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Analyzing the Association of the Alu CD4 Gene with Various Cancer Types in the Naga Tribes of Nagaland

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ABSTRACT Cancer arises through the unchecked proliferation of cells. Some studies have shown association of cancer with Alu CD4 genotypes. In this study, the researchers investigated the association of CD4 gene analyzing different types of cancer among Naga tribes of Nagaland. This study's primary goal was to investigate the relationship between the genetic marker CD4 with the 16 cancers among the Naga Tribes and find the most prevalent type of cancer among the Naga tribes. Samples were taken from various cancer patients (n = 75), while control samples were taken from Naga tribe members who were in good condition. Polymerase chain reaction (PCR) was used for genotyping, and allele-specific primers were used. The study discovered that the II genotype was the most common genotype. Oral cancer ($p=0.006^{*}$), stomach cancer ($p=0.03^{*}$), and cervical cancer ($p=0.00^{*}$) are all strongly associated with the II genotype.

INTRODUCTION

Between 40 and 82 genetic disorders occur for every 1000 live births. One gene's mutation is the primary cause of monogenic diseases, also known as Mendelian disorders (Venugopal et al. 2018). The adult and paediatric populations as well as their families, experience significant rates of sickness, mortality, and economic hardship as a result of this single gene mutation. Because monogenic disorders have a Mendelian inheritance pattern, knowledge of their molecular causes can help with both accurate diagnosis of those who are afflicted and risk assessment for kin. When a few of the body's cells develop out of control and spread to other internal organs, it is called cancer. In the world, cancer ranks third in terms of the causes of illness and mortality. Cancer can appear almost anywhere in the trillions of cells that make up the human body. When the body needs new cells, human cells frequently divide (through a process known as cell proliferation and multiplication).When old cells pass away due to aging or damage, new ones take their place.

In the world, cancer ranks third in terms of morbidity and mortality (Jonathan et al. 2009). Over 60 percentage of cancer cases require radiation therapy, despite the fact that there are no special medications made for it. Radiotherapy (RT) is the primary treatment for cancer. X-ray therapy is a term used to describe RT (Mohan et al. 2019). The DNA of the cancer cells is damaged by radiation, which prevents the cells' growth and division and ultimately kills them. Radiation can also have an impact on healthy cells that are close to cancer cells. Smoking is the leading cause of lung cancer and is also connected to malignancies of the mouth, throat, larynx, oesophagus, stomach, pancreas, kidney, ureter, bladder, colon, and uterine cervix (Balachandar et al. 2008).

CD4 a membrane glycoprotein is a co-receptor in the activation of MHC class II-restricted T cells and a member of the immunoglobulin supergene family. On the surface of MHC class II-restricted T lymphocytes, a single polypeptide chain of the transmembrane glycoprotein CD4, with a molecular weight of 55 kDa, is expressed. The production of cytokines begins in a group of activated CD4+ T cells. The naive T cells' ability to differentiate into effector cells is shown to be aided by the autocrine signalling pathway that the cytokines use

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to multiply and differentiate once they are produced. The kind of cytokine released by T cell subtypes allows for differentiation. Tumor necrosis factor (TNF), interferon-gamma (IFN-1) and IL-2 are released by T-helper type 1 (Th1) cells.

Cancer patients' blood and tumour beds can both be shown to have tumour antigen-specific T cells, proving that the immune system is not blind to malignancies (Boon et al. 2006). Because CD8 T cells have the potential to directly kill tumour cells and because their quantity within tumours appears to suggest a better prognosis, the majority of study to date has concentrated on this topic (Rosenberg et al. 2009). Only recently has CD4 T-cell involvement in anticancer responses been recognised, in addition to their well-known helper functions (Ridge et al. 1998).This is due to the fact that most tumour cells do not express MHC class II (Quezada et al. 2011). Nagaland is one of the states having the highest incidence of cancer in the country. Since there are no facilities for managing cancer, 90 percentages of cases that are discovered must leave the state in search of treatment, placing an excessive financial strain on the state. The lack of awareness of early cancer symptoms and signs contribute to increased prevalence rates, which result in earlier discovery at later stages and higher rates of morbidity and mortality.

