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Molecular Insights of Exonal Polymorphism in Cancer Risk

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Abstract

Single nucleotide polymorphisms are a sort of genetic variations, have been identified in numerous genes that linked to various cancer types. SNPs in exon regions of hub cellular of genes that influence gene expression by variety of ways like affect protein structure, function, mRNA structural conformation and also translation. Exonal or coding SNPs are categorized into two types; non-synonymous and synonymous in accordance with their capability to substitute the encoded amino acid. In this mini-review, we addressed a diverse of genetic pathways that affect cancer risk through exonal SNPs observed in various genomic components. We have also emphasised on exonal SNPs' therapeutic potential and their future research significance.

Introduction

Cancer is an array of complex diseases characterized by modification or alteration in diverse genes, including proto-oncogenes, oncogenes, DNA repair genes, microRNA genes, and tumour-suppressor genes, leading to impaired cellular homeostasis and uncontrolled proliferation [1,2]. Extensive research has been conducted on the link between genetic variations and cancer risk. Genetic alterations, particularly Single Nucleotide Polymorphisms (SNPs) found in several genes such as PARK2, p53, and FOXO, are the main basis of cancer risk in patients [3,4]. The SNPs constitute over 90% of the genetic variation existing in the DNA of the human genome [5]. These SNPs have been connected with the progress of oral, breast, colorectal, and liver cancers [6]. Discovered SNPs, the third generation of DNA genetic markers after RFLPs (Restriction Fragment Length Polymorphisms) and microsatellite polymorphisms. There are approximately 4-5 million SNPs that have been discovered, which is equal to 1 SNP for every 1,000 bases [17]. Till now, in the human genome's coding regions, about 500,000 SNPs have been identified [7]. Various studies have advocated that the molecular pathways underlying region-based and cancer-related diseases SNPs need to be addressed. SNPs are found throughout the genome; however, within the exon regions of various genes, they can alter expression by affecting gene transcription and translation processes and modulating, increasing the risk of cancer development. The most common types of exons SNPs are categorized into two which namely; non-synonymous and synonymous coding SNPs (cSNPs), distinguished by their capacity to substitute the encoded amino acid. Previous research has found that nsSNPs account for about 50% of mutations that linked to hereditary diseases [8,9].

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By studying the genetic changes of exon polymorphisms on cancer progression is a difficult task that necessitates a holistic approach. The genome-wide association study, helps to identify the genetic risk factors that may enhance the risk of cancer implications [10,11]. In the modern era, advancements in genomics, bioinformatics proteomics and, transcriptomics studies have provided a valuable insights into the difficult processes that underlie numerous complex diseases, including cancer, which results in identifying novel therapeutic targets [12]. In this mini-review, we attempted to focus on exonic region polymorphisms and their categories, which enhance cancer risk by altering the structure and functions of several proteins and their expression via various pathways. In addition, polymorphisms in exons have also been studied for their future importance and therapeutic potential in cancer patients.

Non-synonymous coding SNPs affect protein structure and function

Non-synonymous coding (nsSNPs) of the exon in the gene can modify the sequence of Amino Acid (AA), protein functions, protein-protein interaction (PPI), solubility, and protein stability, all of which responsible to induction of cancer risk [13,14]. According to numerous research studies it has been observed that most amino acid modifications occur due to changes to the first two nucleotides of a codon involvement. As a consequence, AA sequence variations may affect protein secondary structure by varying the phosphorylation and hydrogen bonding amount, thereby influencing interactions and functions of protein. Hence, these alterations affect the expression levels of tumor suppressor and oncogenic proteins as well as cell signaling pathways [13].

The coding region contains 50% SNPs, of which each 25% are synonymous, and missense [15]. nsSNPs regulate the physiological and anatomical types of many proteins in human, as well as the various gene interaction pathways through disease-associated proteins [16,17]. However, no every coding region SNPs are functionally significant [18]. A study found that approximately 20% of nsSNPs cause protein damage, which may increase the risk of cancer [19]. It is anticipated that nsSNPs affecting cancer risk through protein conformation chaining will be found. In recent time, many biological and computational software tools are currently available, such as PolyPhen, F-SNP (Functional SNP), SIFT (Sorting Intolerant From Tolerant), CADD, and REVEL which might be helpful to detect the nsSNPs impact on structure and functionality of protein for cancer risk assessment [20,21]. For instance, an insilico studies discovered that 38 nsSNPs in the human CYP1A2 gene are linked to cancer risk and pathogenesis as a result of protein structural changes [22]. According to one study, the functional process underpinning tumour-allied nsSNPs is somewhat easy and convenient as compared to the large number of polymorphisms found in gene non-coding regions [23]. A study has found that in a gene multiple exonal SNPs were linked with an augmented risk of colorectal carcinogenesis after examining the entire exon sequence. As per previous finding, the missense polymorphism rs3184504 (p. trp263ARg) in the SH2B3 domain might affect the function of proteins that control cell proliferation. Further, coding variations may also influence variable shear of UTP23 located SNPs rs16888728 [24].

