Human Molecular Genetics, 2009, Vol. 18, Review Issue 2 ***R146–R155***
doi:10.1093/hmg/ddp412

Thermosensory and mechanosensory perception in human genetic disease

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Received August 4, 2009; Revised and Accepted August 24, 2009

Peripheral sensory perception is established through an elaborate network of specialized neurons that mediate the translation of extraorganismal stimuli through the use of a broad array of receptors and downstream effector molecules. Studies of human genetic disorders, as well as mouse and other animal models, have identified some of the key molecules necessary for peripheral innervation and function. These findings have, in turn, yielded new insights into the developmental networks and homeostatic mechanisms necessary for the transformation of external stimuli into interpretable electrical impulses. In this review, we will summarize and discuss some of the genes/proteins implicated in two particular aspects of sensory perception, thermosensation and mechanosensation, highlighting pathways whose perturbation leads to both isolated and syndromic sensory deficits.

INTRODUCTION

Organisms perceive their surroundings primarily through five sensory modalities: sight, smell, hearing, taste and touch. Whereas the first four senses are detected by anatomically isolated, highly specialized organs (retina, tongue epithelium, cochlea and olfactory epithelium), the perception of touch is anatomically complex and involves the largest mammalian organ, the skin. In addition, an elaborate array of sensory neurons extends from the cerebral cortex to the extremities, where they hyper-specialize to convey discrete touch-based sensory components, including thermosensation (temperature perception), mechanosensation (mechanical perception such as pressure, and hearing), nociception (pain perception) and proprioception (perception of self-regulated spatial orientation, movement and balance).

The network that comprises the somatosensory pathway, including innervation at the periphery (extremities), neurons in the spinal cord and the brain, is vulnerable to defects at numerous anatomical sites. Perturbations of receptors at the periphery, improper neurodevelopment or impaired acquisition, transduction and translation of the sensory input can all lead to the loss of proper thermo- or mechanosensation, often as part of broader neurosensory defects. As a result, defects in thermo- and/or mechanosensation are now recognized as either a primary, secondary or tertiary symptom in several clinical disorders.

Despite a relative dearth of information on the molecular basis of thermal and/or mechanosensory deficits in humans, work driven primarily from model organisms has led to the identification of several key players in the somatosensory pathway, most prominently the members of the transient receptor potential (TRP) and degenerin/epithelial Na^+ channel (DEG/ENaC) families (1–3). Here, we will review the anatomy of the mechano- and thermosensory apparatus in the context of genetic lesions that lead to clinical sensory phenotypes. We will also survey known molecules whose loss of function perturbs either the development of the sensory apparatus or its homeostasis and discuss the broad, emerging mechanistic themes.

NEUROGENESIS AND THE ANATOMY OF THE SENSORY APPARATUS: FROM SKIN TO CORTEX

Neurons that specialize in the somatosensory pathway are located in groups that make up the dorsal root ganglia. These pseudounipolar neurons are born at discrete time points during embryonic development and are specified by different neurogenins, transcription factors that allow for the

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establishment of an array of neuronal subtypes (reviewed in 4). The first neurons to develop are the large and medium diameter A-type neurons (Aβ ≥ 10 μm; Aδ = 2–6 μm) that express either tyrosine kinase receptor C or B (TrkC+, TrkB+), followed by small (<30 μm) diameter C-type neurons that express tyrosine kinase receptor A (TrkA+) (4).

During mammalian embryonic development, two main steps of neurogenesis give rise to the somatosensory pathway. At E14 in the mouse, the somata of the first-order sensory neurons, located at the periphery of the spinal cord, begin peripheral fiber-branching and establish their targets. The large-diameter fibers extend first to the periphery, followed by thin-caliber fibers (4). These peripheral fibers terminate in the skin or muscle either as free nerve endings (if they function to detect temperature and in certain circumstances pressure or pain) or as sensory receptors (if they acquire information based on mechanosensation) and represent the primary stimulus sensors. Subsequently, central fiber-branching takes place, where the A-type and C-type fibers attach to the second-order sensory neurons in the lumbar dorsal horn of the spinal cord and penetrate the gray matter, allowing the received information to be relayed to the central nervous system (CNS), specifically the thalamus, to third-order sensory neurons (5). In contrast to the peripheral branches, central fiber endings are located in specific laminar regions of the dorsal horn, depending on whether they function in pain and temperature (lamina I–II) or pressure (lamina III–IV) (4) (Fig. 1).