Objectives

To study the association of Genetic Marker CD4 with the 16 cancers among the Naga Tribes and find the most prevalent type of cancer among the Naga tribes.

METHODOLOGY

The Eden Medical Centre in Dimapur, Nagaland, is where the cancer samples was obtained. The samples gathered for this investigation are descended from Naga people. A total of 150 samples, including 75 from healthy controls and 75 from various cancer patients, were collected. The healthy donors from the Naga Tribes of Nagaland provided the control samples. The Institutional Human Ethical Committee granted ethical approval for the study with Certificate No. SJU/REG/ZOO/IHEC/2021/03.

Before collecting 2 ml of blood from cancer patients, the subjects were informed and given their consent. The complete blood sample was utilised to extract genomic DNA using the Salting out method (Harun et al. 2014). The isolated DNA was suspended and stored in storage for genotyping in 10mM Tris and 0.1mM EDTA.

PCR Process

The polymorphic loci were genotyped using the standard 35-cycle PCR method. The ideal annealing temperatures and additives were optimised for each system.The PCR processes were completed in accordance with the previously mentioned methods (Harun et al. 2014; Schilter 2015). In a total volume of 20 l, the reaction mixture contained 13.5 l of double-distilled water, 2 l of Agilent's 0.5X PCR buffer, 0.4 l of Genet Bio's 10 mMdNTPs, 1 l of forward and reverse primers, and 0.5 l of Taq DNA polymerase (Agilent). The following temperatures are used: 95°C for five minutes, 30 cycles of 95°C for forty-five seconds, 56°C for thirty seconds, and 72°C for three minutes.

The gels stained with EtBr were observed under ultraviolet light after the amplicons were separated by electrophoresis on 2% agarose gel (Table 1).

Statistical Analysis

Using the software package Epi-Info.exe, the genotype and allele frequencies were examined using the odds ratio (OR). The analysis of allelic connections was carried out using the population

Table 1: PCR primer and conditions

Gene/Locuschromosome	*Primer location sequence*	*Annealing Tem.^{0}C*	*Amplified Product size*	
			+	-
CD4	F-5'-AGGCCTTGTAGGGTTGGTCTGATA-3' R-5'-TGCAGCTGCTGAGTGAAAGAACTG-3'	56	1500 bp	1200 bp

genetics tool POPGENE, with the 2 test and P values 0.05 as significant.

RESULTS

The Naga tribes were the subject of a study that looked at 16 different cancer kinds, and it was discovered that, generally, the II allele was the most common genotype. The II Genotype has demonstrated a substantial value in the case of Cervical Cancer (p=0.000*). While stomach cancer has been significantly associated with all three Genotypes II, ID, and DD (p=0.03, p=0.000, and p=0.0019, respectively). Oral cancer has been significantly associated with the Genotypes II and DD (p=0.006 and p=0.015, respectively). Ovarian cancer has been significantly associated with all three Genotypes II, ID, and DD (p=0.00, p=0.014, and p=0.00, respectively). Oesophageal cancer has been associated with the Genotypes ID and DD and has substantial value (p=0.02 and p=0.03 respectively). The other cancer kinds, such as cancer with an unknown origin, gall bladder, thyroid, bone marrow, nasal, breast, larynx, liver, lung, and oligodendrogina, had not demonstrated any meaningful value (Table 2).

To determine the distribution of CD4 polymorphism among cancer patients and to regulate for overall samples, a dominant and recessive model was developed. The model revealed no significant correlation in either the dominant or recessive model, with the dominant model having a p value of 1 and the recessive model having a p value of 0.06, as shown in Table 3. Of all the malignancies that have been studied, stomach, oral, and cervical cancers have received the greatest research attention.

The distribution of CD4 polymorphism among patients with stomach cancer and controls is shown in Table 4. Both the dominant and recessive models were shown to have a significant association, with the dominant model having a p value of 0.0019 and the recessive model having a p value of 0.03 respectively.

