knockdown of TMEM163 induced increased intracellular zinc levels in 293 cells.	Study type: *In vitro* studies (293 cells; fibroblasts derived from patients with mucolipidosis type IV). Evidence category: Human disease and functional cellular evidence. Altered TMEM163 expression in patient-derived fibroblasts and zinc-accumulation phenotypes after knockdown support a disease-relevant role; the strength of variant-level causal evidence should be clarified; ↓: zinc levels.	(60,61)
TMEM263	Learning defects	TMEM263 was directly associated with Slick and Slack, sodium-activated potassium channels.	Study type: *Ex vivo* proteomic study (mouse brain tissue). Evidence category: Protein-interaction and experimental evidence. Association with Slick and Slack potassium channels was observed in the mouse brain, but direct evidence linking TMEM263 to human learning disorders is lacking; ↑: Slick and Slack.	(50)
TMEM52, TMEM233, TMEM38A and TMEM38B	Aging-related skeletal muscle disorders	These four genes are preferentially expressed in skeletal muscle and/or overlap muscle-specific super-enhancers	Study type: Bioinformatic analysis of human transcriptomic and epigenomic databases (GTEx). Evidence category: Expression, regulatory and genetic evidence. Tissue-expression and enhancer data suggest roles in skeletal muscle biology, whereas TMEM38B has additional mutation-based disease evidence; the evidence is not equivalent among these genes.	(62)
B, Calcium signaling (SOCE)				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM142/ORAI	Immunodeficiency	Pore-forming subunit of the CRAC channel; opened by STIM1 after ER Ca^{2+} depletion. Re-expression of wild-type ORAI1 in patient T cells restored store-operated Ca^{2+} influx and the CRAC current	Study type: Human patient study (family with hereditary severe combined immunodeficiency) with *in vitro* analysis of patient-derived T cells. Loss-of-function mutations (e.g., R91W) cause combined immunodeficiency with autoimmunity, muscle hypotonia and anhidrosis. Evidence category: Established causal human genetic and functional evidence. Complementation of patient T cells with wild-type ORAI1 confirmed the pathogenicity of the mutation.	(63,64)
TMEM142/ORAI1	Immunodeficiency	Orai1-deficient mice showed markedly reduced SOCE, CRAC currents and cytokine production in T cells, together with impaired Ca^{2+} influx and proliferation of B cells.	Study type: Animal study (Orai1-deficient mice) with *ex vivo* T- and B-lymphocyte analyses. Evidence category: Mouse knockout and cellular functional evidence.	(65)
TMEM142/ORAI1	Immunodeficiency	Mast cells derived from Orai1-deficient mice showed defective degranulation, leukotriene C4 release and TNF-α production.	Study type: Animal study (Orai1-deficient mice) with *ex vivo* bone marrow-derived mast cell assays. Evidence category: Mouse knockout and cellular functional evidence.	(66)
TMEM66/SARAF	Acute pancreatitis	ER protein that switches SOCE off (slow Ca^{2+}-dependent inactivation), preventing Ca^{2+} overload. Saraf knockout mice	Study type: *In vitro* studies (293 and Jurkat T cells); animal study (Saraf knockout mice) with human pancreatic tissue expression data. Loss of SARAF increases Ca^{2+} entry. In mice, pancreatic SARAF deletion worsens acute pancreatitis.	(67,68)

		developed more severe caerulein- or L-arginine-induced pancreatitis with increased acinar-cell Ca^{2+} influx, whereas acinar overexpression of SARAF reduced Ca^{2+} influx, inflammation and disease severity; SARAF mRNA was reduced in pancreatic tissue from patients with pancreatitis.	Evidence category: Mouse genetic and pharmacological evidence with supporting human expression data; human genetic evidence is lacking.	