Most temperature or mechanical stimuli are obtained at the periphery where the somatic sensory receptors, like nociceptors, are located, at the superficial layers of the epidermis. These have been classified further into receptor types based on the characteristics of the axons associated with them: (i) polymodal free nerve endings (unmyelinated, nonpeptidergic C-fibers and lightly myelinated Aδ-fibers) that are responsible for sensing pain, temperature or harsh touch and (ii) mechanosensitive Merkel cells (slow adapting, myelinated Aβ-fibers responsive to touch) (6), Pacinian corpuscles (myelinated Aβ-fibers receptive to vibration) or Meissner's corpuscles (myelinated Aβ-fibers; low threshold, rapid adapting mechanoreceptors that respond to low-frequency vibrations and quivering) (7–9).

TRPS AND THERMOSENSORY DEFICITS

The study of genetic defects impacting touch have proven challenging, in part because of the complex anatomy of this sensory modality and its inherent difficulty in phenotyping objectively in humans. Nonetheless, by studying the properties and targets of hot chili peppers and mint, initiated by expression-cloning experiments, some of the key receptors involved in the somatosensory pathway have been identified, most notably the TRP channels (10–13).

The TRP family of proteins is necessary for the initial acquisition and subsequent transduction of sensory stimuli (14). The TRP superfamily consists of seven subfamilies that fall into two larger groups based on their sequence and topology. Group 1 is composed of the TRPC, TRPV, TRPM, TRPA and TRPN subfamilies, whereas group 2 contains the TRPP and TRPML subfamilies (1). Mammals have at least six thermosensitive ion channels (TRPV1-4, TRPM8 and TRPA1) that belong to the TRP group 1 and have been shown to be expressed in primary afferent sensory neurons. Each of these thermosensitive TRPs (thermoTRPs) has different temperature thresholds at which they are activated (TRPV1 at >43°C, TRPV2 at >53°C, TRPV3 at >33–39°C, TRPV4 at 25–34°C, TRPM8 at 23–28°C or ANKTM1/TRPA1 at 17°C), as well as different sensory neurons in which are predominately expressed (1,15).

In vitro studies focusing on the TRPV1 mRNA transcript showed that it is expressed predominately in nociceptive neurons of the dorsal root ganglia and in trigeminal ganglia and exposure to not only capsaicin, but also to heat allows for its excitation (11,16). In 1846, capsaicin was discovered as the pungent component of peppers that caused the 'burning' sensation when eaten and since then, it has been discovered to activate both nociceptive sensory neurons as well as sodium and calcium cation channels (10,17). Elucidating the function of the capsaicin receptor, TRPV1, was a key advance in our understanding of thermosensation; it was observed *in vivo* that knock-out mice for most of the thermoTRPs have impaired responses to certain temperatures. Differences among the phenotypes observed vary, depending on which of the thermoTRPs are affected. By performing behavioral assays, such as tail immersion and the hot plate test to record temperature response, or the von Frey assay to record mechanical response (18), it was shown that $TRPV1^{-/-}$ mice have a decreased sensitivity to noxious heat, >48°C (16), $TRPV3^{-/-}$ mice have a preference for ambient temperatures around 35°C (19), $TRPV4^{-/-}$ mice are unable to distinguish between 30 and 34°C (20), whereas $TRPM8^{-/-}$ mice show an inefficient reaction to cold temperatures, 23–30°C (21), and $TRPA1^{-/-}$ have deficient responses to noxious cold temperatures, ≤0°C (22).

These phenotypic differences can be partially attributed to the different neuronal subtypes in which thermoTRPs are expressed. TRPV1 and TRPA1 are expressed in small-diameter neurons, TRPV2 in medium to large diameter cells, TRPV3 and TRPV4 in keratinocytes and in small-diameter C-fibers, whereas TRPM8 is also expressed in small-diameter neurons that are non-TRPV1, non-nociceptive (15). Interestingly, TRPV2 and TRPV4 (which have been shown previously to be expressed in cells that sense osmotic pressure) as well as other mechanoreceptors (23) have also been reported to be expressed in mechanosensitive nociceptors (24,25).

