Why individual thermo sensation and pain perception varies? Clue of disruptive mutations in TRPVs from 2504 human genome data

Arijit Ghoshab,†, Navneet Kaurc,†, Abhishek Kumard, and Chandan Goswamia,b

aSchool of Biological Sciences, National Institute of Science Education and Research, Institute of Physics Campus, Bhubaneswar, Orissa, India; bSchool of Biological Sciences, National Institute of Science Education and Research, Jatni Campus, Bhubaneswar, Orissa, India; cSchool of Biotechnology, KIIT University, Bhubaneswar, Orissa, India; dMolecular Genetic Epidemiology, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany

ABSTRACT

Every individual varies in character and so do their sensory functions and perceptions. The molecular mechanism and the molecular candidates involved in these processes are assumed to be similar if not same. So far several molecular factors have been identified which are fairly conserved across the phylogenetic tree and are involved in these complex sensory functions. Among all, members belonging to Transient Receptor Potential (TRP) channels have been widely characterized for their involvement in thermo-sensation. These include TRPV1 to TRPV4 channels which reveal complex thermo-gating behavior in response to changes in temperature. The molecular evolution of these channels is highly correlative with the thermal response of different species. However, recent 2504 human genome data suggest that these thermo-sensitive TRPV channels are highly variable and carry possible deleterious mutations in human population. These unexpected findings may explain the individual differences in terms of complex sensory functions.

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Humans and other animals respond to different physiological and environmental stimuli which activate a range of complex sensory processes. The exact molecular mechanisms by which these physical stimuli work is poorly understood. Nevertheless, the ability to sense changes in temperature remain as a conserved phenomenon in all animals. Interestingly, the ability to respond against minute temperature changes differs among species. So far several reports have elucidated the role of Transient Receptor Potential (TRP) channels in the process of sensory functions, a complex process by which individuals can sense different physical stimuli such as temperature, mechanical pressure, osmolarity, etc. Therefore, TRP channels are generally termed as “detectors and protectors” to suggest that proper detection of sensory cues is necessary for animals to protect from potential tissue damage, such as exposure to noxious cold or hot temperature or other noxious compounds. Such conclusions are drawn from extensive earlier studies with temperature-sensitive nerve fibers endogenously expressing diverse TRP channels and the response of these nerve fibers correlates well with the functional properties of TRP channels, suggesting an integrative model of thermo- and pain-reception mediated by these TRPs.1 Nociception (detection of noxious stimuli) is mediated in mammals primarily by different TRP channels and it is well established that these channels work as the molecular detectors of noxious thermal, chemical and mechanical stimuli which activate sensory neurons and thus pain.2

Several reports suggest that during vertebrate evolution, TRP channels have undergone extensive gene deletion, gene duplication, and gene multiplication events. In addition, certain point mutations in these channels in some species provide unique adaptation ability, such as resistance to certain noxious chemical compounds, resistance to extreme acidic conditions, or the insensitivity toward certain stimuli. Therefore these genetic variations induce an altered ability to sense different physical or chemical stimuli, helping the species to either survive in a specific condition
and support reproduction there or avoid that environmental niche. For example, Zebra fish lost TRPM8 during evolution, most likely to increase their reproductive fitness in the cold region of Himalayas where that species have evolved under resource limited conditions. In fact, different species seem to have utilized TRPM8 to respond to different temperatures. This is supported by that fact that African clawed frog *Xenopus laevis* has a very distinct thermal response property compared to its mammalian and avian counterparts. Similarly, Amphibians have probably achieved high sensitivity by multiplying TRPV4 gene several times. African Naked mole rats (Heterocephalus glaber) have a very high acid tolerance, which can be explained by their unique properties of nociceptors that express TRPV1 with various point mutations. Chickens as well as almost all birds show very low sensitivity toward Capsaicin (till 100 μM) and no detectable binding of Resiniferatoxin due to a point mutation (S512Y) making the avian TRPV1 insensitive to these noxious compounds. The ability to detect UV or IR by different TRP channels seems to be species-specific and is restricted in certain insects, reptiles and vampire bats, respectively. In agreement with these reports, recent studies have indeed confirmed that different domains and motifs of TRP channels had undergone differential selection pressure throughout vertebrate evolution. This leads to changes in the sequence of TRP channels, especially in certain key regions affecting its structure – function relationship, which is either beneficial (thus selected) or may become deleterious (thus not selected) during molecular evolution.

In spite of high degree of variance in several parameters such as life style, health, food choice, and physiological status, humans also show signature of adaptations in different ecological niches characterized by different temperatures and other factors. Though the involvement of thermo-sensitive TRP channels in the context of pain and thermo-reception in human is well established, the underlying mechanisms are poorly understood. The involvement of TRP channels in sensory functions in human is not well characterized mainly due to individual variations and in most cases, molecular understanding is derived from studies in rodents or other animals. However, crucial inference can be drawn from the 1092 and now from 2504 human genome data which provides suitable platform for comparative studies.

