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Insights Into Functional and Structural Impacts of nsSNPs in XPA-DNA Repairing Gene

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ABSTRACT

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation in people. SNPs are valuable resources for exploring the genetic basis of disease. The XPA gene provides a way to produce a protein used to repair damaged DNA. This study used the computational methods to classify SNPs and estimate their probability of being neutral or deleterious. The purpose of this analysis is to predict the effect of nsSNPs on the structure and function of XPA proteins. Data was collected from the NCBI-hosted dbSNP. The authors examined the pathogenic effect of 194 nsSNPs in the XPA gene with computational tools. Four nsSNPs (C126S, C126W, R158S, and R227Q) that potentially affect the structure and function of the XPA protein were identified with combination of SIFT, PolyPhen, Provean, PHD-SNP, I-Mutant, ConSurf server, and Project HOPE. This is the first comprehensive analysis in which XPA gene variants have been studied using in silico methods, and this research gains further insight into XPA protein variants and function.

KEYWORDS

I-Mutant, In Silico Analysis, Non-Synonymous SNPs, Polyphen 2, Sift

INTRODUCTION

Single nucleotide polymorphisms (SNPs) are most common type of genetic variation in humans(Ke, Taylor, & Cardon, 2008). SNPs are a useful resource for the study of the spread of the disease genetic base(E Capriotti, Calabrese, & Casadio, 2006). The variants may be used as markers in studies of genetic mapping and genome interaction. Some of those polymorphisms may prevent people from developing diseases such as diabetes, high blood pressure or cancer or effect the progression of diseases(Zhu & Zhao, 2007). Each SNPs is a variance in one Deoxyribonucleic acid (DNA) building block(E Capriotti et al., 2006). SNPs normally happen in DNA in an individual. They take place almost 1 in each one thousand DNA bases, meaning that in a person genome there are about 4 to 5 million SNPs. For many people around the world these differences are rare and more than 100 million SNPs are known by scientists. Variations are most often observed between DNA genes. They function as

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biological markers enabling scientists to classify disease associated genes. When SNPs occur in a regulatory area within or close the gene, by influencing gene function they can be more involved in the disease(*What Are Single Nucleotide Polymorphisms (SNPs)? - Genetics Home Reference - NIH*, n.d.).

Although SNPs cause variations in DNA but still most SNPs do not have any clinical impact. Nevertheless, some of these genetic differences in human health studies have proved to be very important. SNPs have been identified by researchers to help predict individual reactions to certain drugs, their susceptibility and ability to acquire various diseases to environmental factors such as toxins. In order to monitor gene transmission from diseases within families, SNPs might be used. Future investigations can often classify SNPs associated with chronic conditions, those include cardiac disease, diabetes, and cancer.(*What Are Single Nucleotide Polymorphisms (SNPs)? - Genetics Home Reference - NIH*, n.d.).

The gene xeroderma pigmentosum, complementation group A (XPA) codes a zinc-fiber protein, a specialized form of DNA repair, that plays vital role in the nucleotide excision repair (NER) repair (E Capriotti et al., 2006). NER is responsible for the regeneration of photoproducts and DNA adducts caused by ultra violet (UV) radiation from organic carcinogens and chemotherapeutic drugs. It interacts with DNA and other NER proteins and is used to build up the NER incision complex at sites which harm the DNA. Mutations produced in this gene, Sunlight hypersensitive autosomal recessive skin disorder and increased risk of skin cancer(*XPA, DNA Damage Recognition and Repair Factor [Homo Sapiens (Human)] - Gene - NCBI*, n.d.). xeroderma pigmentosum XPA gene provides instructions on how to make a protein to repair damaged DNA. Sun UV rays and toxic chemicals as well as emission and volatility of free radicals and can damage the DNA. Normally, common cells can repair DNA damage before it can cause problems. The NER is one of the most essential pathways used by cells to repair DNA. The XPA protein helps to track and protect DNA damage, as it is repaired in this repair process. XPA is linked to damaging DNA areas in which XPA interacts as part of with several other proteins. In this way removes abnormal unit and replaces the damaged area with correct DNA where the damage has happened (*XPA Gene - Genetics Home Reference - NIH*, n.d.).

Mutations in XPA gene effect Japanese population more commonly than others to develop a very serious form of disorder. Many Japanese people have xeroderma mutations of the same gene, G > C. It prevents the cells produce any XPA protein that is functional. Some mutations in XPA gene found in people of Japan and elsewhere lead to the development or substantial reduction of a faulty form of cell produced XPA protein. Partially or completely loss of XPA protein prevents DNA damage from being repaired by cells. Otherwise, mutations caused the cell damage which lead to cancer and death. These issues with DNA repair make people with incredibly sensitive to UV rays from sunlight. Cells can develop too quickly and uncontrolled if UV rays disrupt the genes that regulate growth and division cell. As a result, the risk of developing cancer in people with xeroderma pigmentosum is significantly increased. Normally these cancers may occur in areas of the body that are exposed to the sun, such as the skin and eyes. Progressive neurological diseases are often associated with xeroderma pigmentosum when it is affected by XPA gene mutations. Which can cause problems in the nervous system including loss of vision, impaired balance, loss of mobility, loss of cognitive capacity, difficulty swallowing and communicating and seizures. It is suspected that the brain is not UV exposed, neurological disorders arise from the increase in DNA damage.

In the identification and analysis of SNPs, bioinformatics approaches play a prominent part. We used computer methods (SIFT, Polyphen 2.0, I-Mutant 2.0 etc.) to classify SNPs and to determine whether they are neutral or deleterious(CLIFFORD et al., 2004). Review of the literature showed that no previous studies have been conducted on the influence of such variations on XPA structure and function. The aim of this research is therefore to perform a systematic in silico XPA nsSNP analysis using biological information systems to research the possible impact of genetic modifications on protein structure and function. Computational study of XPA gene is the demand of time. In silico analysis help us to better understand the disease and prescribing more precise treatment measures for