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Review

Human Mendelian pain disorders: a key to discovery and validation of novel analgesics

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We have utilized a novel application of human genetics, illuminating the important role that rare genetic disorders can play in the development of novel drugs that may be of relevance for the treatment of both rare and common diseases. By studying a very rare Mendelian disorder of absent pain perception, congenital indifference to pain, we have defined Nav1.7 (endocded by *SCN9A*) as a critical and novel target for analgesic development. Strong human validation has emerged with *SCN9A* gain-of-function mutations causing inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder, both Mendelian disorder of spontaneous or easily evoked pain. Furthermore, variations in the Nav1.7 channel also modulate pain perception in healthy subjects as well as in painful conditions such as osteoarthritis and Parkinson disease. On the basis of this, we have developed a novel compound (XEN402) that exhibits potent, voltage-dependent block of Nav1.7. In a small pilot study, we showed that XEN402 blocks Nav1.7 mediated pain associated with IEM thereby demonstrating the use of rare genetic disorders with mutant target channels as a novel approach to rapid proof-of-concept. Our approach underscores the critical role that human genetics can play by illuminating novel and critical pathways pertinent for drug discovery.

Conflict of interest

YPG, SNP, RN, NP, CC, RPS are employees of Xenon Pharmaceuticals and MRH is a consultant to Xenon Pharmaceuticals.

YP Goldberg[a], SN Pimstone[a], R Namdari[a], N Price[a], C Cohen[a], RP Sherrington[a] and MR Hayden[a,b]

[a]Department of Clinical Development, Xenon Pharmaceuticals Inc, Burnaby, British Columbia, Canada and [b]Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada

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Corresponding author: Y Paul Goldberg, Department of Clinical Development, Xenon Pharmaceuticals Inc., 3650 Gilmore Way, Burnaby, British Columbia V5G 4 W8, Canada.
Tel.: +001 604 484 3362;
fax: +001 604 484 3321;
e-mail: pgoldberg@xenon-pharma.com

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Pain has been defined as 'an unpleasant sensory and emotional experience associated with tissue damage' (1). It is a normal protective homeostatic mechanism to avoid or reduce the environmental injury. Trauma or disease can result in the development of chronic, often intractable pain such as that associated with inflammatory disorders, cancer and neuropathies. In the United States, pain affects more people than diabetes, coronary artery disease and cancer combined, (2) and remains an area of major unmet medical need and a focus of the pharmaceutical industry. Current therapeutics offer only limited efficacy with approved gold standard therapeutics substantially improving pain (≥50%) in no more than 40–50% of subjects in controlled clinical trials (3). Available therapies generally have dose-limiting adverse effects, and in the case of opioids, pose a small but significant risk of dependence (4).

The pharmaceutical industry worldwide is currently amidst a crisis because of escalating R&D spending, yet a reduction in productivity as measured by product approvals (5). This situation is further compounded by the loss of patent protection for numerous successful brands as generic versions continue to cannibalize innovative drug markets. The current drug development model is unsustainable. A key part of the solution is the need for differentiated products, particularly those that are based on disease mechanisms. By modulating drug targets critical to the disease, greater prediction of success in clinical development might be expected.

The role of human validation and drug target selection

We have adopted a novel application of human genetics, illustrating the important role that rare genetic disorders

can play in the development of novel drugs. Our approach to drug development is predicated upon the identification of an unprecedented novel targets, which when antagonized will produce a desired phenotype in humans. This approach examines the families having both the opposite and extreme version of the disease we plan to treat. These rare opposite phenotypes represent Mendelian conditions that are surrogates for the mechanism of action for the desired drug. The advantage of this approach is that many of the mutations discovered as causing a phenotype in humans have been loss-of-function, and thus antagonism of the drug target will have the expected and clinically relevant outcome in humans. For example, a novel approach for the treatment of osteoporosis in the general population was derived from the identification of the gene which, when disrupted, causes sclerosteosis, a rare autosomal recessive disorder of increased bone density found in the South African Afrikaner population. In collaboration with the Department of Medical Genetics at the University of Cape Town, we were able to collect DNA and corresponding phenotypic information from families with sclerosteosis. Subsequently, in collaboration with Darwin Molecular, the gene and its protein product, sclerostin, was identified (6–8). Today antibodies to sclerostin, the gene product underlying sclerosteosis are in late stage clinical development for the treatment of osteoporosis (6–8).

