Genetic and epigenetic of pain perception

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Abstract Pain is the common reason why patient seeking for medical help. Recent studies, shows that there are various type of genes that have a role in pain perception. Genetic’s role include pain sensation Genome Wide Association Study, Single Nucleotide Polymorphism, and epigenetic in pain modulation. Recent studies shows that epigenetic mechanism can alter the expression of pronSetyaociceptive or antinociceptive gene that useful in managing pain from now on. In genes there are one or more polymorphisms that effect the expression of the protein products that later affect the pain response. Ion Channel is a protein membrrane that transporting ion in and out of a cell. This ion channel can change depends on the genes that made the protein. Recent studies shown that there’s more than 450 ion channel genes. From all of those ion channels, voltage gated sodium channel (Na⁺) tend to be investigated more deeply because Na⁺ is the most common and widely distributed in human cell. Changes on those channels can cause neuropathic pain. Small Fibre Neuropathy caused by defect of fiber myelinated A-delta and unmyelinated C. Substitution of a single aminoalkanoic acid in gene SCN9A, a gene that encoding for Na⁺ channel Na⁺V₁.7, can cause changes in channel Na⁺V₁.7. Study shows that Small Fibre Neuropathy lesion in gene SCN9A has decreased after surgical pain sensitivity in cohort patients. There’s two types of inherited traits of pain sensation which is Mendellian and Non-Mendellian. Mendellian Inherited Traits show a relation between gene and a specific pain sensation that in recent studies show mutation in Na⁺V₁.7 ion channel. However, the Non Mendellian Inherited Traits said that Catechol O Methyltrasnferase, Guanosin Trifosfat, Cyclo Hydrolase and Na⁺V₁.9 have a very important role in pain sensation. This gene mutation information can help the clinician to give a better treatment strategies for patients.

1. Introduction
Unpleasant lamentation caused by pain is one of the common reason patient looking for medical help. Different people can feel different level of pain, this can be happened because of different people will react differently to the same stimulation. This condition can be influenced by many factors such as genetic factors and environmental factors. It is a challenge to study human pain, because it depend on race, ethnicity (related to different ethnicity and different environment they live in) [1], gender [2], socioeconomic status, and different personal interpretation of pain [3]. Recent study shows us that there are several genes that have a role in pain sensation, sensitivity of pain, development of chronic pain, and patient’s responses to pain after surgical procedure [4]. Recent study has showed us the establishment of genetic’s role especially in pain sensation, Genome Wide Association Study, Single Nucleotide Polymorphism, and epigenetic in pain modulation [4].

2. Pain gene
Definition of pain gene is ‘a gene for which there are one or more polymorphisms that affect the expression or the functioning of its protein product in a way that affects pain response’ [5]. Study of gene involving in pain perception can be performed in two ways, Linkage Analysis (a study of large families) or Association Analysis (a large cohort study of matched and unrelated individuals observation that has or don’t have the same condition). Another method that used is twin study to observe pain expression in twins. In 2007, Norbury performed a twin study that showed a statistically significant genetic components in female twin subjects’s sensitivy of pain (the variation is between 22% and 55% ) [6]. William et al performed another twin study that observing pain in musculoskeletal in different sites of the body, the result showed that there was statistically significant similarity in reporting pain between the monozygotic twins and the dizygotic twins [7]. From both study performed by Norbury et al and William et al showed that monozygotic twins have a stronger correlation in musculoskeletal pain than dizygotic twins [6] [7]. From that statement we can conclude, there is a genetic components that have a role in pain heritability.