Since the TRPs are key players in the somatosensory pathway, it is probable that thermoTRP-defective clinical phenotypes have been unappreciated due to the primary phenotypes associated with the disease. To date, there is only one thermoTRP that has been shown to result in human disease. Mutations in *TRPV4* have been shown to cause bone dysplasias (brachyolma type 3, spondylometaphyseal dysplasia and metatropic dysplasia) (26), whereas loss of the same protein has also been proposed as a deafness candidate (27), as well as being associated with human hyponatremia (28). It might be important to ask whether patients with TRPV4 mutations also manifest more subtle thermosensory phenotypes and whether mutations in any of the other thermoTRPs also contribute to the pathogenicity of disease.

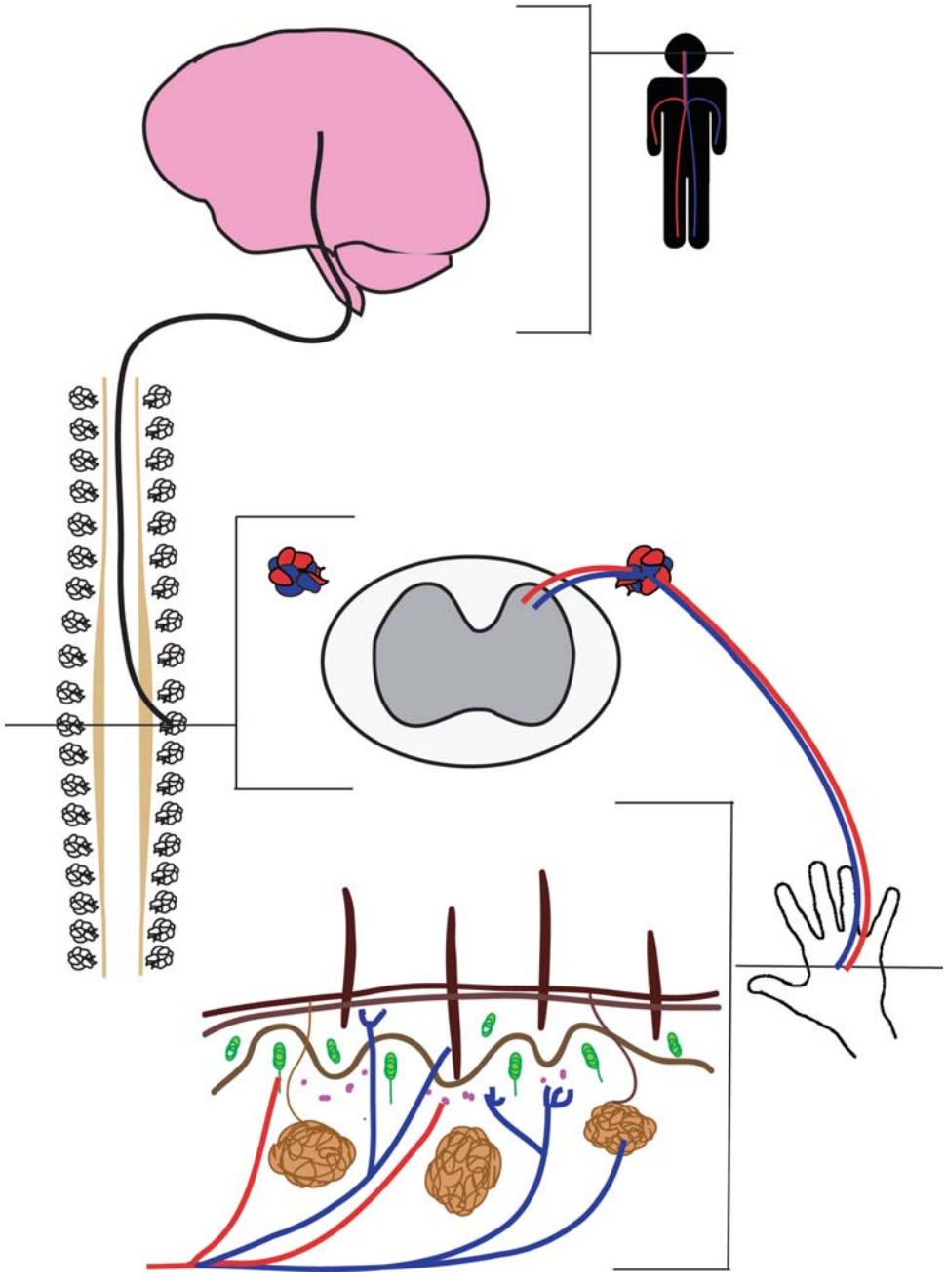

Figure 1. A broad overview of the anatomy of the sensory apparatus (thermo- and mechanosensory). Neurogenesis pertaining to the PNS in the developing mouse begins when the first-order sensory neurons located at the periphery of the spine extend and branch towards the periphery. Diagramed here are large and medium diameter neurons (in red) and small diameter neurons (in blue) terminating at the epidermis (in green are the mechanoreceptors and in tan are the sweat glands). Once the stimulus is received at the periphery, transmission from the first-order sensory neurons to the second-order sensory neurons (located in the dorsal horn of the spinal cord in gray) receive the information, which is then relayed to the brain (in pink), specifically the thalamus, to be translated by the third-order sensory neurons.