In contrast to the small effects seen in genome-wide association studies (GWAS) studies, Mendelian recessive diseases which are typically caused by complete loss-of-function mutations are chosen for study as the causal genes generally have a large effects size. This suggests that targeting this protein therapeutically should have a significant phenotypic impact in humans. Furthermore, because of the carefully selected disease phenotype devoid of undesirable effects these Mendelian disorders allow for the accurate prediction of target-related adverse effects.

We have applied our extreme and opposite phenotypic strategies to address the unmet medical need for analgesics in an effort to find a more optimal, highly validated target for analgesic drug discovery. We began with the recognition of the important condition, congenital indifference to pain (CIP). We hypothesized that discovery of the causal gene would catapult us into a novel pathway critical to pain perception in humans.

Congenital indifference to pain

The CIP is a rare autosomal recessive disorder characterized by the complete absence of pain perception typically associated with noxious stimuli (9–14). For example, patients have reported pain free episodes of childbirth, corneal abrasions, fractures and severe burns (9, 10). Dearborn first reported this condition in 1932, describing a man who made a living as a human pincushion act at the circus (15). CIP patients are aware of a stimulus which would be perceived as pain by others, but have lost the affective-motivational component of pain perception and therefore, their ability to determine the noxious content of a painful stimulus (11, 12, 14), i.e. for patients with CIP, pain is not perceived. However, patients with CIP have normal joint position sense, vibration, light-touch, and temperature perception. Patients find it possible to distinguish between sharp and dull, and between hot and cold, but lack the ability to sense the extreme conditions normally considered painful. Thus, analgesia in these patients is universal, yet all other sensory modalities remain intact. Besides the absence of pain sensation and the secondary sequelae related to this, the only other significant clinical feature is the presence of anosmia or hyposmia (absence or reduction of smell) (10, 16–20).

Additionally, motor examination, cranial nerve examination (except cranial nerve I), intelligence and electroencephalogram are typically normal (10, 14, 18, 19, 21–25). Furthermore, CIP patients have an absence of overt abnormalities of the autonomic nervous system. CIP patients typically have normal blood pressure without postural fluctuations, normal tear formation, normal sweating and normal body temperature regulation. The histamine flare test is also normal indicating an intact axon reflex (10).

There are secondary clinical consequences of CIP and these patients highlight the critical defensive role nociception plays in our day to day interactions with our environment. As infants and young children, CIP patients suffer from self-mutilating oral and finger lesions due to repeated self-biting, and sustain multiple injuries as the result of repeated trauma such as repeatedly banging their head against objects. They are also highly prone to burn related injuries such as scalding themselves with boiling water, or burning their hands on hot stoves or irons (16, 18). Orthopedic manifestations are seen later in life and are characterized by multiple untreated fractures causing bone deformities, neuropathic joints, and osteomyelitis (17–19, 22, 25).

Identification of the CIP gene: the critical importance of phenotype

To identify the CIP gene we accessed our worldwide network of clinical colleagues including geneticists, neurologists and pain specialists to identify the affected individuals who met the diagnostic criteria for CIP. Correct disease ascertainment and assignment of affection status within a family are critical to finding a disease gene. In this regard, it was critical to differentiate CIP from other disorders of reduced or absent pain perception. This presented a challenge to ensure that all the affected individuals met the diagnostic criteria for CIP with definitive exclusion of all other reduced pain perception syndromes such as, for example, hereditary sensory and autonomic neuropathies (HSANs) (26, 27) and congenital insensitivity to pain with anhidrosis (28, 29). We developed a detailed history and examination protocol for our collaborators to conduct. This proved to be highly successful allowing us to confidently assign phenotypical status including a high measure of confidence that normal family members were correctly assigned.

The cardinal differentiating feature of CIP from other diseases of reduced pain perception, is that in CIP only pain perception is disturbed with all other sensory, autonomic and motor modalities completely intact (except for cranial nerve I). For example, pertinent distinguishing features of CIP from hereditary sensory autonomic neuropathies are that CIP patients have normal peripheral nervous system fibers as determined by sural nerve and skin biopsies, while in the HSAN disorders, nerve biopsies are abnormal showing reductions in myelinated and/or unmyelinated fibers; the presence of an intact axon reflex upon subcutaneous injection of histamine (presence of wheal and flare) which is abnormal in HSANs, and normal nerve conduction velocities which are usually markedly diminished in the HSANs.

