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GENE MUTATIONS, GENETIC DISEASE AND PHARMACOGENETIC GENES DISORDER

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ABSTRACT
Somatic cell mutation is able to create genetic variance in a cell population and can induce cancer and tumor when gene mutations took place at repressor gene in controlling cell cycles such as p53 gene. Whereas germline cell mutation can cause genetic disease such as sickle cell anemia, breast cancer, thalassemia, parkinson's as well as defect of biochemical pathway that influence drug-receptor interaction, which has negative effect and lead to hospitalized of patient. Most of reports mentioned that point mutation such as a single base of nucleotide substitution (purine replaced by purine or transversion (purine replaced by pyrimidine or vice versa) that affected genetic disease as well as adverse drug reaction that involved genetic factors. Mutation that occurred in germline cell would be inherited to the progeny, and these mutated genes can spread in a population through fertilization process. Mutation that occur in coding frame of DNA region which of their expression are responsible for synthesis of specific products could be rise of genetic disease, because the lost of gene function. Similarly, mutation that take place for CYP450 gene family which related to drug metabolism included pharmacokinetic and pharmacodynamic gene function could affect drug biosynthesis and degradation. Abnormality of drug metabolism that results in pharmacogenetic effect which is indicated by adverse drug reaction to individual that severe metabolite defect. On the future, therapy of genetic disease as well as abnormal of drug metabolism can be directed into gene therapy techniques with using stem cell engineering.

KEYWORDS: Gene mutations, genetic disease, pharmacogenetic genes disorder

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INTRODUCTION

Gene mutation in human genome is difficult to predict when alteration of DNA structures took place by environmental factors, such as chemical mutagen or cosmic radiation. A lot of factors caused mutation occurs in gene level especially for somatic cell mutation. Gene mutation (point mutation) can occur spontaneously that is caused by several of source or occurred error during DNA replication, chemical carcinogenic, virogenic, and ionic radiation. Similarly, methylation, and transposable genetic element could give abnormal gene product with behave like gene mutation, but DNA methylation and transposable genetic element, sometimes only provide temporary prevents of normal gene expression that lead to change of phenotypic performance called as epigenetic effect. Even recent report mentioned that epigenetic can be inherited and give several effects on genetic diseases. Epigenetic is an biological term, methylation is one of cause factor of epigenetic, which usually occur methylation at Cytosine (CpG) become methyl cytosine[12,45,] while lysine 9 of histon H3 methylation influenced assembly of chromatin structure[59]. Histon modification was affected by methylation that influenced gene transcription and expression; hence DNA methylation modified histone structures are disrupted in cancer cell[24].

One of gene mutation source is chemical that enter into body through food and air. Mutation effect can be harmful to the life when coding region of the gene occur mutation, which causes alteration of amino acid sequence in a polypeptide chain. These alteration affected protein function when compared to original one (wild type). When alteration of protein function related to disorder of metabolism some drugs or biochemical pathway which influences importance characters can create disease related to genetic. Abnormality of protein function related to gene mutation, genotypically as well as phenotypic performance can be observed by identification of amino sequence from a polypeptide chain which related to phenotypic abnormality.

Gene mutation is source of genetic variance and genetic polymorphism, these gene mutations can arise several possibilities i.e. genetic diseases, receptor mutation, and adverse drug reaction (ADR) in human. This adverse drug reaction in human body can be harmful for health and the life, most of cases are reported that mutation type is point mutation that brings about defective some P450 enzymes, examples: CYP2D6 and CYP2C9 gene mutation[23,39,79]. Both of the gene mutation of drug-metabolizing enzymes and another defective protein function in human can make shorter human life span. A lot examples, gene mutation influences biochemical pathway that caused metabolite disorder such as Parkinson's, Alzheimer, x, thalassemia, and hemophilia[14,31,55]. Parkinson's gene mutation has been investigated from Parkinson's family history[14,22,31], the gene called Park 8 and make protein named "dardarin" for the basque word for tremor, which indicate a symptom of the progressive and fatal nerve disease[61]. Other genetic disorders are Hemoglobinopathies and thalassemias, while most of cases were reported that mutation in coding frame of these gene occurred substitution of amino acid that arrange a polypeptide chain of hemoglobin[15]. Hemoglobin (Hb) is a four chain (tetrameric) oxygen carrying protein of red blood cell (erythrocytes). Two mayor globins genes product, i.e., .α and β chain, two symbols for α- globin genes are HBA1 and HBA2, whereas symbol for β globin gene is HBB. To make easy understanding, sometimes researcher provides symbols for hemoglobin gene mutation such as Hbs (HBB, Glu6Val) and HbMiyano (HBA1, Thr41Ser). The meanings of the symbols are: Hbs, hemoglobin associated with sickle cell anemia; whereas Glu6Val substitution glutamate (6) to Valine. Hundreds variant of allele were detected from patient which has sickle cell anemia for examples it found that 189 allelic variant from HBA1, 34 for HBA2, 276 for HBB[19]. According to Stamatoyanopoulus, et al., cit. Albertini et al.[3] RBCs variant that was caused by somatic mutation has degree complexity. Disease that is caused by gene mutation which caused hemoglobin reduction was thalassemia (Cooley anemia) [13,58]. This disease was caused by low production of .α or β globins chain.