The human phenotypes most commonly associated with thermo- and mechanosensory defects are those that result from improper neuronal maintenance. For example, accumulation of Ca^{2+} can lead to neurodegeneration (29) and consequently, thermosensation defects, as seen in the case of Huntington (HD), Alzheimer (AD) and Parkinson (PD). However, the primary site of sensory dysfunction, which can vary from receptors at the periphery, the soma of the sensory neuron and the brain itself, is still unclear.

TRPS, DEG/ENAC AND MECHANOSENSATION

Mechanosensitive receptors are present in most, if not all, major organs. For instance, mechanical stimuli resulting from fluid flow have been shown to be necessary for kidney morphogenesis (30), bone development (31) as well as proper vascular development (32). Mechanosensitive receptors also play a vital role in sensory perception; mechanical stimulation of stereociliary bundles is essential for

auditory function (33) as well for the sense of touch, for which many of the mechanosensitive receptors localize to the epidermis (9).

In the skin, the primary sites of low-threshold mechanosensory receptors are thought to lie in Merkel cells, Pacinian corpuscles, Meissner corpuscles and in a small subset of low-threshold C-fiber free nerve endings (6,8,9). Initial screens in *Caenorhabditis elegans*, which have six different touch receptors, has identified 17 'mechanosensory abnormal' (MEC) genes, as well as four DEG/ENaC proteins (2), all expressed in sensory neurons (3). The MEC genes, responsible for the gentle sense of touch, are thought to form a Na^+ ion channel complex that establishes a 15-protofilament microtubule core, as well as its associated proteins, to allow for proper touch-receptor function (2,34). The exact role of this structure is unclear, although it has been suggested that it may be essential for the expression of transduction machinery, transport of channel subunits, mediating the adaption rate of the channel or even play a role in the activation of the channel (35). It is not surprising that the MEC genes have human homologs that may also be involved in sensory perception, especially mechanosensation. In particular, we identify two human homologs of MECs, *mec-9*, a NOTCH2 homolog, as well as *mec-2*, which is a stomatin homolog. Notch is an essential developmental pathway, and consequently, its disruption will lead to developmental deficits including, but not limited to, defects in the proliferation and differentiation of neural precursor populations, affecting a broad range of tissues. Stomatin, the human mec-2 ortholog, has been implicated in sensory sensation including thermo/mechanosensation, as well as olfaction (36). These data support the idea that genes and proteins that are involved in sensory sensation are likely to have multiple roles and that defects in any given sensory modality may also uncover deficits in other senses.

Similar to the MECs, the degenerin family (DEG/ENaC) proteins have homologs in various organisms, including *C. elegans*, *Drosophila* and mammals (2), which are essential for proper postnatal neuronal maintenance (37) and can also form Na^+ ion channels in which a subset of them play a role in mechanosensation. Interestingly, at least two members of the MEC family, *mec-4* and *mec-10*, are also members of the DEG/ENaC family (2), and they also have ENaC homologs in humans. Unlike *C. elegans* or *Drosophila*, which have discrete sensory neurons or organs, the mechanism(s) of mammalian mechanosensation is still largely unknown; only a small number of genes contributing to mechanosensation have been identified by studying orthologs in invertebrate systems. These include two members of the DEG/ENaC ion channel (γ-ENaC and BCN1), ASIC3 and TRPV4 (2), both of which are thought to be components of ion channels that assist in transducing mechanical stimuli or sensing changes in cell volume (34).

Although TRPs, MECs and DEG/ENaC channels have been studied extensively, the transduction process by which temperature and mechanical stimuli are perceived is still largely unknown, especially in the context of other clinical findings. We will therefore focus on mammalian systems and human diseases to understand the potential underlying causes of their thermal and mechanosensory deficits.