Using this approach, we identified and collected DNA from individuals from 15 families in which the affected individuals met the diagnostic criteria for CIP. The principal family that was critical to the success of the gene identification was a large multigenerational family from a Canadian founder population with four individuals affected with CIP (CIP-14) (10). Neurological examination was completely normal except for absent pain perception. Skin and nerve biopsies and a normal histamine flare response confirmed the diagnosis. Because of the substantial interest in this phenotype, additional evaluations were performed on this family. Electron microscopy of muscle, skin, periosteum, and nerve biopsies showed no abnormalities. The periosteum (which has nociceptive nerve endings) in particular showed normal innervation of nerve fibers, and sural nerve microscopy showed no evidence of active demyelination or hypertrophic changes commonly seen in the sensory neuropathies. Furthermore, the parents of the affected CIP patients were found to be clinically and neurologically normal.

Using homozygosity mapping and haplotype sharing methods, we rapidly narrowed the CIP locus to chromosome 2q24-q31, a region known to contain a cluster of voltage-gated sodium channel genes. From these prioritized candidate sodium channels, we identified in nine families, ten mutations in the sodium channel 9A (SCN9A) gene encoding the sodium channel protein Nav1.7 (10). The mutations completely co-segregated with the disease phenotype, and nine of these SCN9A mutations resulted in truncation and loss-of-function of Nav1.7 channel, providing incontrovertible evidence that SCN9A was the causative gene for CIP. Cox et al. (9) independently identified SCN9A mutations in three CIP families of Pakistani descent. These combined findings clearly demonstrated that truncating mutations in the SCN9A gene result in the loss of a functional Nav1.7 protein, which is the cause of CIP in multiple human populations (9, 10).

Developing an antagonist therapy is significantly less challenging compared to developing an agonist, and therefore it was encouraging to note that the mutations predicted loss-of-function of the Nav1.7 channel indicating that an antagonist was required to mimic the CIP phenotype to produce analgesia. In order to confirm the loss-of-function of the Canadian founder (CIP-14) mutation, whole-cell patch-clamp recordings were made in HEK293 cells expressing human Nav1.7. In contrast to the wild-type channel, the CIP-14 Nav1.7 mutant channel expressed in the human embryonic kidney 293 (HEK293) cells had a tetrodotoxin (TTX)-sensitive current that was essentially equivalent to background, demonstrating the predicted loss-of-function of the channel (data not shown).

Further human genetic validation of the target is underscored by the identification of causative mutations in SCN9A in another hereditary disorder of pain perception, inherited erythromelalgia (IEM).

Inherited erythromelalgia

IEM is an autosomal dominant condition caused by gain-of-function mutations in the SCN9A gene (11, 30–32). It is characterized by attacks of debilitating symmetrical burning pain in the feet and hands, together with elevated skin temperature, mild swelling and erythema of affected areas (30, 33, 34). The incidence of erythromelalgia (EM) in a Norwegian population was estimated to be 0.25–0.33 per 100,000 people per year, and in that same study, prevalence was estimated to be 1/100,000 (35). A population-based analysis of EM in Olmsted County, Minnesota found that the overall age- and sex-adjusted incidence rate of EM was 1.3 per 100,000 people per year (36).

Symptoms usually begin at a young age, mostly within the first decade of life (30), but onset can be somewhat delayed presenting for the first time in middle age. The pain is usually described as intense burning and is localized to the extremities with the feet more commonly and severely affected. Symptoms can be induced by exercise and exposure to warmth (32–34, 37). Changes in humidity, although not previously described, are consistently reported by our patients as a major reliable trigger of the pain. Patients report being able to accurately predict weather changes because of this phenomenon. Similarly, stress and anxiety are also reported by some patients to exacerbate the condition. Certain foods can induce the pain in some patients (30), but this is not universal. For example, several patients have reported avoiding watermelon because of its pain triggering properties. Similarly, for some, alcohol should be avoided. Any pyrexial illness is a common trigger, while one patient reported avoiding hot drinks to avoid pain induction. Cooling the extremities universally alleviates the pain, and many patients immerse their feet in ice cold water, and do not wear socks or closed shoes even in the winter months (34, 37). A significant complication of repeated ice water immersions is trench foot with skin infections which, in some, can lead to limb amputation.