Genetic variant arise in human genome in successive generation are caused by germline cells mutation, probable was inherited by their parental or it occurred spontaneous mutation during spermatogenesis or oogenesis. Example, these spontaneous mutation happened at Royal family history in Europe, which suffer the classic hemophilia, they are coming from both normal parental[30]. This classic hemophilia, is also called as hemophilia A, is a sex linked recessive disorder and characterized by a deficiency of factor VIII, located on chromosomes 8[42]. Hemophilia A disease affects 1 in 10.000 males, because X–linked

disease, spontaneous mutation of this gene contributed and wide-spread in a population[62]. Nonsense mutation in coding frame such as Ser1395stop and Arg427stop are found in severe hemophilia[36] and occur inversion breaking intone 1 of factor VIII gene[4].

Gene mutation related to drug response in human individual called as pharmacogenetic, this new field that constitute integration of pharmacology and genetic factor into study drug metabolism and its effect in human body. Whereas understanding pharmacogenomic can be interchangeable with pharmacogenetic, because in a pharmacogenomic study about adverse drug reaction deal with genome, while pharmacogenetic deal with individual gene in a genome. The study of adverse drug reaction into individual related to genetic defect, especially for CY P450 gene family can be directed onto Marker Aid Selection (MAS), when molecular markers are ready to be used for identifying specific gene. DNA sequence of human genome was completely finished in 2002, and already known gene sequence for specific trait, hence, it can be used as marker to detect gene mutation of individual when they are suspected to severe genetic disease based or metabolic defect based on phenotype performance. Molecular biology techniques are common techniques which share between plants and human system as well as for DNA identification, DNA separation, RNA isolation, and DNA detection for genetic polymorphism.

SOMATIC AND GERM CELLS MUTATION

Eukaryotic organism consisted of billion of cells included both reproductive and somatic cells. The mature eukaryotic organism, there are two cells types i.e. Somatic cells (diploid) and germ cells or reproductive cell (haploid). Reproductive cells are produced by meiosis cell division derived from. Diploid cell in mammals, somatic cell mutation cannot be inherited to progeny, whereas mutation take place in germ cell lines will be transmitted to progeny during fertilization process. Somatic cells are diploid and they have one set of chromosomes, they are descended half from mother and half from father, while reproductive cells have half set of chromosomes called haploid. A lot of reports concerning with somatic cell mutation that caused tumor or cancer in human such as prostate cancer[43,63,65], as well as p53 gene mutation result in breast tumor or cancer[6,81]. Somatic loss of BRCA1 and p53 that cause repressor gene function such as p53 in active and lead to BRCA1 and BRCA2 tumor [6, 82], BRCA1 transcriptionally regulate genes involved in breast tumorigenesis[86]. Most of cases BRCA1 and BRCA2 germline mutation can be detected to early onset of familial breast cancer and there are predisposition to ovarian and another cancer[6,37,57,82]. Environmental factor, chemical substances, and error occurred during DNA replication can lead to somatic cell as well as germline mutation. *In vivo* somatic cell mutation can occur by methylation at nitrogen base such as methylation at cytosine (C) becomes methyl cytosine or guanine (G) changes into methyl guanine. According to Chang *et al*[13] that exposure to vinclozolin act as endocrine disruptor indicated permanent DNA methylation, and inherited to the next generartion. This pattern can be used for studying genetic disease caused by methylation. Methylated nitrogen base, possibility could not be recognized by RNA polymerase during transcription processes while transposable genetic element which occupy at coding frame of DNA or promoter in front of start point of transcription site can losses gene expression. Spontaneous somatic and germinal cell mutation reported by Kuick *et al*.[49] that similarity of spontaneous mutation rate was found between germinal and somatic cell. Several factors which of gene can be mutated by physical and chemical mutagen, error during DNA replication, and radiation occur from cosmic (**Fig. 1**). DNA chain is fragile to be disrupted by chemical and physical substance, hence gamma radiation can be used for induced mutation research, especially in a crop improvement and cell cancer research