A systemic analysis of 2504 genome data suggests that there is a high variability in all TRPV family members including the thermo-sensitive channels namely in TRPV1-TRPV4 (Table 1). To investigate the substitutions occurring in human population

**Table 1.** Variant analysis from human genome. The hTRPV variants computed from 2504 (1000G Phase3 v5 Reference) genomes from 26 different ethnic populations demonstrate that Intron variants, NMD transcript variants, Non-coding transcript variants, upstream gene variants, downstream gene variants are predominant variant classes present in different TRP channels (according to general variant classification).

| Variants                          | TRPV1 | TRPV2 | TRPV3 | TRPV4 | TRPV5 | TRPV6 |
|----------------------------------|-------|-------|-------|-------|-------|-------|
| Transcript ablation              | 0     | 0     | 0     | 0     | 0     | 0     |
| Splice donor variant             | 7     | 5     | 21    | 1     | 12    | 3     |
| Splice acceptor variant          | 8     | 0     | 21    | 0     | 12    | 8     |
| Stop gained                      | 14    | 18    | 24    | 78    | 36    | 4     |
| Frame-shift variant              | 20    | 6     | 10    | 50    | 14    | 2     |
| Stop lost                        | 1     | 0     | 2     | 0     | 0     | 0     |
| Start lost                       | 1     | 1     | 5     | 0     | 2     | 3     |
| In frame insertion               | 0     | 4     | 6     | 0     | 0     | 0     |
| In frame deletion                | 2     | 8     | 0     | 0     | 0     | 0     |
| Missense variant                 | 434   | 397   | 715   | 1759  | 658   | 273   |
| Splice region variant            | 65    | 65    | 151   | 170   | 57    | 104   |
| Incomplete terminal codon variant| 0     | 0     | 0     | 0     | 0     | 0     |
| Synonymous variant               | 240   | 211   | 425   | 1156  | 276   | 121   |
| Stop retained variant            | 0     | 0     | 0     | 0     | 2     | 1     |
| Coding sequence variant          | 3     | 0     | 1     | 376   | 2     | 0     |
| Mature mi RNA variant            | 0     | 0     | 0     | 0     | 0     | 0     |
| 5 prime UTR variant              | 29    | 159   | 43    | 9     | 37    | 48    |
| 3 prime UTR variant              | 538   | 92    | 967   | 231   | 50    | 26    |
| Non coding transcript exon variant| 0 | 170 | 316 | 19 | 0 | 1316 |
| Intron variant                   | 4412  | 3400  | 13385 | 14195 | 2291 | 1541 |
| NMD transcript variant           | 2847  | 0     | 7665  | 2284  | 0     | 0     |
| Non coding transcript variant    | 0     | 547   | 679   | 670   | 0     | 1767  |
| Upstream gene variant            | 505   | 2557  | 2669  | 1772  | 644   | 1838  |
| Downstream gene variant          | 650   | 3101  | 2489  | 1942  | 592   | 3346  |
(which is ~1% of total population), the use of SIFT, PolyPhen and GD scores proved to be very helpful, especially in categorizing various probably deleterious mutations (Fig. 1). Many of these mutations have already been reported to affect channel functions. Our study predicted other substitutions in TRPV channels

**Figure 1.** Analysis of missense variants of hTRPVs. Mutational analysis of TRPV ion channels on the basis of Grantham Deviation, SIFT and PolyPhen 2 Score are shown. The deleterious mutations reported in the 2504 (1000G Phase3 v5 Reference) genomes from 26 different ethnic populations were plotted in X-axis (labeled as the amino acid coordinates) and GD scores of the respective mutations were plotted in Y-axis. The red spheres denote mutations which are most likely damaging the structure function relationship of TRPVs according to all three mutation prediction methods (GD, SIFT and PolyPhen), the blue spheres denote the mutations which are probably damaging according to only two of these methods and the green spheres denote ones which are probably damaging according to only one of these methods.
which may affect their function in humans adversely. The 2504 genome data was obtained from Human Genome Consortium. SNPs associated with TRPs were retrieved from the single nucleotide polymorphism database (dbSNP) (https://www.ncbi.nlm.nih.gov/snp/), and were commonly referred by their reference SNP (rsSNP).14-15

Single amino acid substitution in a protein sequence, also termed as rsSNPs can potentially indicate if a mutation can affect the function of a protein by altering the phenotype of the carrier.16 SIFT (Sorting Intolerant From Tolerant) uses Dirichlet mixtures extracted from PMSAs (Protein Multiple Sequence Alignments) to create PSSMs (Position Specific Scoring Matrices) and score missense substitutions. The output score is a normalized probability for each of the 19 possible mutations at each position in the aligned target gene (in this case, the respective TRP sequences).17 Thus, by sequence homology, SIFT predicts the effects of all possible substitutions at each position in the protein sequence. All the SNPs from the six TRP channels were subjected to SIFT analysis by its websolver (http://www.sift.jcvi.org).18 Only SIFT scores of ≤0.05 were considered as indicative of deleterious substitutions. PolyPhen (Polymorphism Phenotyping) is the best known classifier from a family of rule or decision tree-based classifiers which focuses on a series of features annotated onto the individual amino acid positions of a human protein. However, the features may also include a PSSM derived from a sequence alignment, an amino acid substitution is then predicted to affect protein function if the substitution violates an empirically determined condition. The mutations obtained from the 2504 genome project were subjected to PolyPhen predictions using the website (http://www.embl.de/PolyPhen/).19-20 PolyPhen scores ≥ 0.9 were considered harmful for the structure-function relationship of the protein considered in this study. For calculating the Grantham Deviation (GD) for missense substitutions at given positions, the Align GV-GD websolver (http://www.agvgd.iarc.fr/) was used.21-22 Mutations having a GD score more than 60 were considered highly deleterious.16