C, Lysosomal biology and autophagy				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM106B	Lysosomal disorder	Elevated TMEM106B was shown in neuronal ceroid lipofuscinosis model mice and the brains of patients with FTLD-TDP/GRN.	Study type: Animal studies (mouse models of neuronal ceroid lipofuscinosis/progranulin deficiency); human post-mortem brain tissue. Evidence category: Genetic modifier, biomarker and experimental evidence. Susceptibility associations, patient-tissue accumulation and cellular/mouse studies support a modifying or disease-related role, rather than a universally established causal role.	(69)
TMEM106B	Neuron disorder	Accumulation of TMEM106B C-terminal fragments was found in cases of neuron degeneration and neurologically normal aging.	Study type: Human post-mortem brain tissue studies. Evidence category: Biomarker and susceptibility evidence. Genetic associations and accumulation of TMEM106B fragments in patient and aged brain tissue support a disease-related association, but do not by themselves establish causality.	(38,70)
TMEM240	SCA21	TMEM240 mutations were found in patients with SCA21 and were related with dendritic development and motor coordination.	Study type: *In vitro* studies (HeLa cells; primary rat Purkinje cells); animal study (mice expressing SCA21-mutant TMEM240). Evidence category: Strong causal genetic evidence with experimental support. Patient mutations are supported by cellular and mouse studies showing lysosomal, neuronal and motor phenotypes; ↓: autophagic lysosomal proteins.	(71-73)
TMEM39A	Autoimmune diseases	TMEM39A mutant showed reduced mobility and improper distribution of lysosomes.	Study type: Invertebrate study (*C. elegans*); *in vitro* study (293T cells). Evidence category: Invertebrate and cellular mechanistic evidence; a direct link to human autoimmune disease has not been shown; ↑: DYNC1I2, mTOR signaling	(74)
TMEM175 and TMEM163	Parkinson's disease	Variants of TMEM175 (p.K176E) and TMEM163 (p.P33R) were associated with Parkinson's disease. TMEM175 functions as a K^+ channel in endosomes and lysosomes and regulates lysosomal function, providing a candidate mechanism for these variants.	Study type: Human patient cohort study (whole-exome sequencing of 743 patients with early-onset Parkinson's disease). Evidence category: Preliminary genetic association evidence. Rare variants were identified in patients, but causality and disease mechanisms remain insufficiently established. Mechanistic support for TMEM175 comes from separate *in vitro* electrophysiological and cell-biological studies.	(47,75)
D, Mitochondrial homeostasis				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM126B	Metabolism dysfunction	TMEM126B knockdown decreased mitochondrial derived ROS.	Study type: Human patient case series (exome sequencing of three affected adults); *in vitro* knockdown study (human macrophage-like cells).	(32,76)

			Evidence category: Human genetic and mechanistic evidence. Exome-sequencing findings in affected individuals and mitochondrial functional studies support TMEM126B as a disease-related complex-I assembly factor; the strength of causality depends on variant-level validation; ↑: SDHA, HIF-1α, IL-1β.	
TMEM135	Age-related retinal degeneration	Disruption of TMEM135 resulted in increased size and decreased number of mitochondria.	Study type: Mouse genetic studies (ENU-induced TMEM135 mutant mice and TMEM135-overexpressing transgenic mice) with confocal and electron microscopy. Evidence category: Cellular and animal mechanistic evidence. Localization, overexpression and loss-of-function studies implicate TMEM135 in mitochondrial dynamics and metabolism; direct human causal evidence is limited; ↑: DRP1.	(77,78)
TMEM70 and TMEM242	Mitochondrial ATP synthase and complex I assembly defects	Deletion of TMEM70 and TMEM242 inhibited the assembly of ATP synthase and the mitochondrial complex I.	Study type: *In vitro* study (human cell lines with gene deletion). Evidence category: Experimental genetic and biochemical evidence. Deletion and interaction studies demonstrate roles in mitochondrial complex assembly; ↑: ATP synthase, mitochondrial complex I.	(33)
E, ER function and membrane trafficking				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM39	Aging	Knockdown of TMEM39 led to defects in collagen secretion and high ER stress response.	Study type: Invertebrate studies (*C. elegans*, *Drosophila*); *in vitro* human cell studies. Evidence category: Cross-species experimental and mechanistic evidence. Invertebrate knockdown, human cellular studies and protein-interaction data support roles in collagen secretion and ER homeostasis; direct human causal evidence for aging-related disease is limited; ↑: Sec23A	(22)