Patients are often misunderstood and ostracized by peers, teachers or co-workers as they appear normal, yet are unable and unwilling to function and participate in regular daily activities. As their only visible symptom is skin erythema, they are often deemed to be malingering. Many patients report that their physicians are unaware of this condition and unable to help them.

IEM is a highly variable condition, even within the same family. It can range from mild, with minimal impact on lifestyle, to a severe, crippling disorder where patients are house-bound or bedridden (34). Many patients with mild to moderate disease may be pain free, or have minimal pain between attacks. They manage their condition with varying degrees of success by preventing or limiting the extent of exacerbations, either by modulating their environment or limiting their activities, for example, avoiding or curtailing walking. Patients control their environmental temperature with fans and air conditioning, some requiring temperatures that are cold and unpleasant, but necessary to reduce their pain. Patients with mild to moderate disease may have tried various prescription and over the counter analgesics, but the majority report that they do not derive any meaningful benefits. The more severely affected patients have constant severe pain with further exacerbations related to minimal exertion or slight increases in ambient temperature and/or humidity. They are often house-bound and some even bedridden (34). At the severe end of the spectrum, simply placing their legs in the dependent position can precipitate a pain crisis (34), so these patients remain in bed or lying on a couch for the whole day. They also deploy environmental modulation usually to an even more extreme degree than less severely affected patients. However, these measures alone are insufficient to control their excruciating burning pain. Severely affected patients describe their pain as 'being on fire' or 'hands on the barbeque'. One patient, for example, sustained a second degree burn from a stove flame as she failed to withdraw her hand from the heat source because she reported that it felt no different to the burning sensation that she normally experienced.

Lack of sleep is a further significant, and for some, debilitating issue. For many patients, symptoms appear to be worse at night and for some, pain interrupts sleep throughout the night. Many patients sleep without any covering on their feet and use cooling fans throughout the night. Recurrent poor sleep can result in chronic fatigue, impacting a patient's ability to be productive during the day. It is, therefore, not surprising that there appears to be an increased rate of suicide amongst patients with severe IEM (34, 38). The persistent excruciating pain, combined with lack of sleep, chronic fatigue, drug side effects, markedly restricted activities including impaired social activities and the progressive nature of the condition, all contribute to feelings of desperation and a lack of hope.

Mutations in the SCN9A gene encoding the Nav1.7 sodium channel have been described in multiple families with IEM (11, 31, 39–41). Even in the presence of a family history, however, only approximately 10% of families have an SCN9A mutation (J. Drenth, personal communication). Most of the mutations detected to date are missense mutations that change important highly conserved amino acid residues of the Nav1.7 channel (11). These IEM mutations cause a shift in the voltage dependence of the channel activation, which allows the channel to be activated by smaller than normal depolarizations, thereby enhancing the activity of Nav1.7 (12, 42). Thus, it is clear that the mutations underlying IEM lead to a gain-of-function of the mutant Nav1.7 channel. In the absence of a family history, it is important to exclude secondary causes of EM such as myeloproliferative disease, diabetes, cutaneous vasculitis, systemic lupus erythematosus, hypertension, rheumatoid arthritis, mercury poisoning, and drugs, for example, the calcium channel blockers (12, 34, 43).

Many severely affected patients would have evaluated a wide variety of analgesics including opioids, antidepressants, and anticonvulsants, usually with limited to minimal effect. Nevertheless, they remain on high dose combinations of medications in an effort to blunt the impact of their debilitating pain. Consequently, they often experience side effects from the high dose poly-pharmacy compounding their dire situation. Erythromelalgia is a poorly recognized and inadequately treated condition with increased morbidity and mortality (34). Hence, there is an urgent need for greater awareness of EM among physicians and the general public, coupled with a greater effort to discover and develop safe and efficacious treatments for this devastating and debilitating condition.

Phenotypic heterogeneity is not uncommon in the channelopathies where different mutational mechanisms lead to clinically distinct phenotypes (44). The critical role of Nav1.7 in pain perception is further underscored by the discovery that gain-of-function missense mutations in SCN9A not only cause IEM, but also lead to a very disparate, spontaneous pain syndrome, paroxysmal extreme pain disorder (PEPD).