3. Ion Channel’s role in pain
Ion channel is a membrane spanning protein functioned in transporting ions into and out af a cell selectively. That ion channel can be divided into voltage gated and ligand gated. Nowadays have been known that human genome has more that 450 ion channel genes [8]. From all of those ion channels, voltage gated sodium channel (Na\(_v\)) are the most investigated because Na\(_v\) is the most distributed widely in human cell. In recent days there are nine Na\(_v\) that has been identified, but only four Na\(_v\) that mainly expressed in nerve sensors. Those voltage gated sodium channels are Na\(_v\).1.3, Na\(_v\).1.7, Na\(_v\).1.8 and Na\(_v\).1.9. Changes on those channels can cause neuropathic pain that involved in upregulation or/and downregulation in surround fibres.

**Figure 1.** Voltage Gated Na\(^{+}\) Channels
Subject that suffered from Small Fibre Neuropathy will show sign and symptom of neuropathic pain and/or autonomic dysfunction. The cause of this condition is an injury that caused selective defect to fibres specifically myelinated A-delta and unmyelinated C. Substitution of a single aminoalkanoic acid in gene SCN9A, a gene that encoding for Na\(^+\) channel Na\(^{1.7}\), can cause changes in channel Na\(^{1.7}\), as a result, function escalation in Na\(^{1.7}\) has been indicated in patients. This result has been detected in a study performed by Faber et al with subjects two cohort patients with Small Fiber Neuropathy. This study also showed a gain of function also detected in Na\(^{1.8}\) and caused peripheral neuropathy [9]. In 2013 Duan performed a study that point out SNP’s lesion in gene SCN9A has decreased after surgical pain sensitivity in cohort patients. That study also showed SNP’s lesion in KCNS1, a gene that encoding for K\(^+\) channel, and CACNG2, a gene that encoding gamma 2 sub-unit of voltage gated Ca\(^{2+}\), has increased the insidens of experimental pain and pain after surgical. A SNP’s lesion in CACNA2D3, a gene that encoding alpha 2 delta 3 sub-unit voltage gated Ca\(^{2+}\), has reduced chronic lower back pain after the patients followed surgical procedures [10].

4. Mendellian inherited traits of pain sensation
Mendellian trait is a trait that follow the Law of Mendell saying only two possible version of a gene, a dominant and a recessive. The specific relation between a gene and a specific pain sensation has been indicated, eventhough that condition is very rare, loss of function mutation that cause pain insensitivity and gain of function mutation that cause pain intensification has been found. Recent study of patients with those rare mutation has showed mutation in the Na\(^{1.7}\) ion channel which is specifically happened inside the dorsal root ganglion neurons. Those study has showed several genes are indicated of causing insensitivity to pain, gene SPTLC1 has been indicated of causing HSANI (Hereditary Sensory and Autonomic Neuropathy type I), while gene HSAN2 has been indicated of causing HSANII (Hereditary Sensory and Autonomic Neuropathy type II), gene IKBKAP has been indicated of causing HSANIII (Hereditary Sensory and Autonomic Neuropathy type III), gene NTRK1 has been indicated of causing HSANIV (Hereditary Sensory and Autonomic Neuropathy type IV) and gene trkA has been indicated of causing HSANV (Hereditary Sensory and Autonomic Neuropathy type V) [11] [12].

Beside those pain insensitivity condition, there’s also pain intensification in Mendellian pain sensation inherited trait. This condition caused by several gene mutation such as SCN9A mutation that caused function escalation of Na\(^{1.7}\) ion channel in Primary Erythromelalgia and Paroxymal Xtreme
Pain Disorder, mutation of CACNA1A that encoding calcium channel caused gain of function of calcium channel in Familial Hemiplegic Migraine type 1, mutated gene ATP1A2 that encoding ATPase pump of exchange has caused loff of function ATPase pump activity, this condition cause the pump transporting Na\(^+\) and K\(^+\) ineffectively through membrane of cell in Familial Hemiplegic Migraine type 2 and mutation of gene SCN1A that encoding Na\(_{v}1.1\) in Familial Hemiplegic Migraine type 3 and 4.