Somatic cell mutation in plant can be inherited into progeny because functional cells are able to differentiate into mature plant. One of example for somatic cell mutation is transgenic plant (insertion mutant). Insertion of foreign gene into single somatic cell (vegetative cell) that is able to provide totipotence into mature plants that will give reproductive cells (ovum and pollen) that bring inserted gene, and it is transmitted into next generation. Another somatic cell mutation which is caused by chemical mutagen (EMS, nitrosamine, NOx) or physical mutagen (gamma rays, neutron, and X rays) was obtained superior alleles in crops plant, these mutated gene can be inherited to progeny when plant can be obtained

through somatic embryogenesis. We have experienced the use of physical mutagen such as gamma rays to irradiate rice scutellum of embryos, this scutellum is diploid cell (2n), induced mutation using gamma rays with dose of 15 Gy. Embryogenic callus derived from these irradiated scutellum were obtained during tissue culture processes. These embryogenic callus were able to produce plantlet and given seeds. Observation under stereo microscope showed that morphologically gave normal performance of pollen and ovary, even genotypic ally, these reproductive cell occurred gene mutation. DNA fingerprinting has been carried out on subsequent generation of this mutant line called R_1M_2 generation, we were detected genetic polymorphism on mutant lines when compared to their parental.

Technology of mammalian cell culture left behind compared to plant tissue culture. Somatic cell culture of mammalian are still restricted only for cell proliferation. Animal stem cell culture has not been yet ready for differentiation into intact organism like plant tissue culture, even the research ethically is not allowed to be carried out in human. The success of Dolly story in cloning strategy using diploid nuclear genome, at least, it opened new era in research of mammalian cell culture, even though it is not purely cell differentiation derived from somatic cell, because they only took nuclear genome (2n) and transferred to egg cell without nucleus which is removed from the cell.