Nav1.7 gain-of-function in PEPD

PEPD (previously known as familial rectal pain syndrome), is an autosomal dominant spontaneous or easily evoked pain syndrome characterized by paroxysms of rectal, ocular, or mandibular pain associated with autonomic disturbances such as skin flushing (45). PEPD symptoms usually start at birth and the rectal pain is triggered by bowel movements, falling on the buttocks, or probing of the genital area. The rectal pain episodes can decline with age, with ocular and mandibular pain becoming more prominent. Temperature fluctuation, especially cold, as well as food can trigger the facial pain in PEPD. In 2007, Fertleman et al. (45) identified missense mutations in the Nav1.7 channels in 11 families and 2 sporadic PEPD cases. The mutant Nav1.7 channels show a reduction in fast inactivation, leading to enhanced persistent sodium current. Thus different mutational mechanisms underlying IEM and PEPD lead to clinically distinct phenotypes which appear to correlate with the functional impact on the biophysical properties of the mutant channel with either lowered thresholds of activation (IEM) or defective inactivation (PEPD) underlying the clinical phenotype (11, 32, 42). For some patients with PEPD, the anti-epilepsy drug carbamazepine which blocks persistent sodium current, may be effective (40).

Thus, mutant Nav1.7 is directly implicated in several rare pain perception genetic disorders (CIP, IEM, PEPD). However, exciting new findings are now emerging showing the direct relevance of mutant Nav1.7 to pain perception for a more common condition seen in the general population such as burning peripheral neuropathy.

Nav1.7 gain-of-function in SFN

Small fiber neuropathy (SFN) presents with distal neuropathic (typically burning) pain which differs from that seen in EM in that it is not typically inducible nor associated with erythema (46). Etiologically, SFN is a highly heterogeneous disorder (46, 47). It is characterized by reduced intraepidermal nerve fibers which can be reliably diagnosed by a superficial skin biopsy (47, 48). Approximately 29% of biopsy-proven cases of idiopathic SFN manifesting mainly as distal severe pain were found to have gain-of-function mutations in the Nav1.7 channel rendering dorsal root ganglion (DRG) neurons hyperexcitable (49). Thus, idiopathic SFN is on the same disease continuum as EM with a relatively milder clinical phenotype (Fig. 1), and presumably corresponding milder disturbances in the biophysical properties of the Nav1.7 channel.

Nav1.7 small molecule inhibitors reduce pain in IEM patients

As highlighted above, there has been tremendous validation of Nav1.7 as a target for analgesic development. Targeting the Nav1.7 channel fitted well with our validation strategy where Nav1.7 loss-of-function represents an extreme and opposite phenotype (i.e. no pain) to that which we intend to treat (i.e. excess pain). Nav1.7 loss-of-function results in CIP, with essentially isolated global analgesia which represents an outstanding surrogate of the intended drug effect. Furthermore, given the phenotype associated with Nav1.7 loss-of-function in humans is essentially limited to altered pain perception, much has also been learned about the low potential for target related adverse effects with drugs modulating the Nav1.7 target in humans. Thus we attempted to mimic the CIP phenotype by embarking on a program to discover and develop small molecule inhibitors of Nav1.7 for the purpose of treating pain. Through our research program we have discovered and are developing XEN402, a small molecule compound with potent block of the Nav1.7 channel which is now in phase 2 clinical development. XEN402 exhibits potent, voltage-dependent block of Nav1.7 (IC_{50} 80 nM) (50).

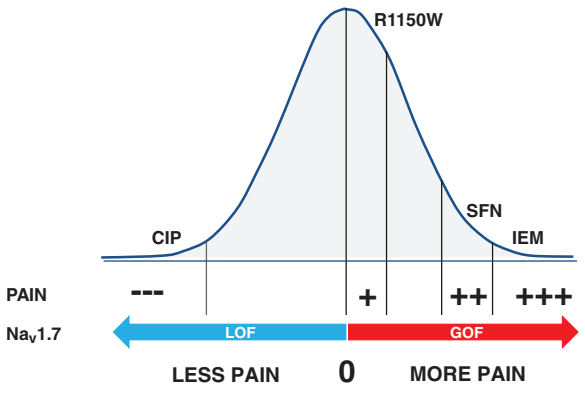

Fig. 1. Spectrum of Nav1.7 related pain phenotypes. CIP, congenital indifference to pain; GOF, gain-of-function; IEM, inherited erythromelalgia; LOF, loss-of-function; R1150W, arginine to tryptophan SNP at position 1150 of Nav1.7; SFN, small fiber neuropathy.