TMEM45A	Epidermal keratinization	TMEM45A expression was upregulated in keratinocytes *in vitro* and *in vivo.*	Study type: *In vitro* study (primary human keratinocytes; reconstructed epidermis); human skin tissue. Evidence category: Human and cellular expression evidence. Localization and expression in keratinocytes support a role in epidermal differentiation, but direct disease causality has not been demonstrated; ↑: KRT10, FLG.	(25)
TMEM16A	Non-alcoholic fatty liver disease	Hepatocyte-specific TMEM16A deletion ameliorated hepatic glucose metabolic disorder in mice.	Study type: Animal study (knockout and hepatocyte-specific transgenic mice); human liver tissue. Evidence category: Mouse genetic and mechanistic evidence with human expression support. Mouse knockout/transgenic studies and patient-tissue expression findings implicate TMEM16A in hepatic glucose metabolism, but human causality is not established; ↓: VAMP3/syntaxin 4, VAMP3/synaptosome-associated protein 23 complexes, glucose transporter 2.	(79)
F, Immune sensing				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM176A and TMEM176B	Spinal cord injury	TMEM176A and TMEM176B were upregulated in peripheral blood mononuclear cells from patients with	Study type: Human patient study (peripheral blood mononuclear cells from patients with chronic spinal cord injury). Evidence category: Patient expression and experimental immune-cell evidence.	(80)

		chronic spinal cord injury.	Increased expression in patient blood cells and functional studies suggest altered dendritic-cell activity, but causality in spinal cord injury remains unresolved.	
TMEM39A	Autoimmune diseases	TMEM39A interacted with seven molecules involved in immune system.	Study type: Human genome-wide association study with multi-ancestry replication cohorts, combined with protein-interaction analysis. Evidence category: Genetic susceptibility plus experimental mechanistic evidence. GWAS findings support association with autoimmune disease, while cell and invertebrate studies suggest effects on lysosomal trafficking; causality in humans remains unresolved; ↑: TNFSF13B, BTNL8, HTR3C, IL9R.	(44,74,81)
TMEM160	Pain	TMEM160 knockout male mice showed delayed establishment of tactile hypersensitivity.	Study type: Animal study (knockout mice) with *Ex vivo* dorsal root ganglion cultures. Evidence category: Preclinical mouse evidence. Sex-specific behavioral and neuroimmune phenotypes in knockout mice suggest a role in pain responses; human evidence is unavailable; ↑: TRPA1.	(82)
TMEM176A and TMEM176B	Immune-mediated diseases	Double knockout mice showed that they were required for antigen processing in dendritic cells.	Study type: Animal study (knockout mice) with *Ex vivo* dendritic-cell assays. Evidence category: Mouse knockout and cellular mechanistic evidence. Knockout models support roles in antigen presentation and dendritic-cell function, but individual human disease contributions of each paralog remain uncertain.	(26)
G, Mechanotransduction				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM120A	Reproductive system defects	TMEM120 mutant displayed a deformed germline, maternal sterility, reduced brood size and damaged spermathecal contraction.	Study type: Invertebrate study (*C. elegans*). Evidence category: Invertebrate genetic evidence. Deletion in *C. elegans* produces reproductive and contractility phenotypes, but relevance to human reproductive disease remains unestablished.	(46)
TMEM16A	Neuropathic pain	TMEM16A, the MEK/ERK pathway and NK-1 were activated in the dorsal root ganglion of SD rats after neuropathic pain induced by spared nerve injury.	Study type: Animal study (rat spared nerve injury model). Evidence category: Preclinical animal and pharmacological evidence. Genetic, pharmacological and pathway-interaction studies support involvement in nociceptive signaling, but clinical validation is lacking; ↑: p-ERK/NK-1.	(84)
TMEM16A	Neuropathic pain	The number of TMEM16A-positive cells and the TMEM16A expression level were high in ganglion of chronic constriction injury-induced neuropathic pain rats.	Study type: Animal study (rat chronic constriction injury model). Evidence category: Preclinical animal and pharmacological evidence. These changes were reversed by the TMEM16A antagonist T16Ainh-A01; clinical validation is lacking.	(85)
TMEM16A	Acute/inflammatory pain	TMEM16A physically interacted with TRPV1 and amplifies capsaicin-evoked action potentials and pain-related behaviors.	Study type: *In vitro* electrophysiology and co-immunoprecipitation (293T cells; mouse dorsal root ganglion neurons) with mouse behavioral analysis. Evidence category: Preclinical cellular and animal mechanistic evidence; ↑: TRPV1	(86)
TMEM16A	Neuropathic pain	TMEM16A and PAR2 were co-expressed to increase IP3 in the dorsal root ganglion neurons of chronic constriction	Study type: Animal study (rat chronic constriction injury model). Evidence category: Preclinical animal expression evidence; ↑: PAR2, IP3	(88)

		injury rats.		