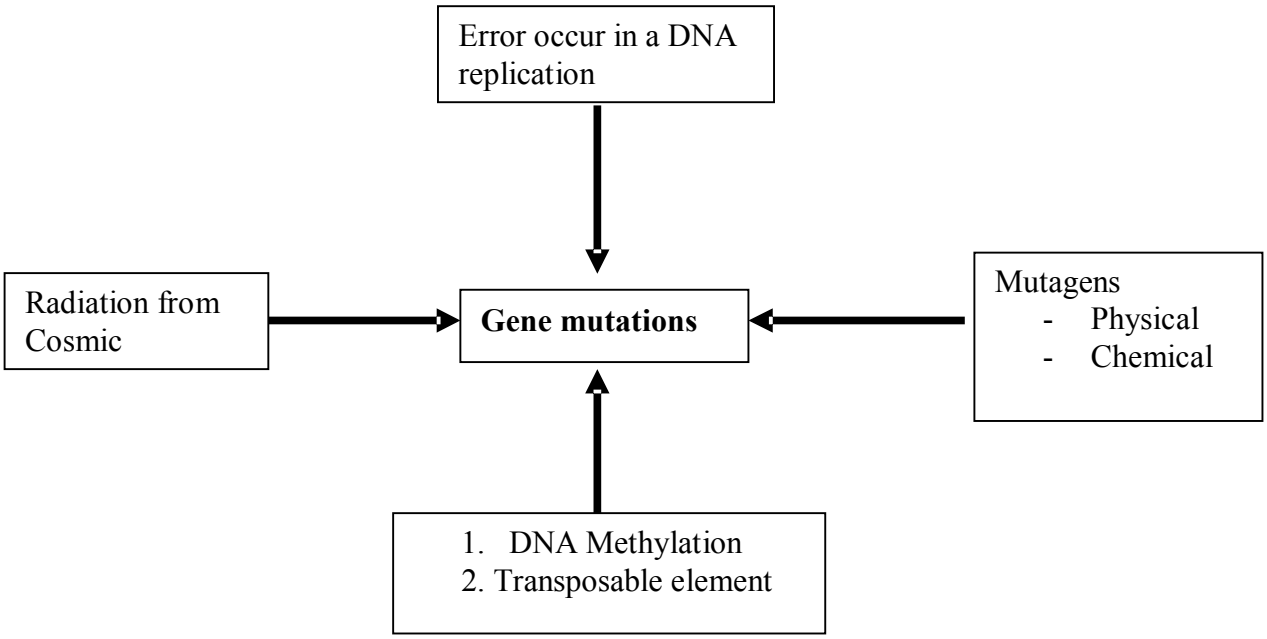

Figure 1: Several factors can cause gene mutations in human genome like indigenous factors e.g. error occur during nature DNA replication and methylation as well as transposable genetic element. Whereas external factor such as physical(X rays, gamma rays, fast neutron, and ultraviolet) and chemical (EMS and Knox) mutagen and radiation from cosmic also can create randomly mutation in a genome as well

CYTOCHROME P450 GENE MUTATION

CYP450 enzymes present in plants, animals and human, the study of this enzyme function in human has focused on drug-metabolizing enzyme which is responsible for the oxidative metabolism of numerous endogenous compounds[18]. These CYP enzymes have been identified more than 7700 in various organisms in the year 2007. CYP450s are heme-containing protein, the term of CYP450 based on their initial identification in red liver pigment (P) which of protein produced a characteristic absorption spectrum peak at 450 nm[32]. CYP450 enzymes in bacteria, fungi, insect, plant, and mammals can be also considered as oxygen-utilizing enzymes that catalyze diverse compounds that serve as substrate such as cholesterol, steroid hormones, fatty acid, drugs, food additive, and etc[20,32]. CYP71AVI in plant (*Artemisia annua*) was key role in biosynthesis of sesquiterpene lacton artemisinin as anti malaria[77]. Cytochrome

P450 proteins are super family that containing hundreds of genes, their gene products have been studied in relationship with drug action such as inhibition or induction of adverse drug reaction, production of steroid hormones, and prevent cellular damage with produce reactive molecule. Human CYP450 enzymes can be found in the inner membrane of mitochondria, endoplasmic reticulum of the liver. Most of scientists are interesting to study in drug metabolism and toxicity related to CYP450 enzymes as catalyst. Mutation that occurs on CYP gene that acts as drug-metabolizing enzymes will influence individual drug response. Individual genetic variation related to drug response influence pharmacokinetic such as absorption, distribution, metabolism and excretion as well as pharmacodynamic, cause lack of efficacy and toxic effects[7]. Cytochrome P450 (CYP450) play importance role in drug metabolism and drug-drug interaction[10]. Alteration of metabolic enzymes function from CYP450 caused by mutation, these enzymes can act as inducer or inhibitor, hence understanding genetic related to these enzymes function in a drug interaction is importance to help individual from adverse drug reaction

Mutation in CYP450 genes which are related to drug metabolism is arisen new term i.e. Pharmacogenetic. The term of pharmacogenetic is different individual response to drug which due to genetic variance, it is caused by gene mutation. When two persons get similar disease with the same disease symptom, they are treated with similar drug by medical doctor, one of them get therapeutic effect, but another one get adverse drug reaction. Why this one can happen into some one, the answer is gene mutation occur at gene level, which is responsible for metabolize of these drug reaction. Genetic polymorphism related to drug response in human has been observed recently, especially for CYP2D6, TPMT (Thiopurine methyltransferase**),** and CYP2C9 [23,38,39,67,71,72,74,79,85], CYP2D6 enzyme has function to metabolize codeine into morphine and another substrate, most of this enzyme involved in drugs metabolism. Mutations of CYP2D6 gene that cause ultra rapid metabolize codeine into morphine or very slow[29,35,74]. CYP2D6 gene is located on chromosomes 22, together with pseudogenes CYP2D7P. Another case is mutation at CYP2C9 gene related to metabolize warfarin that used as oral anticoagulant for people suffer coronary artery disease and venous thrombosis. Genetic variant at CYP2C9 gene alter rate of its metabolism, can lead to rapid or slow warfarin metabolism[1,68,90],