To date, XEN402 has been studied in several clinical trials. In phase 1 healthy volunteer studies, XEN402 was found to be safe and well tolerated. We adopted a novel approach to the assessment of proof-of-concept of XEN402 in humans taking advantage of the disorder IEM, where gain-of-function mutations underlie the severe episodic and inducible pain phenotype in affected persons. As opposed to the usually large proof-of-concept trials required to show human efficacy with an analgesic, we tested the effect of XEN402 in a small number of subjects with IEM. The trial was an exploratory, randomized, double-blind, two-period crossover in four SCN9A mutation-proven IEM patients (50). XEN402 or matching placebo was dosed orally in each treatment period (2 days), separated by a 2-day washout period. In three patients pain was induced by heat or exercise during each treatment arm while a fourth patient who was in constant severe pain, required no induction. The ability to induce pain in IEM patients, as measured by the amount of pain for the 2 h following the pain induction stimulus ($AUC_{0\text{-}2}$), was significantly suppressed by XEN402 compared to placebo (42% less, $p = 0.014$) (50). This pilot study showed that XEN402 blocks Nav1.7 mediated pain associated with IEM, thereby demonstrating the use of rare genetic disorders with mutant target channels as a novel approach to rapid proof-of-concept.

Summary

We have used a novel application of human genetics, illuminating the important role that rare genetic disorders can play in the development of novel drugs that may be of relevance for the treatment of both rare and common diseases. By studying a very rare Mendelian phenotype of absent pain perception (CIP), we have defined a critical and novel target for analgesic development. Strong human validation has emerged with gain-of-function mutations causing IEM and PEPD, both Mendelian disorder of spontaneous or easily evoked pain. Furthermore, variations in the Nav1.7 channel also modulate pain perception in healthy subjects (51) as well as in painful conditions such as osteoarthritis (51) and Parkinson disease (52). The clinical phenotype of idiopathic SFN overlaps considerably with that of IEM both sharing burning distal pain, and it is thus not surprising that gain-of-function mutations in the SCN9A gene are found in biopsy proven idiopathic SFN. Hence the Nav1.7 channel is a highly validated target for analgesic development from a human genetics perspective with strong supporting validation

from mouse gene ablation studies (53, 54). It is not surprising that many major pharmaceutical companies have Nav1.7 as a key target in their pain pipeline.

Over a decade of studying patients without any pain and those with excessive pain, we have learned a tremendous amount about these rare phenotypes. We have definitively confirmed the anosmia reported in the early CIP literature. We have expanded the phenotype of IEM, gaining a more in depth understanding of the huge variability of the disease and also a better appreciation of the consistent and variable triggers of the pain. We now recognize humidity as a key trigger, and in some, a particular food, alcohol or stress can reliably induce the pain. We have also identified several families with these classical phenotypes (no or excess pain) which as best as we can define, do not have mutations in the SCN9A gene, indicating that there are likely other genetic contributors to these extreme pain phenotypes.

This has been a remarkable journey, from the concept that defining the CIP gene would yield a pertinent target, to the collection of patients with the right phenotype, to the gene identification, to developing small molecule compound inhibitors, to demonstrating proof-of-concept in the clinic. This is the first example, to our knowledge, of going from the concept using a rare genetic disease to the clinic, with the testing of the derived therapeutic in another rare genetic disease of the opposite phenotype to elicit rapid proof-of-concept. Our approach underscores the critical role that human genetics can play by illuminating novel and critical pathways pertinent for drug discovery.