TMEM16A	Neuropathic and inflammatory pain	TMEM16A generated depolarizing Ca^{2+}-activated Cl^- currents that enhance action potential firing and nocifensive behaviors in rodent models.	Study type: *In vitro* and animal studies. Evidence category: Preclinical pharmacological and genetic evidence. TMEM16A inhibition or genetic ablation attenuates inflammatory and neuropathic hyperalgesia/allodynia and reduces TRPV1-mediated nociception.	(89,91,92)
TMEM16A	Itch	TMEM16A ablation showed a reduction in scratching behaviors.	Study type: Animal study (conditional knockout and overexpression in mouse dorsal root ganglion neurons). Evidence category: Preclinical animal and mechanistic evidence. Neuronal ablation and overexpression studies implicate TMEM16A in itch signaling, but human disease causality remains unconfirmed.	(95)
H, Nuclear envelope organization				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM48	Embryonic development defects	Loss of TMEM48 interfered with nuclear pore complex assembly of human cells and increased larval and embryonic mortality of *C. elegans.*	Study type: *In vitro* study (HeLa cells); invertebrate study (*C. elegans*). Evidence category: Experimental genetic evidence. Cellular knockdown and *C. elegans* loss-of-function studies demonstrate a role in nuclear-pore assembly and reproduction; direct human reproductive-disease evidence is limited.	(40)
TMEM201	Emery-Dreifuss muscular dystrophy	TMEM201 is absent from the nuclear poles in lamin A-linked Emery-Dreifuss muscular dystrophy.	Study type: *In vitro* study of muscle cells derived from patients with Emery-Dreifuss muscular dystrophy. Evidence category: Human disease-associated and cellular localization evidence. Altered TMEM201 localization was observed in patient-related muscular-dystrophy contexts, but the available data support a possible modifier or mechanistic role rather than definitive causality.	(96)
I, Cytoskeletal regulation and neuronal morphogenesis				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM132	Neurological disorders	TMEM132 family member RNAs were detected in both the central and peripheral nervous system.	Study type: Animal study (mouse embryos; *in situ* hybridization). Evidence category: Expression and developmental evidence. Mouse expression studies suggest a role in nervous-system development, but a direct causal relationship with human neurological disease has not been established.	(97)
TMEM132 and TMEM132D	Panic disorders	Loss-of-function mutants of TMEM132 resulted in abnormal dopaminergic posterior deirid neurons in *C. elegans*.	Study type: Invertebrate study (*C. elegans*); *in vitro* mammalian cell studies. Evidence category: Experimental model evidence. Invertebrate loss-of-function and mammalian cell studies support a possible neuronal mechanism, but the relevance to human panic disorder remains uncertain; ↓: WAVE regulatory complex.	(98)
TMEM132E	Panic disorder	A total of three TMEM132E SNPs were associated with panic disorder.	Study type: Human case-control genetic association study (Danish, Faroese and German cohorts). Evidence category: Limited genetic susceptibility evidence. SNP associations were reported in a restricted cohort, with no established causal variant or validated disease mechanism.	(99)
J, Signal transduction and RNA regulation				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)

TMEM11	Cardiac injury	TMEM11 interacted with METTL1 to activate ATF5 and suppress cardiomyocyte proliferation.	Study type: Animal study (mice); in vitro neonatal cardiomyocytes. Evidence category: Preclinical mechanistic evidence. Mouse cardiomyocyte studies and protein-interaction experiments suggest that TMEM11 may influence cardiac regeneration through the METTL1-ATF5 pathway; ↑: ATF5, INCA1.	(100)