On the other hand, a study has demonstrated that non-synonymous cSNPs in the Epidermal Growth Factor Receptor (EGFR) gene reduces the Tyrosine Kinase Domain (TKD), which is due to two TKIs (tyrosine kinase inhibitors), particularly erlotinib and gefitinib. In the case of erlotinib which makes one H-bond with the AA Met769 in the EGFR, while gefitinib generates two H-bonds with the Gly772 AA. Therefore, this study analysed that gefitinib molecules have a higher binding affinity for EGFR proteins containing five different variants as compare to EGFR protein wild-type. EGFR-TKD polymorphisms cause structural modifications that improve protein sensitivity and activity to TKIs [25]. According to previous data analysis, the N-Acetyltransferase 2 (NAT2) gene SNP rs752955201 replaces valine with a bulkier isoleucine, resulting in lower affinity for substrates N-acetyltransferase 2 and increased affinity for substrates N-acetyltransferase 1 [26]. The process by which SNPs found in gene coding regions influence cancer risk is inextricably linked to the function of coded proteins. Evidence suggests that the Leu858Arg mutation enhances EGFR's dimer formation and promotes cell proliferation [27]. Interestingly, protein-protein interactions can detect a large number of previously unidentified mutations. Various scientific groups and researchers have tended to focus on particular signalling pathways, genes, and genetic changes that are intriguing although likewise conducting complete-exon association studies to identify any associated exon SNPs with significant impacts on these molecules and their mechanisms [28].

Effect of Synonymous cSNPs Indirectly Modify Protein Structure and Function

The sequence of AA which is encoded by the protein is unaffected by synonymous cSNPs. The most common nucleotide alteration is a substitution in the codon's third base. These proteins were previously considered insignificant because their amino acid sequence is identical to the wild type. Nevertheless, recent investigation demonstrates that synonymous cSNPs influence gene function as well as expression via modulating the expression level of genes in the vicinity. Multiple scientific researches have proven that synonymous mutations impair protein expression, structure and also function.

Synonymous cSNPs alter mRNAs and proteins structural conformation

These types of cSNPs generate distinct haplotype SNPs that influence mRNA secondary structure, especially stem-ring like structure, stability, and decreasing activity of the enzyme. As per instance, two synonymous and one nsSNPs generate distinct haplotype SNPs in the COMT (Catechol-O-Methyltransferase) gene. The primary COMT haplotypes differ in messenger RNA's local stem-loop configurations. mRNAs with stable secondary structures have inhibited the expression level and activity of COMT gene [29]. Previous studies have also revealed that a synonymous SNP in the MDR1 (multidrug transporter) gene influences the P-glycoprotein production which is an essential drug transport protein [30]. This influences its expression as well as their function that ultimately leading to drug resistance. It has analysed that SNPs located in MDR1, including 2677G→T, 1236C→T, and 3435C→T, are found in India, China, and Malaysia at a range of 31-49%. High linkage disequilibrium between these all three polymorphisms results in a haplotype that reduces MDR1 protein activity via minor alteration in the configuration of their ATP-binding position. The MDR1 SNPs T1236C and C3435T can potentially affect nsSNPs. The SNPs C3435T alters the P-glycoprotein insertion into the membrane and co- translational folding, influencing the substrate-inhibitor structure interface sites [31]. The three SNPs correspond to unusual wild-form codons allied with changes in translation and termination rates [32]. The observed transformations in drug-

substrate binding point to a process by which synonymous polymorphisms influence nsSNPs, resulting in diverse clinical outcomes [33]. Synonymous polymorphisms cause several changes in mRNA including splicing, structure, stability, and protein folding. These modifications significantly impact protein function, subsequent differences in cellular reactions to therapeutic sites, which clarifies why individual patients respond differently to drugs [34]. Similarly, a study identified the rs74090726 synonymous SNPs situated in 5th exon regions of gene MCAD which disables the exonal splicing enhancer, resulting in exon skipping, insufficient MCAD, as well as functional protein damage [35]. Recent finding supported that in the exon region, the ELP2 gene influences pre-mRNA splicing mediated by splicing a quantitative trait locus due to variation in the single base. In addition, a study also suggested by insilico analysis that exonal SNPs can also influence the mechanism of RNA processing. Such as, SNPs rs78378222 situated in the 3′ UTR site of TP53 changes the sequence, modifying TP53's polyadenylation signal and subsequent deficient at 3′-terminal processing of TP53 mRNA [36].