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References

1. Merskey H, Watson GD. The lateralisation of pain. Pain 1979: 7: 271–280.
2. American Academy of Pain. http://www.painmed.org/patientcenter/facts_on_pain.aspx. Accessed on June 26, 2012.
3. Dworkin RH, Turk DC. Accelerating the development of improved analgesic treatments: the ACTION public-private partnership. Pain Med 2011: 12 (Suppl. 3): S109–S117.
4. Woodcock J. A difficult balance-pain management, drug safety, and the FDA. N Engl J Med 2009: 361: 2105–2107.
5. Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. Nat Rev Drug Discov 2011: 10: 428–438.
6. Balemans W, Van HW. Identification of the disease-causing gene in sclerosteosis-discovery of a novel bone anabolic target? J Musculoskelet Neuronal Interact 2004: 4: 139–142.
7. Paszty C, Turner CH, Robinson MK. Sclerostin: a gem from the genome leads to bone-building antibodies. J Bone Miner Res 2010: 25: 1897–1904.
8. Lewiecki EM. Sclerostin: a novel target for intervention in the treatment of osteoporosis. Discov Med 2011: 12: 263–273.
9. Cox JJ, Reimann F, Nicholas AK et al. An SCN9A channelopathy causes congenital inability to experience pain. Nature 2006: 444: 894–898.
10. Goldberg YP, MacFarlane J, MacDonald ML et al. Loss-of-function mutations in the Nav1.7 gene underlie congenital indifference to pain in multiple human populations. Clin Genet 2007: 71: 311–319.
11. Waxman SG. Nav1.7, its mutations, and the syndromes that they cause. Neurology 2007: 69: 505–507.
12. Lampert A, O'Reilly AO, Reeh P, Leffler A. Sodium channelopathies and pain. Pflugers Arch 2010: 460: 249–263.
13. Danziger N, Willer JC. Congenital insensitivity to pain. Rev Neurol (Paris) 2009: 165: 129–136.
14. Gorke W. The differential diagnosis of congenital analgesia and other diseases with diminished pain perception in childhood. Case report and review. Neuropediatrics 1981: 12: 33–44.
15. Dearborn G. A case of congenital pure analgesia. J Nerv Ment Dis 1932: 75: 612–615.
16. Guillermo A, Grinspan A. Congenital indifference to pain, apropos of a case with antecedents of consanguinity. Rev Neurol (Paris) 1970: 123: 434–435.
17. Lievre JA, Camus JP, Guillien P, Duclos M. Congenital generalized analgesia (congenital indifference to pain) in 2 brothers decended from first cousins. Bull Mem Soc Med Hop Paris 1968: 119: 447–456.
18. Hirsch E, Moye D, Dimon JH III. Congenital indifference to pain: long-term follow-up of two cases. South Med J 1995: 88: 851–857.
19. Losa M, Scheier H, Rohner P et al. Long-term course in congenital analgesia. Schweiz Med Wochenschr 1989: 119: 1303–1308.
20. Toscano E, Simonati A, Indo Y, Andria G. No mutation in the TRKA (NTRK1) gene encoding a receptor tyrosine kinase for nerve growth factor in a patient with hereditary sensory and autonomic neuropathy type V. Ann Neurol 2002: 52: 224–227.
21. Nagasako EM, Oaklander AL, Dworkin RH. Congenital insensitivity to pain: an update. Pain 2003: 101: 213–219.
22. Dimon JH III, Funk FJ Jr, Wells RE. Congenital indifference to pain with associated orthopedic abnormalities. South Med J 1965: 58: 524–529.
23. Sibley BG, Broussard CD, Vincent DS. A report of congenital indifference to pain as diagnosed in infancy. J La State Med Soc 1999: 151: 310–312.
24. Thrush DC. Congenital insensitivity to pain. A clinical, genetic and neurophysiological study of four children from the same family. Brain 1973: 96: 369–386.
25. Boltshauser E, Isler W. Congenital analgesia (CA). Ther Umsch 1983: 40: 725–727.
26. Axelrod FB, Gold-von SG. Hereditary sensory and autonomic neuropathies: types II, III, and IV. Orphanet J Rare Dis 2007: 2: 39.
27. Verhoeven K, Timmerman V, Mauko B, Pieber TR, De JP, Auer-Grumbach M. Recent advances in hereditary sensory and autonomic neuropathies. Curr Opin Neurol 2006: 19: 474–480.
28. Indo Y, Tsuruta M, Hayashida Y et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. Nat Genet 1996: 13: 485–488.
29. Indo Y. Genetics of congenital insensitivity to pain with anhidrosis (CIPA) or hereditary sensory and autonomic neuropathy type IV. Clinical, biological and molecular aspects of mutations in TRKA(NTRK1) gene encoding the receptor tyrosine kinase for nerve growth factor. Clin Auton Res 2002: Suppl. 12 (1): I20–I32.
30. Hisama FM, Dib-Hajj SD, Waxman SG. GeneReviews™:SCN9A-Related Inherited Erythromelalgia. Seattle, WA: University of Washington, 2008.
31. Yang Y, Wang Y, Li S et al. Mutations in SCN9A, encoding a sodium channel alpha subunit, in patients with primary erythermalgia. J Med Genet 2004: 41: 171–174.
32. Fischer TZ, Waxman SG. Familial pain syndromes from mutations of the NaV1.7 sodium channel. Ann N Y Acad Sci 2010: 1184: 196–207.
33. Davis MD, Rooke T. Erythromelalgia. Curr Treat Options Cardiovasc Med 2006: 8: 153–165.
34. Davis MD, O'Fallon WM, Rogers RS III, Rooke TW. Natural history of erythromelalgia: presentation and outcome in 168 patients. Arch Dermatol 2000: 136: 330–336.
35. Kvernebo K. Erythromelalgia: a condition caused by microvascular arteriovenous shunting. Chapter 4: incidence and prevalence. Vasa Suppl 1998: 51: 13.
36. Reed KB, Davis MD. Incidence of erythromelalgia: a population-based study in Olmsted County, Minnesota. J Eur Acad Dermatol Venereol 2009: 23: 13–15.