Most of cytochrome P450 protein in human was found in endoplasmic reticulum in hepatocytes act as electron donor to flavoprotein was NADPH, was then become CYP450 Reductase, and mutated CYP450 gene has implication in drug response in human body, and sometimes has harmful effect to life[32]. Mutation of CYP450 gene related to drug metabolism should be known as early as possible through genetic test, in order to avoid hospitalized patient from effects of ADR. Guttmachers and Collin[35] mentioned that how importance of genetic test from the case to save life of kid four years old, who is suffering acute lymphoblastic leukemia that have to receive oral mercaptopurine daily, but the kid is homozygous for gene that encodes thiopurine S-methyltransferase, an enzyme catalysis mercaptopurine.

GENETIC BASIS OF RECEPTOR AND MUTATION

Receptors are macromolecule (protein) involve in chemical signaling between intra and extra cellular. They are located on the cell surface and trans membrane examples: receptor of acetylcholine, GABA, growth factors, and insulin receptor, whereas nuclear receptor present in cytoplasm such as steroid hormone receptor, thyroid hormone receptors and androgen receptor. According to Laudet et al. (1992), nuclear receptor derived from common progeny based on the DNA binding C domain, which can be grouped into three sub families i.e. thyroid hormone and retinoic receptor, orphan receptor, and steroid hormone receptors. Based on the types and function of receptor, it can be divided four types i.e. ion channels (Ligand-gated ion channels), G-coupled receptors, enzymes-linked receptors, nuclear hormone receptors. Receptor can be activated by physiological process in the cells and ligand binding site such as drugs, hormone and neurotransmitters. Molecular biology development techniques aided to study drug-receptor interaction at molecular level. With advance molecular biology knowledge, it is possible to design precisely drug based on their receptor-binding site. Gene regulation for receptor synthesis in a cell is following the rule of eukaryotic gene regulation. Characteristic of a receptor is much depends on their gene constituent that give their product into protein. Mutation in coding frame (exon) a receptor gene will influence characteristic these receptor such as: ligand-binding site for receptor activation, hormone

function and receptor-drug interaction. Both of aging and genetic mutation influenced receptor activity, it was shown in clonidine biosynthesis which occur up rate like β-blockers for up-regulate of β-receptors or down regulates e.g. rapid withdrawal of clonidine caused hypertensive crisis . Clonidine has been used for decreasing arterial blood pressure[75,84].

A lot of report mentioned about receptor mutation which created receptor polymorphism, especially for nuclear receptor. One of example was an androgen receptor gene mutation that caused androgen insensitivity syndrome[53,66,80]. Nuclear receptor Mutation Database (NRMD) showed that 893 mutations in 54 nuclear receptors[81]. Another nuclear receptor function as ligand–inducible transcription factors like steroid receptor[5,33]. Androgen receptor (AR) that belongs to nuclear receptor family, this receptor function as ligand–inducible transcription factors[33]. Most of nuclear hormone receptor is hormone-regulated transcription factors such as thyroid hormone. In human, nuclear receptor family were found 48 genes with diverse roles in metabolic homeostasis development, and detoxification[47,80,89] reported patient with partial androgen insensitivity (AIS), because mutation occur in androgen receptor gene, which occur substitution of a glutamine by a lysine at position 902. Another receptor gene mutation cause phenotypic abnormality of male sexual development that range from a female phenotype such as complete testicular feminization undervitilized or infertile men[56], The androgen receptor gene mutation database (ARDB) in 2004 was reported by Gottlieb *et al*[34] that total receptor gene mutation 605, while AR-interacting protein are 70. Gluco corticoid receptor (GR) polymorphism in genetic hypertension also reported by Kenyon, et al. [46], this receptor is responsible for blood pressure, mutation of GR gene can affect blood pressure in rat, because of negative feedback regulation of corticosterone synthesis is reduced, because hormone access to glucocorticoid receptor is impaired. Mutation in the nuclear receptor gene such as NR2E3 that cause a disorder of human retinal photoreceptor development characterized by hyper function and excess of the minority S (short wave length or blue) cone photoreceptor type, but near absence of function the majority rod receptor, it can also affected blindness[16,41]. NR2E3 mutations are also associated with a unique autosomal recessive retinal disease, the enhanced S cone syndrome[33].