Synonymous cSNPs affect translational rates by genetic linkage

A haplotype defined as a group of single nucleotide variations on a one chromatid which are statistically linked. The number of variations on one chromosome might offer insights into alterations to gene function, including cumulative and synergistic effects. Surprisingly, multiple investigations have shown that the polymorphisms in exon 4 are in substantial linkage disequilibrium [37]. Numerous recent studies have indicated that cSNPs can increase or decrease the mobility of ribosomes along mRNA, affecting translation dynamics, accuracy and, as a result, changes in structure and function of protein. These processes can generate secondary structures of mRNA and proteins, including α helix β folding [38]. Furthermore, in synonymous codon families the usage of codon is non arbitrary, and base structure selection is determined by the codon's 2nd base position [39]. In few conditions, the preference for structure of the base extends to the 3rd base [40]. Moreover, codon usage has a significant impact on mRNA expression levels via based on translation impacts on mRNA degeneration while translation-independent impacts on posttranscriptional and transcriptional events [41].

Figure 1: Shown the nsSNPs and cSNPs in various gene related to cancer risk.

SNPs	Gene	cSNPs / nsSNPs	References
rs3184504	SH2B3	nsSNPs	[24]
rs752955201	NAT2	nsSNPs	[26]
rs78378222	TP53	cSNPs	[36]
rs74090726	MCAD	cSNPs	[35]
T1236C and C3435T	MDR1	cSNPs	[31]

Exonal SNPs in cancer therapeutics and research

The introduction of new technologies, such as microarray-based genotyping, genome-wide association study and high throughput next generation sequencing, has created new opportunities for SNPs to be employed in therapeutic methods. It is expected that the use of exonal SNPs to understand the processes and biology of varying medication response, as well as treatment individualization depending on an individual's genomic makeup, will become indispensable in the near future. As a result, pharmacogenomics could assist address the question

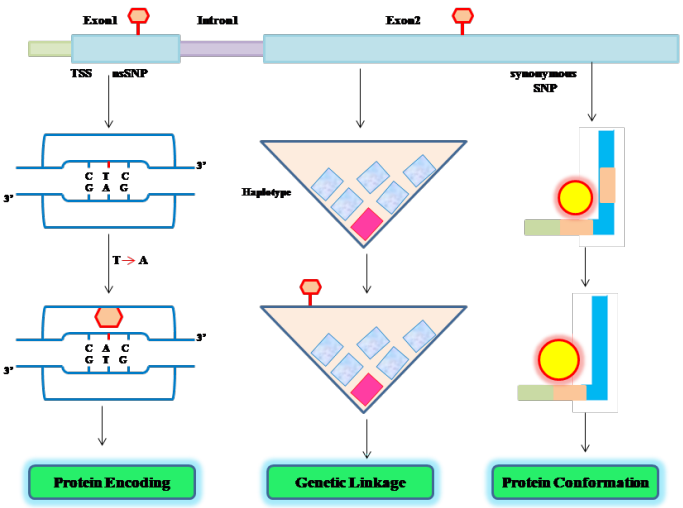

Figure 1: (Modified and adapted from [13]): Figure depicts the processes that relate exon regions located SNPs to cancer risk. nsSNPs alter the AA sequence of the encoded protein. Through genetic linkage synonymous exon cSNPs alter protein conformation and function.

of how inherited changes in a single gene affect drug mobilization and biological action. For example, a study has recognized that synonymous SNPs of exon in ABCB1 (P-glycoprotein), which is involved in multidrug resistance and pharmacokinetics in human cancer cells that might affect both the structure and function of proteins [32]. Likewise, exonal SNPs act as a predictive and prognostic biomarker for cancer, which is beneficial in determining medication and therapy decisions in cancer patients.

Future perspective

This present mini-review addressed the role of exonal SNPs in several genes leads to cancer risk in individuals. Several notable affected structure and functions of various genes are compiling a comprehensive list of nsSNPs and synonymous SNPs that may be linked to cancer development. As a result, the role of both nsSNPs and synonymous SNPs in cancer progression has been confirmed. However, the precise role of exonal SNPs in many genes in cancer remains unknown. Although genetic data robustly links exonal polymorphisms to cancer risk, on the other side the biochemical and cell biology effects of non-synonymous cSNPs remain unclear. Further research is needed to fully understand how synonymous SNPs affect translation kinetics. A thorough analysis of exonic region SNPs in cancer is required to provide adequate literature. This review builds the way for future investigations into the recognition of new genetic biomarkers for cancer diagnosis and treatment.

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