37. Skeik N, Rooke TW, Davis MD et al. Severe case and literature review of primary erythromelalgia: novel SCN9A gene mutation. Vasc Med 2012: 17: 44–49.
38. Cook-Norris RH, Tollefson MM, Cruz-Inigo AE, Sandroni P, Davis MD, Davis DM. Pediatric erythromelalgia: a retrospective review of 32 cases evaluated at Mayo Clinic over a 37-year period. J Am Acad Dermatol 2012: 66: 416–423.
39. Drenth JP, Waxman SG. Mutations in sodium-channel gene SCN9A cause a spectrum of human genetic pain disorders. J Clin Invest 2007: 117: 3603–3609.
40. Fischer TZ, Gilmore ES, Estacion M et al. A novel Nav1.7 mutation producing carbamazepine-responsive erythromelalgia. Ann Neurol 2009: 65: 733–741.
41. Samuels ME, Te Morsche RH, Lynch ME, Drenth JP. Compound heterozygosity in sodium channel Nav1.7 in a family with hereditary erythermalgia. Mol Pain 2008: 4: 21.
42. Cummins TR, Dib-Hajj SD, Waxman SG. Electrophysiological properties of mutant Nav1.7 sodium channels in a painful inherited neuropathy. J Neurosci 2004: 24: 8232–8236.
43. Cohen JS. Erythromelalgia: new theories and new therapies. J Am Acad Dermatol 2000: 43: 841–847.
44. Bernard G, Shevell MI. Channelopathies: a review. Pediatr Neurol 2008: 38: 73–85.
45. Fertleman CR, Baker MD, Parker KA et al. SCN9A mutations in paroxysmal extreme pain disorder: allelic variants underlie distinct channel defects and phenotypes. Neuron 2006: 52: 767–774.
46. Devigili G, Tugnoli V, Penza P et al. The diagnostic criteria for small fibre neuropathy: from symptoms to neuropathology. Brain 2008: 131: 1912–1925.
47. Hovaguimian A, Gibbons CH. Diagnosis and treatment of pain in small-fiber neuropathy. Curr Pain Headache Rep 2011: 15: 193–200.
48. Lauria G, Lombardi R. Small fiber neuropathy: is skin biopsy the holy grail? Curr Diab Rep 2012: 12 (4): 384–392.
49. Faber CG, Hoeijmakers JG, Ahn HS et al. Gain of function Nanu1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol 2012: 71: 26–39.
50. Goldberg YP, Price N, Namdari R et al. Treatment of Na(v)1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker. Pain 2012: 153: 80–85.
51. Reimann F, Cox JJ, Belfer I et al. Pain perception is altered by a nucleotide polymorphism in SCN9A. Proc Natl Acad Sci U S A 2010: 107: 5148–5153.
52. Greenbaum L, Tegeder I, Barhum Y, Melamed E, Roditi Y, Djaldetti R. Contribution of genetic variants to pain susceptibility in Parkinson disease. Eur J Pain 2012: doi: 10.1002/j.1532-2149.2012.00134.x.
53. Nassar MA, Stirling LC, Forlani G et al. Nociceptor-specific gene deletion reveals a major role for Nav1.7 (PN1) in acute and inflammatory pain. Proc Natl Acad Sci U S A 2004: 101: 12706–12711.
54. Minett MS, Nassar MA, Clark AK et al. Distinct Nav1.7-dependent pain sensations require different sets of sensory and sympathetic neurons. Nat Commun 2012: 3: 791.