G protein - coupled receptors (GPCRs), which represent over 50% of all drug target, these GPCRs importance for pharmacogenetic investigation that related to gene polymorphism, which can influence drug target[44]. Receptor-drug interaction involved two distinct processes: formation of drug-receptor complex, and receptor activation. The ability of the drug-receptor complex to produce a physiological response will determine its potency. The study of genetic variation in GPCRs is associated a wide spectrum of genetic diseases and predisposition are important part to understand receptor function, because they are target of therapeutic agent[78]. The GPCRs-ligand binding site can be studied by combining site-directed mutagenesis and computer simulation and it will give some information about molecular mechanism of ligand binding, receptor folding, and receptor activation[48]. Application of molecular biology technique for receptor cloning has given precise information about receptor binding ligand, Because G protein-coupled receptor for endogenous extra cellular ligands already known as multiple receptor subtypes for a ligand e.g. two distinct classes of acetylcholine receptor, they were called nicotinic and muscarinic receptors.

The syndrome of resistance to thyroid hormone (RTH) was characterized by an impaired physiological response to thyroid hormone, because mutation occurs in thyroid hormone β gene, which influences interaction between receptor and thyroid hormones. According to Yoh *et al*[88] that two of the RTH mutations uncouple co repressor dissociation from hormone binding; two additional RTH mutants exhibit an unusually strong interaction with co repressor under all hormone conditions tested, and artificial mutants that abolish co repressor binding abrogate the dominant negative activity of RTH mutant.

PHARMACOGENETIC AND METABOLIC DISORDER

The term of pharmacogenetic has been accepted by wide-range of scientist, especially Pharmacogenetic Working Group (PWG, an international representation from the pharmaceutical industry[70]. Gene mutation related to drug metabolism and action in human created new discipline in pharmacology, which is involved genetic factors that evoke adverse drug reaction has been studied. In

recent year, study of drug reaction and metabolism in human have to be understood till molecular level, these studies involve metabolite defect that is caused mutation CYP450 gene family as well as receptor mutation as drug transporter and blocker. According to Alfirevic and Pirmohamed[2], about 6.5% of hospitalized patients in UK have been caused by adverse drug reaction (ADR). ADR has not been only caused by metabolite defect or gene mutation, but the possibility also poor prescribing by medical doctor. According WHO[87] there is increasing evidence that pharmacogenetics will soon be playing an important role in public health and understanding of genetic factors becomes necessary in medicinal treatment. Understanding about molecular pharmacokinetic and pharmacodynamic of drugs in human body will help to recognize as soon as possible when deviation of drug reaction occurs in body. Pharmacokinetic is studying on drug concentration and disposition, whereas pharmacodynamic related to drugs mechanism such as intensity and time responses to drugs in human body. Bioavailability of a drug depends on drug design, absorption, distribution and elimination. Drug distribution and metabolism are started in liver enzymes of Cytochrome P450 play a vital role in carrying out biosynthesis of drugs during metabolism, in the long run transferred to kidney and urine respectively. Metabolite defect has not only influenced drugs metabolite, but also arisen some disease related to genetic According to Guttmacher and Collin[35] that human gene mutation can lead to disease such as hypertension, diabetes, asthma, cancer and others. Many reports mentioned that genetic disease derived from single gene mutation (point mutation). Parkinson's, Alzheimer's and Huntington's diseases are neurodegenerative disorder diseases that are caused by point gene mutation. Missense mutation in the amyloid precursor gene of Alzheimer's has been reported by Goate *et al*[31], this point mutation causes an amino acid substitution (Val → Ile) close to the carboxy terminus of the β amyloid peptide. Recent report mentioned that Alzheimer's disease can be caused by more than one gene mutation which occupy at different chromosomes[9,25,27,53,76, 83]. According to Waring and Rosenberg[83] that putative Alzheimer's disease gene such as PSEN1, PSEN2, and APP arise on early-onset disease bellow 60 years old, whereas cause of Alzheimer's disease ≥ 65 years old rather complicated. Genetic evidence showed that cerebral accumulation of β amyloid (A β) was one of cause of Alzheimer disease, Aβ accumulate was observed from a familial Alzheimer's disease and that assume occur at PEN-2 gene mutation[25]. Other genes that indicated Alzheimer was mutation in presenilin gene 1 and 2 were reported by several authors[23,53,76]. Presenilin gene mutation and precursor protein genes mutation can cause early-onset Alzheimer's disease[53].