Table 1. Diseases with a thermosensory and/or mechanosensory phenotype

Disease	Thermosensory/ mechanosensory phenotype	Reference
Stüve–Wiedemann syndrome/ neonatal Schwartz–Jampel syndrome type 2	Temperature instability, excessive sweating, reduced pain sensation	(46,47)
Tangier disease	Widespread loss of pain and temperature sensation	(63–69)
Charcot–Marie–Tooth disease	Decreased sensation of pain and vibration in feet	(70)
Neuropathy type I/HSAN1	Loss of pain and temperature sensation in thighs and hands; sensory dysfunction	(71–76)
Neuropathy type III/HSAN3/ Riley–Day syndrome/ familial dysautonomia	Indifference to pain and temperature	(77,78)
Spinocerebellar ataxia 6	Impaired temperature discrimination	(79–81)
Machado–Joseph disease/ spinocerebellar ataxia 3	Impaired temperature discrimination	(82)
Neuropathy, hereditary sensory and autonomic type 2/ HSAN2/Morvan disease	Loss of pain sensation, diminished touch and temperature sense	(83–87)
Insensitivity to pain, congenital, with anhidrosis/ HSAN4	High pain threshold and heat intolerance	(88–92)
Neuropathy, hereditary sensory and autonomic/HSAN5/ insensitivity to pain, congenital	Loss of pain and thermal sensation in extremities	(93,94)
Spinocerebellar ataxia	Decreased vibration sensation	(81,82)
Charcot–Marie–Tooth disease	Decreased sensation of pain and vibration in feet	(70)
Spastic paraplegia 27	Decrease of vibration sensation in feet	(95)
Neuropathy	Distal sensory loss; loss of pain, touch, heat and cold sensation in feet	(71,72)
Freidreich ataxia 1	Impaired vibration sense	(96)
Fabry disease	Decreased vibration sense	(97)
Masa syndrome	Less sensitive to touch and pain (mice)	(98)
Kanzaki disease	Impairment of all sensory modalities in the distal extremities	(99)
BBS	Decreased thermo- and mechanosensation	(18)
PWS	High pain threshold	(43)

HUMAN GENETIC DISORDERS OF THERMO- AND MECHANOSENSORY PERCEPTION

Although there are no human genetic disorders characterized exclusively by thermo- or mechanosensory deficits, a comprehensive survey of phenotyping studies and clinical case reports reveals a wide spectrum of pleiotropic disorders with a thermo- and/or mechanosensory phenotypic component. Associated phenotypes include, but are not limited to, skeletal abnormalities, muscle wasting, fevers, ataxia, self-mutilation, lack of or excessive sweating, mental retardation, loss of axons or axonal myelination, death of neuronal ganglia and/or other neuropathic defects (Table 1). Moreover, mouse models of either human genetic disease (Table 2) or simply ablation of molecules of biochemical interest have also unearthed a plethora of proteins whose loss of function yields thermo- and mechanosensory phenotypes.

Table 2. Mouse models of human disease with thermo/mechanosensory defects

Gene	Phenotype	Disease model	Reference
Apoe	Abnormal thermal nociception	Alzheimer disease (AD; OMIM ID 104300)	(100)
Clcn6	Increased thermal threshold	Ceroid lipofuscinosis, neuronal, 3 (CLN3; OMIM ID 204200)	(101)
Ctsc	Increased thermal threshold	Schizophrenia (SCZD; OMIM ID 181500)	(102)
Ndn	Decreased thermal threshold	Prader–Willi syndrome (PWS; OMIM ID 176270)	(44)
Ntrk1	Increased thermal threshold; unresponsive to tactile stimuli	Insensitivity to pain, congenital, with anhidrosis (CIPA; OMIM ID 256800)	(103)
Prx	Decreased thermal threshold; Hyporesponsive to tactile stimuli	Hypertrophic neuropathy of Dejerine–Sottas (OMIM ID 145900)	(104)
Bbs2	Hyporesponsive to tactile stimuli	Bardet–Biedl syndrome (BBS; OMIM ID 209900)	(105)
Bbs4	Hyporesponsive to tactile stimuli	Bardet–Biedl syndrome (BBS; OMIM ID 209900)	(18)
Kif1b	Unresponsive to tactile stimuli	Charcot–Marie–Tooth disease, axonal, type 2a1 (CMT2A1; OMIM ID 118210)	(106)
Trpv4	Abnormal response to tactile stimuli	Deafness, autosomal dominant nonsyndromic sensorineural 25 (DFNA25; OMIM ID 605583)	(102,107)