5. Non mendellian inherited traits of pain sensation

Catecholamine consist of adrenaline, noradrenaline and dopamine have several functions in human brain and spinal cord, the function of those substance are to increase or to decrease pain sensitivity [13]. Catechol O Methyltransferase, Guanosin Trifosfat, Cyclo Hydrolase and Na\(_{v}1.9\) have a very important role in pain sensation [14]. Nav1.9 is indicated to be the cause of hypersensitivity because of various kind of inflammatory mediators, and influencing peripheral sensitization. Therefore mutation of SCNIIA (gene that encoding Na\(_{v}1.9\) ion channel alpha type II) has been indicated as the cause of thermal sensation alteration or in other word cause hypersensitivity in an experiment conducted by Amaya et al in their study [15]. Study conducted by Zubieta showed that polymorphism of gene COMT is the reason of variation in pain sensation, the in hibition of gene COMT will intensificate sensitivity of pain while depressed gene COMT will increase pain sensitivity of thermal and mechanic[16]. Therefore, the information about this mutation will help clinician to build a better treatment strategies.

Gene GCH1 is a gene responsible in encoding Guanosin Trifosphate cyclohidrolase. SNPs in the gene GCH1 has been indicated the cause of variation of pain perception like persistent low back pain after surgical procedure. A study conducted by Ichinose et al has showed that mutation in gene GCH1, a gene that encode cyclohidrolase 1, will decrease the risk of pain in patients with cancer; mutation in gene SLC6A4, a gene that encode transportation of serotonin, will increase the risk of emotional pain regulation; mutation in gene ADRB2, a gene that encode beta 2 adrenergenic receptor, will increase the risk of the prolonged duration of chronic pain; and mutation in gene HTR2A, a gene that encode serotonin receptor, will increase the risk of prolonged pain after surgical procedure [17].

Recent study has indicated that SNPs in several genes can cause variation of pain sensation, for example a SNPs in gene CASP9, a gene that encode aspartic acid specific protease, will increase the reportage of pain disregard to the progression of the diseases. A Polymorism of gene IL16, a gene that encode interleukin16, will increase the insidens of endometriosis in female [18].

6. The future of epigenetic of pain

By definition, epigenetic is the interaction between nature (genes) and nurture (environment). In this definition, environment consist of age, lifestyle (smoking and exercise), nutrition, chemical contact, stress and love. Recent study performed by Buchheit et al has showed us that mechanism of epigenetic can either inhibiting or enhancing the expressions of pronociceptive gene or antinoicceptive gene. Beside that, mechanisms of epigenetic has been indicated not only in the transitions from acute to chronic pain but also in the propagation of pain after surgical procedure [14].

Rapid development of mapping human genome has led us to better comprehension of human diseases especially the genetic nature of disease. In the term of pain perception, recent studies has led us to a better comprehension about the function of genes in pain perception, including the expression of pain, enabling us to predict the risk of chronic pain after surgical procedure and promises therapy for pain management. For example, the improvement of our knowledge has led us to identify the gene CACNG2 that responsible in causing neuropathic pain. The invention of that gene has take us one step further to develop a simple test to predict the patient’s risk to developing pain after surgical procedure or even we will be able to predict patient’s response to certain medication. Golberg et al has performed an experimental in four patients with erythromelalgia syndrome and showed us a succesful result of XEN402 distribution, an antagonist of Na\(_{v}1.7\) channel, compared to placebo [20].

Pain management with gene therapy is a unique procedure involving the decrement of an active antinoicceptive gene, as a result the pain expression can be suppressed or prevented. We’re still in the beginning of gene therapy era, but we’re about to go in the right direction. Phase I of NP2 clinical trial
has been completed in ten patients with chronic pain because of cancer. The injection of lower dose of NP2 showed no significant changes in pain expression, but the patients that received middle and higher dose of NP2 reported significant relief in their pain expression [21]. Gene therapy for pain management is still evolving, not only for therapy of patients with cancer, but also for pain in general causes by other diseases.

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