Relationship gene mutation with genetic disease, pharmacogenetic, and receptor mutation can be seen on **figure 2**. Gene mutation can create genetic polymorphism, type of mutation can be transition i.e. Purine to Purine or Pyrimidin to Pyrimidin, or transversion i.e. purin to pyrimidin or vice versa. The term of missense mutation deal with substitution of single base example A (adenine) to T (thymine) in a codon which affected alteration of amino acid code, of course, it influence amino acid sequence in a polypeptide chain. These cases happen commonly in genetic disease and adverse drug reaction. Sickle cell anemia is one of example from missense mutation, which occurring alteration of adenine to thymine in a codon which affects alteration of glue to val. Single nucleotide alteration in a coding frame will influence genetic code for specific amino acid. Alteration of protein characteristic which is caused by mutation threatens life span and lead to death. According to Splawski *et al*[73] around 450,000 individual every year in United States die suddenly of cardiac arrhythmia, SCN5A sodium channel mutation is causal factors of arrhythmia. The study proved that a homozygous missense mutation in SCN5A associated with atypical ventricular arrhythmias and right structural abnormalities[28]. Nuclear receptor mutation has been reported more than 893 nuclear receptors polymorphism. The functions of nuclear receptors are very important to regulate gene expression, and they are important target for pharmaceutical industry[81]. One of NR gene mutation related to disease is somatic androgen receptor mutation, cause of progression to hormone-refractory growth of prostate cancer [40].