Not surprisingly, the majority of clinical disorders with secondary or tertiary thermo- and mechanosensory defects are generalized disorders of the nervous system. Neurodegeneration, cerebral atrophy, deficits in myelination as well as axonal loss (38) can all affect the somatosensory pathway and result in motor and/or sensory impairments. However, the notion that thermo- and mechanosensory defects are exclusively the outcome of generalized neurological dysfunction or degeneration might be overly simplistic, not least because such a model cannot fully explain the range and type of thermo- and/or mechanosensory phenotypes observed. One example is hereditary sensory and autonomic neuropathy 4 (HSAN4), in which patients have been reported to lack afferent neurons. HSAN4 is caused by mutations in TRKA, a neurotrophic tyrosine kinase receptor, that in the presence of neurotrophins, specifically nerve growth factor (NGF), is autophosphorylated, allowing for the activation of signal transduction cascades that are essential for proper development of NGF-dependent sensory neurons (39). However, TrkA also has a specialized role in the development of small-diameter C-fibers, which are responsible for pain, temperature or harsh touch sensation. More recently, it was discovered that mutations in a sodium ion channel, SCN9A, resulting in the functional loss channel activity, can also lead to congenital insensitivity to pain (HSAN4 and HSAN5) (40,41). It is therefore possible that the sensory phenotypes in HSAN4 patients might be due to the loss of the sensory neuron-specific functions of this molecule. In addition, it is interesting to note that ion channel function is implicated in the sensory phenotypes observed in some HSAN patients since the majority of molecules that have been identified as thermo- or mechanosensory receptors are ion channels.

The importance of factors such as neurogenins in thermo- and mechanosensation is also highlighted in other diseases. Prader–Willi syndrome (PWS), for example, is a pleiotropic disease in which defective thermo- and mechanosensory phenotypes have also been reported (43). Necdin, a candidate gene for PWS (42), is a protein that belongs to the type II melanoma antigen gene expression family. Patients with PWS exhibit increased mechanosensory deficits; the necdin knock out mouse has abnormal thermal thresholds (43). Interestingly, necdin has an anti-apoptotic role (44), and necdin-deficient mice exhibit increased caspase 3-dependent apoptosis of TrkA and TrkC in peripheral sensory neurons (44,45) which are essential factors for neurodevelopment.

It is also important to note that even within the group of broad neurological disorders, the sensory phenotype is not necessarily one of loss of thermo- and/or mechanosensory functions (as might be expected). Rather, both hyposensitivity and hypersensitivity have been reported. The identification of what factors result in this distinction may help contribute to our understanding of the molecular basis of the disease, especially since, on several cases, such studies have uncovered novel components of the sensory molecular apparatus. One example is Stüve–Wiedemann syndrome (STWS; OMIM 601559) (46,47). STWS is a pleiotropic disorder identified predominately as a bent-bone dysplasia, often associated with other skeletal abnormalities, as well as improper thermal regulation and reduced nociception. STWS is caused by mutations in the gene encoding the leukemia inhibitory factor receptor (LIFR). LIFR directly affects and alters LIF-mediated JAK-STAT3 (JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3—a transcription factor) signaling by binding LIF. This interaction allows for JAK to phosphorylate STAT3, which is required for proper development of sympathetic neurons (48). This LIFR–LIF interaction is especially important for motor neuron maintenance and though the function of LIFR in the CNS cannot be excluded, given that LIFR has been shown to be expressed in the hindbrain and in the glia limitans as well as the fact that LIFR-deficient mice have a reduced number of astrocytes in the brain stem and spinal cord, LIFR mutations may also affect sensory neurons (49,50). Similar to STWS, Bardet–Biedl syndrome (BBS), a pleiotropic disease which results from dysfunctional cilia (51), is another disorder that manifests thermal and mechanosensory deficits as a secondary and largely underappreciated feature (18). In a recent study, it was observed that mice, worms and humans deficient for some BBS proteins presented abnormal responses to thermal and mechanical stimuli. These were not likely caused by defective cortical processing but were attributed to perturbed sensory innervation at the periphery as well as defective localization of TRPV1 in the somata of sensory neurons (18).