All these substitutions were divided into three main categories: (a) the most deleterious mutations by all three methods used (SIFT score ≤0.05, PolyPhen score ≥0.9, GD score ≥60), (b) mutations which were shown to be probably deleterious by at least two methods and (c) mutations which were shown to be probably deleterious by only one method. It is worth mentioning that all the substitutions reported in the study were found to be deleterious by at least one method. The mutational analysis of TRPV1 in human population revealed that there are 90 probably harmful mutations which are prevalent in the 2504 human sequences considered for this study.

Interestingly, this analysis reveals that deleterious mutations as well as other mutations are mainly clustered in certain regions of the TRPVs, suggesting the variability as well as evolutionary stability of TRPVs in the human population. For TRPV1, the N-terminal portion is relatively mutation-free whereas most of the mutations are clustered at the C-terminal region, especially in the loop 6 and TM6 regions. The TM1 and loop 1 regions also contain high number of deleterious mutations. These clusters of harmful mutations in distinct regions of TRPV1 suggest the evolutionary stability of this region and thus reveal the possible functional repercussion of these mutations in TRPV1 in the context of pathophysiology. Similarly, in TRPV2, the clusters of 20 harmful mutations were mainly present in the N-terminal of the protein encompassing the ARDs. The mutational analysis of TRPV3 in human population revealed small clusters (30) of probable deleterious mutations distributed throughout the N-terminal of the protein and a few of the harmful mutations in the C-terminal region. Altogether, the transmembrane regions were devoid of clusters of mutations suggesting that the TM regions are evolutionary stable and mutations in these regions are not tolerable. According to this prediction, TRPV4 had much fewer harmful mutations (25) suggesting that mutations in TRPV4 as such may not be tolerable. This is in agreement with the many mutations in TRPV4 which have been linked with the developmental disorders commonly termed as “channelopathies.”23 In TRPV5, the substitutions were not clustered in the any particular region. Though there are several mutations detected, according to the analysis only very few (14) of them seem to be deleterious. In case of TRPV6, very few destabilizing mutations were found in human population.

Overall, these human mutational analysis indicate that in the human population, TRPV channels are still undergoing “mutation and selection” processes and for some TRPVs, (such as in case of TRPV1 and TRPV3) their rate is rapid compared to others. The distribution of the mutations in specific clusters in
different regions suggests certain key facts: first, these regions can tolerate mutations and second: these regions are actively undergoing changes in the human population which may in future give rise to channels which are more stable in terms of architecture, and efficient in terms of functionality. Some of these harmful mutations predicted may also result in severe disruption in channel function if present homozygously, thus leading to pathophysiological conditions.

Indeed, these predictions matched well with the previous findings demonstrating mutations in TRPVs, which are linked with the development of pathophysiological conditions. For example, in TRPV1, a Pro-91-Ser mutation leads to increased protein expression. An Ile-315-Met change is associated with functional dyspepsia and an Ile-585-Val change is associated with decreased risk of Asthma. In case of TRPV3, G573S, G573C, G573A, and W692G are involved in the development of Olmsted Syndrome. In case of TRPV4, a Pro-19-Ser change is associated with hypo-natraemia. Similarly, Thr-89-Ile, Lys-197-Arg, and Leu-199-Phe mutations in TRPV4 individually lead to metatropic dysplasia. Similarly, a Glu-183-Lys is associated with spondyloepiphyseal dysplasia Maroteux type, and an Arg-232-Cys change with scapuloperoneal spinal muscular atrophy. Accordingly, Arg-269-His and Arg-269-His changes lead to Charcot-Marie-Tooth disease 2C. Spondylometaphyseal dysplasia Kozlowski type is associated with a Glu-278-Lys change in TRPV4. In case of TRPV5, an Ala-563-Thr mutation leads to increased Ca\(^{2+}\)-influx and thus the mutation may affect the gating properties.

So far, no systemic study has been conducted to identify the mutations prevalent in human populations. Analysis of 2504 human genome data reveals that the mutations reported to date are inconspicuously predictable among human population and also indicate that other relevant mutations present in different individuals may have a potential impact in the development of pathological situations due to altered channel functions/regulations. Such aspects can potentially also be used as potential bio-marker for individual health diagnostics.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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