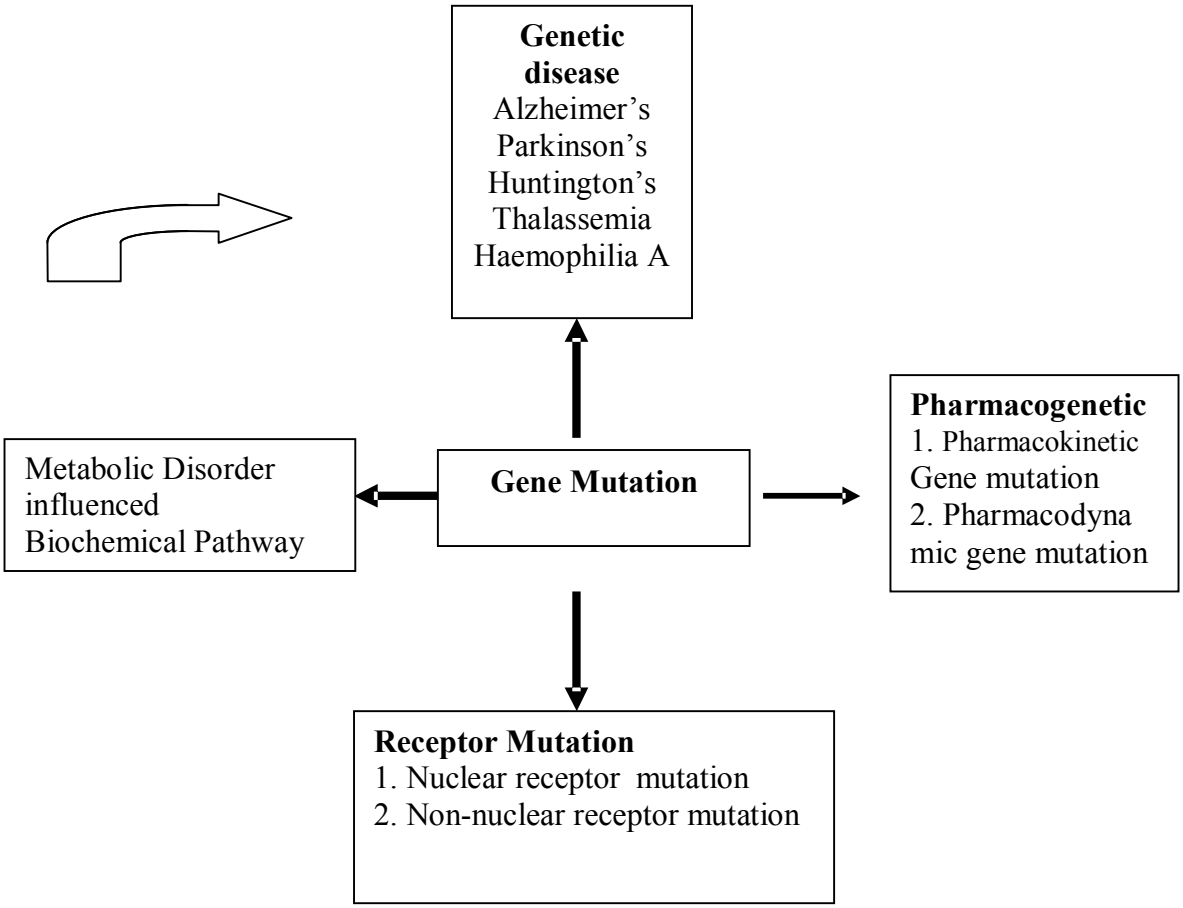

Figure 2: Gene mutation has affected in abnormality of different tissue and metabolic pathway into human, when gene mutation occur in non nuclear receptor. pharmacokinetic and pharmacodynamic of drugs action will be influenced in human body, while gene mutation which involved metabolic pathway which is responsible for synthesis or degradation of chemical substances related to drug metabolism such as CYP450 enzymes can create adverse drug reaction in human body. While gene mutation which of their products (proteins) are responsible for building block such as hemoglobin, alteration of these protein characteristic can create genetic disease like hemophilia.

GENE MUTATION DETECTION METHODS

DNA polymorphism in eukaryotic genome can be caused by insertion or deletion of nucleotides chain and single nucleotide alteration as well. Insertion of foreign gene into host genome can cause rearrangement host genome and disturbing another gene in host genome, hence, these foreign genes integration in host genome occur randomly during cell cycle stage. Several methods have been developed to detect gene mutation in human, animal and plants, most of these methods were PCR-based method. Gene mutation detection methods are sharing together between human and plant for example; PCR-Based Single nucleotide polymorphism (SNPs) screening methods i.e. single strand conformation polymorphism (SSCP), micro satellite DNA and microarray[11,52,60,69], Cleaved Amplified Polymorphic Sequences (CAPs),

According to Cooper *et al*[19] that DNA sequence of human genome more or less 99.9% identical from one to another, because 0.1% from 3.2 billion base pair different from one to another person[19]. Around 3.2 million nucleotides alteration occurred in individual which is caused by single nucleotide mutation in a coding frame or non-coding frame. Recently, detection of single nucleotide alteration in a

target sequence has been developed into efficient and inexpensive method. Genotyping for single nucleotide polymorphism (SNP) can be met the need, even no one method for all[50].

PCR-based single nucleotide polymorphism (SNP) screening method in a mutated gene is used more frequent methods to detect single base change at polynucleotide chain. Screening methods can be vary to detect single base mutation in genomic DNA such as microsatellite DNA, RT-PCR, SSCP, high-throughput method and multiplex mutagenically separated PCR. Allele-specific amplication (ASA) technique, and sequence polymorphism-derived (SPD) marker can be used for detect single base alteration in sickle cell anemia and others[60]. Single nucleotide mutation on coding frame of gene provided commonly disease related genetic. Several genetics diseases that are caused by single nucleotide alteration such as sickle cell anemia, hemophilia, Parkinson, and thalassemia showed missense mutation in coding frame. Sufficient technology to detect single nucleotide change give rapidly results in making a decision for patient therapy.

CONCLUSION

Mutation of CYP450 gene family can alter biochemical pathway of drugs metabolism because, a lot of gene products of CYP450 related to drugs metabolism such as CYP2D6 and CYP2C9 which involved pharmacokinetic and pharmacodynamic genes function and can lead to adverse drug reaction in human. Similar phenomena was founded on gene mutation that involved drug receptor interaction that influenced drug transport into cell target, it can be rapid or slow, hence consideration about genetic factors that influence drug metabolism should be a part of medication for patient. Concerning to CYP450 gene mutation or receptor mutation related to drug metabolism or drug transport was necessary to develop understanding between genetic factor and drug function in point of view of pharmacokinetic and pharmacodynamic related to drug metabolism into human.

Genetic disease such as Alzheimer, Parkinson, Sickle cell anemia, and Hemophilia which provided common phenomena for gene defect function towards normal condition . Genetic disease that is caused by point mutation such as thalassemia and hemophilia, it seem to be great possibility that gene therapy method can be applied to these disease by mean of engineering their pluripotent stem cells and then inserted back to related tissue in order to be able to produce new healthy cell.

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