MOLECULAR LESSONS FROM GENES IMPLICATED IN THERMO/MECHANOSENSATION

A compilation of the known proteins whose dysfunction leads to either increased or decreased sensory function highlights the

complexity of the peripheral sensory neuronal architecture and function. Despite such complexity, an examination of the known functions of these molecules reveals three major functional modules: neurogenesis, cell signaling and metabolism. There are at least 171 proteins shown to be involved in pain and specifically have a nociceptive phenotype (http://www.jbldesign.com/jmogil/enter.html) (52). Within this set, there are 54 proteins whose perturbation leads to increased sensitivity to nociception, versus 117 with decreased sensitivity. Interestingly, some 79% of the proteins associated with nociceptive phenotypes have also been implicated in cell signaling, whereas the other ~21% have roles in metabolism (~11%), cell structure (~6%), gene regulation (~3%) and cell division (~1%). It is important to recognize that only approximately 20 genes from this list have associated phenotypes in humans, potentially reflecting insufficient clinical phenotyping. Nonetheless, from a mechanistic perspective, some major lessons emerge, which might also offer therapeutic benefits.

As stated earlier, some neurodegenerative disorders have also been associated with thermo- and/or mechanosensory deficit. However, in most instances, the molecular basis of the phenotype is unclear. A basic analysis of the genes associated with thermo and mechano defects highlights the breadth of processes. By using the Gene Set Enrichment Analysis Database (GSEA: http://www.broadinstitute.org/gsea/) (53), we observe enrichment in three major functional categories: (i) proteins involved in neuroactive ligand–receptor interactions; (ii) G-protein-coupled receptors (GPCRs) related to rhodopsin and (iii) the calcium signaling pathway. Neuroactive ligand–receptor interactions can function in modulating neuronal activity and are therefore obviously essential in maintaining and developing neuronal function. Similarly, the rhodopsin-type GPCRs have been reported to act as chemosensory receptors in the sea urchin (54). In addition, GPCRs function in multiple sensory pathways involved in, for example, odorant and gustatory functions, predominately by regulating and specifying channel activity as well as modulating the activity of other channels such as G-protein-coupled inwardly rectifying K+ channels that are essential for regulating membrane potential (55); it is plausible that the proteins implicated in defective nociceptive phenotypes that belong to this pathway act in a similar manner. Finally, the overrepresentation of calcium signaling is not surprising. Proper ion permeability is important in maintaining cellular, especially neuronal health (17), and in particular, deficits in Ca^{2+} that lead to its accumulation can lead to neurodegeneration (29).

In addition to highlighting the importance of the aforementioned functional modules, the study of patients and animal models with thermo- and mechanosensory phenotypes has also highlighted the importance of the primary cilium for proper sensory sensation. Though the role of this organelle is well documented in other sensory modalities, most prominently vision, smell and hearing (33,56,57), the presence of cilia in the somata of peripheral sensory neurons had not been recognized until recently. However, recent studies have shown that the somata of sensory neurons possess a likely

Table 3. Ciliary genes associated with thermo/mechanosensory deficits

Ciliary genes	Phenotype	Associated disorder	Reference
Gabrb3	Increased nociception	Autism	(108,109)
Gabbr1	Increased nociception (hyporesponsive mechanosensation)	Epilepsy	(110,111)
Dbh	Increased nociception	ADHD	(112)
Anxa1	Increased nociception		
Uchl1	Increased nociception	PD	(102)
Ncam1	Increased nociception	Bipolar disorder	(113)
Kcnk2	Increased nociception		
Kcna1	Decreased nociception		
Htr1b	Increased nociception		
Gria2	Increased nociception		
Gnao1	Decreased nociception		
Syn2	Decreased nociception	Susceptibility to schizophrenia	(102,114)
Slc6a1	Decreased nociception		
Slc12a5	Decreased nociception		
Slc12a2	Decreased nociception	Deafness	(115)
Scn9a	Increased nociception	Erythermalgia/ paroxysmal extreme pain disorder	(116–118)
Scn10a	Decreased nociception		
Prkar1b	Decreased nociception		
Plcb4	Decreased nociception		
Npepps	Increased nociception		
Kif1a	Decreased nociception		
Hmox2	Decreased nociception		
Gucy1b3	Decreased nociception		
Fmr1	Decreased nociception	Fragile X mental retardation	(119–121)
Faah	Decreased nociception	Obesity	(122)
Dlg2	Decreased nociception		
Camk2a	Decreased nociception		
Cacna1h	Decreased nociception	Epilepsy	(123–125)
Cacna1b	Decreased nociception		
Bbs4	Decreased nociception	BBS	(18)
Bbs1	Decreased nociception	BBS	(18)
Fxr2	Increased thermosensation		
Gria3	Increased thermosensation		
Atp1a2	Unresponsive mechanosensation	Familial hemiplegic migraine	(126)
Bbs2	Hyporesponsive mechanosensation	BBS	(105)
Cacna1a	Hyporesponsive mechanosensation	SCA6	(79–81)
Flnc	Hyporesponsive mechanosensation		
Gna11	Hyporesponsive mechanosensation		
Gnaq	Hyporesponsive mechanosensation		
Madd	Hyporesponsive mechanosensation		
Snap25	Unresponsive mechanosensation	ADHD	(127)
Ncs1	Thermosensationtaxis		
Unc97	Abnormal mechanosensation		
Sptlc1	Decreased nociception	Neuropathy type I/ HSAN1	(71–76)
Ikbkap	Decreased nociception	Neuropathy type III/ HSAN3	(77,78)