TMEM88	Pleural fibrosis	TMEM88 inhibited the proliferation of human pleural mesothelial Met-5A cells and TGF-β1/Smad signaling.	Study type: *In vitro* study (human pleural mesothelial Met-5A cells). Evidence category: Cellular mechanistic evidence. Overexpression studies in human mesothelial cells support an anti-fibrotic effect through TGF-β/Smad signaling; *in vivo* and human causal evidence remain limited; ↓: TGF-β1/Smad signaling.	(101)
TMEM88	Keloids	Overexpressed TMEM88 inhibited the proliferation, migration and extracellular matrix expression of keloid-derived fibroblasts.	Study type: Human keloid tissue; in vitro study (patient-derived keloid fibroblasts). Evidence category: Cellular mechanistic evidence. Overexpression studies in keloid-derived fibroblasts suggest inhibition of proliferation, migration and extracellular matrix production; clinical and causal evidence are lacking; ↓: β-catenin, cyclin D1, c-Myc.	(102)
TMEM63C	Renal diseases	Knockdown of TMEM63C decreased cell viability and Akt signaling but increased the apoptosis of angiotensin II-activated human podocytes.	Study type: *In vitro* study (human podocytes). Evidence category: Cellular functional evidence. Knockdown studies in angiotensin II-treated human podocytes suggest a pro-survival role through Akt signaling, but *in vivo* and human disease evidence are limited; ↑: Akt signaling.	(103)
TMEM168	Anxiety	TMEM168 enhances anxiety.	Study type: Animal study (mice; adeno-associated virus-mediated overexpression). Preclinical animal and mechanistic evidence: Mouse behavioral studies and neurotransmitters analysis suggest a role in anxiety-related behavior; human causal evidence is unavailable. ↓: GABA	(106)
TMEM168	Dependence symptoms	TMEM168 attenuated methamphetamine-induced hyperlocomotion and dopamine elevation.	Study type: Animal study (mice; adeno-associated virus-mediated overexpression). Evidence category: Preclinical animal and mechanistic evidence. Altered TMEM168 expression and mouse overexpression studies suggest involvement in drug-related behavioral responses; human disease causality has not been demonstrated; ↓: dopamine.	(107)
TMEM59	Neural diseases	siTMEM59 treatment induced neural stem cells to differentiate into neurons and astrocytes.	Study type: *In vitro* studies (C17.2 mouse neural stem cell line; primary neural stem cells). Evidence category: Experimental functional evidence. Overexpression and knockdown studies in mouse neural stem cells support a role in neural differentiation, but direct human disease evidence is limited.	(108,109)
TMEM16A	Inflammation	TMEM16A expression and activity was promoted under inflammatory conditions.	Study type: Review article. Evidence category: Summarized experimental evidence. Cellular and animal studies reviewed therein implicate TMEM16A in inflammatory signaling, but direct human genetic evidence was not established. This review is cited since the statement spans multiple studies and no single primary study covers it; ↑: IP3R-	(105)

			mediated Ca^{2+} signaling, NF-κB and ERK signaling pathways.	
TMEM16A	Kidney injury in aging	TMEM16A inhibitor prevented changes in the senescence-associated secretory phenotype of kidney injury in aging.	Study type: Animal study (aged mice); *in vitro* kidney cell studies. Evidence category: Preclinical cellular, mouse and pharmacological evidence. Age-related signaling changes and inhibitor responses implicate TMEM16A in kidney injury, but human causal evidence is unavailable; ↓: AMPK signaling; ↑: mTORC1 signaling.	(104)
K, Disease associations without a defined mechanism				
Name	Disease	Effects	Study type/evidence category[a]	(Refs.)