primary cilium. More importantly, loss of ciliary/basal body proteins through the genetic ablation of BBS proteins in various model organisms, as well as in humans, leads to thermo- and mechanosensory defects that are not due to cortical interpretation defects (18). These findings are not unique to the BBS protein group; TRPP2, a ciliary protein implicated in polycystic kidney disease, acts as a thermo- and mechanosensor in concert with TRPV4 (18,58), and genetic ablation of this molecule in the mouse largely phenocopies the thermosensory phenotypes of the Bbs mouse mutants (58). A torrent of studies have shown the cilium to be essential for various signaling processes, most prominently calcium sensing, Wnt and Hh signaling (59). We therefore asked what the representation of *bona fide* nociceptive proteins might be in the ciliary proteome database, a meta-analysis of 11 proteomic, transcriptomic and comparative genomic studies that enrich for likely ciliary and basal body proteins (www.ciliaproteome.org) (60). This collection contains approximately 1000 genes or ~5% of the annotated human transcriptome. However, parsing the known genes with nociceptive phenotypes against the ciliary proteome identified 45/171 transcripts, or 26% of the nociceptive gene collection (Table 3). Even though this analysis is but an approximation and is certain to contain both false positives and false negatives, the five-fold enrichment of ciliary proteins in the thermo- and mechanodefective mutant set is a significant enrichment that suggests a potentially major role for this organelle in the transmission of sensory stimuli in the peripheral nervous system.

CONCLUDING REMARKS

Much progress has been made in understanding the developmental and homeostatic processes that control thermo- and mechanosensation and, more broadly, the sense of touch. Nonetheless, the field appears to lag behind other senses. One possible explanation might be that, in contrast to other sensory disorders (most prominently of vision and hearing), which are readily diagnosable and of acute importance to the patient, defects in skin sensation are presently confined to secondary or tertiary characteristics of either generalized neuropathies or complex syndromes. The plethora of mouse (and other model organisms) mutants with such phenotypes argues against a dearth of defects in humans. More likely, we speculate that such defects might be underappreciated and might warrant a more careful evaluation in the clinical setting. The relatively modest information available to us argues against a model wherein defective peripheral sensation is persistently a side effect of generalized neuropathy. However, the challenge remains on how to (i) phenotype patients objectively, especially for a subjective sensory modality; and (ii) separate cortical interpretation defects from peripheral dysfunction. In contrast to other sensory organs, the sense of touch is not anatomically isolated and involves both neuronal circuitry and the skin itself, further hampering our efforts to dissect the relative contribution of each component of this system. Despite these difficulties, understanding how we interact with our environment through the skin is of critical importance, not only in the context of genetic disorders, but also in the continuous and acute need for pain management. Several studies have targeted TRPV1 as a candidate for developing analgesics (61), whereas knockout *Trpv1* mice were desensitized to pain after surgical or inflamed states (62). There is every reason to believe that the identification of further nociceptive molecules will expand our targetable repertoire while informing the physiology of the most anatomically complex of our sensory organs.

ACKNOWLEDGEMENTS

We thank Michael J. Caterina, Norann A. Zaghloul, Erica E. Davis, Jon F. Robinson and Jose L. Badano for their thoughtful comments on the manuscript.

Conflict of Interest statement. None declared.

FUNDING

This work was supported by grant R01HD04260 from the National Institute of Child Health and Development (N.K.), R01DK072301 and DK075972 from the National Institute of Diabetes, Digestive and Kidney disorders (N.K.) and a Conte Center grant from the National Institute of Mental Health (N.K.).

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