TMEM187	ASD	TMEM187 was predicted to interact with four ASD-related genes.	Study type: Single-patient case report (whole-exome sequencing) with in silico protein-interaction analysis. Evidence category: Preliminary candidate-gene evidence. A candidate variant and predicted/interacting ASD-related proteins suggest a possible association, but the evidence is insufficient to establish TMEM187 as a causal autism gene.	(110)
TMEM26	Obesity	The expression of TMEM26 was increased in brown adipose tissue.	Study type: Animal study (mice). Evidence category: Preclinical expression and intervention evidence. Increased TMEM26 expression accompanies flavan-3-ol-induced adipose browning in mice; whether TMEM26 is causal or merely a marker remains unresolved.	(113)
TMEM187	Rheumatoid arthritis	The TMEM187 rs13397 polymorphism in the Xq28 region was associated with rheumatoid arthritis.	Study type: Human case-control genetic association study (100 patients and 100 controls). Evidence category: Limited population-specific genetic association evidence. A polymorphism was associated with rheumatoid arthritis in a small Egyptian cohort; replication and functional validation are required.	(111)
TMEM57	Hyperlipidemia	The rs873308 SNP near TMEM57 was associated with serum lipid levels, with allele effects differing between the Han and Mulao populations.	Study type: Human population-based genetic association study (Han Chinese and Mulao cohorts). Evidence category: GWAS and population-association evidence. Variants near TMEM57 correlate with serum lipid traits in human populations, but the causal gene and biological mechanism remain unresolved.	(112)
TMEM230 TMEM59 TMEM108	Parkinson's disease	Gene mutations of TMEM230, TMEM59 and TMEM108 associated with different types of Parkinson's disease.	Study type: Human patient cohort study (case-control sequencing analysis). Evidence category: Rare-variant association evidence. Damaging variants were reported in patient cohorts; independent replication and functional validation are still required.	(48)

[a]The evidence cited within each category reflects the strongest evidence from those specific studies and does not imply an equal degree of disease causality. Causal evidence refers to human disease-associated variants supported by functional or mechanistic validation. By contrast, susceptibility evidence includes GWA study findings, candidate variants and population associations. Experimental evidence includes cell-based, animal, protein-interaction, localization and pathway studies. Finally, biomarker or expression evidence indicates disease-associated changes without establishing whether the alteration is causal or consequential. Study type indicates the experimental basis of the cited findings: Human genetic, cohort or population-based studies; single-patient case reports; human tissue or patient-derived cells; *in vitro* experiments (cell lines or primary cells); animal models (mouse or rat); invertebrate models (*C. elegans* or *Drosophila*); or review articles (cited only where a statement summarizes a broad body of literature). *In silico refers to* computational protein-interaction or database analysis. ↑: Positively regulated, ↓: Negatively regulated. Akt, protein kinase B; CaCCs, Ca^{2+}-activated Cl^- channels; TMEMs, transmembrane proteins; SNPs, single-nucleotide polymorphisms; ASD, autism spectrum disorder; VAMP3, vesicle-associated membrane protein 3; IL9R, interleukin-9 receptor; TNFSF13B, tumor necrosis factor ligand superfamily member 13B; BTNL8, butyrophilin-like protein 8; ER, endoplasmic reticulum; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; AQP5, aquaporin 5; ATF5, activating transcription factor 5; CRAC, Ca^{2+} release-activated Ca2+;

DRP1, dynamin-related protein 1; DYNC1I2, cytoplasmic dynein 1 intermediate chain 2; FLG, filaggrin; FTLD, frontotemporal lobar degeneration; GRN, progranulin; GTEx, Genotype-Tissue Expression; GWAS, genome-wide association study; HIF-1α, hypoxia-inducible factor-1α; HTR3C, 5-hydroxytryptamine receptor 3C; INCA1, inhibitor of CDK interacting with cyclin A1; IP3, inositol 1,4,5-trisphosphate; KRT10, keratin 10; METTL1, methyltransferase-like 1; mTORC1, mTOR complex 1; NK-1, neurokinin-1 receptor; PAR2, protease-activated receptor 2; PLSCR, phospholipid scramblase; SCA21, spinocerebellar ataxia type 21; SD, Sprague-Dawley; SDHA, succinate dehydrogenase flavoprotein subunit A; SOCE, store-operated Ca^{2+} entry; STIM1, stromal interaction molecule 1; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1.