The distribution of CD4 polymorphism among oral cancer patients and controls is shown in Table 5. Both the dominant and recessive models were found to have a significant connection, with the dominant model having a p value of 0.015* and the recessive model having a p value of 0.006*.

The distribution of CD4 polymorphism among cervical cancer patients and controls is shown in Table 6. Both the dominant and recessive models were shown to have a significant connection, with the dominant model having a p value of 0.015 and the recessive model having a p value of 0.000.

DISCUSSION

Overall, the study showed that the most prevalent genotype was the II allele. In the case of cervical cancer, the II Genotype has shown significant value (p=0.000*). The three Genotypes II, ID, and DD, however, have all shown significance for stomach cancer with significant values (p=0.03, p=0.000, and p=0.0019, respectively). Significant values for the Genotypes II and DD have been linked to oral cancer (p=0.006 and p=0.015, respectively). Significant values for ovarian cancer were found for all three genotypes II, ID, and DD (p=0.00, p=0.014, and p=0.00, respectively). Oesophageal cancer has been significantly related (p=0.02 and p=0.03*) with the Genotypes ID and DD, respectively.

Cancer is a complex, multifaceted disease (Wogan et al. 2004). Ageing, HPV infection, and lung cancer are only a handful of the many well-known risk factors for cancer (Schiffman et al. 2007; DePinho 2000). In 1990, Hall et al. and in 1994, Wooster et al. undertook an epidemiological investigation that led to the identification of the BRCA1 and BRCA2 genes, which are essential for DNA repair and highly penetrant breast and ovarian cancer risk factors.

Better clinical results in TNBC were found to be substantially correlated with high levels of CD8 + iTILs and CD4 + sTILs (Jorgensen et al. 2021). Even while the prognostication cannot be generalised for all subtypes of invasive breast cancer, they found a significant connection between both CD4 + and CD8 + TILs and higher histologic grade that is comparable to that seen in invasive breast cancer in general.

Several polymorphisms in the CYP2A6 area were found by Patel et al. in 2016 and were highly linked to CYP2A6 activity throughout the genome (measured by the ratio of total 3-hydroxycotinine to cotinine). They discovered a significant correlation between higher CYP2A6 activity and higher nicotine absorption, as measured by TNE, supporting the idea that users smoke more frequently when CYP2A6 activity is higher. The vast majority of their individual impacts were directionally con-

Table 2: Distribution of genotype frequencies of polymorphisms in Cancer patients and controls

SNP	*Disease*	*Genotype*	*Case % n=75*	*Control % n=75*	*OR*	*95% CI*	X^2	*P-value*
Alu CD4	*All Cancer* (Case n=75 and Control =75)	II	6	12	0.5	0.177-1.1173	2.32	0.12
		ID	30	24	1.4	0.79-2.54	1.06	0.302
		DD	39	39	1	0.52-1.74	0.0	1.0
	Cervical Cancer (Case n=11 and Control =11)	II	0	3	1.45	0-0.0896	28.94	0.000*
		ID	5	4	1.45	0.82-2.57	1.327	0.249
		DD	6	4	2.08	1.1803-3.69	0	1
	Stomach Cancer (Case n=16 and Control =16)	II	4	6	0.5	0.26-0.95	4.46	0.03*
		ID	9	3	5.09	2.70-9.62	25.99	0.000*
		DD	3	6	0.35	0.183-0.66	9.615	0.0019*
	Oral (Case n=11 and Control=11)	II	0	1	0	0-0.319	7.44	0.006*
		ID	5	6	0.69	0.39-1.21	1.28	0.25
		DD	6	4	2.08	1.18-3.69	5.83	0.015*
	Nasopharynx (Case n=5 and Control =5)	II	1	0	-1	0.52- -1	0	1.00
		ID	2	0	-1	0.3- -1	0.50	0.47
		DD	2	5	0.	0.50-2.02	0.59	0.43
	Ovarian (Case n=6 and Control=6	II	0	1	0	0-19	16.45	0.000*
		ID	1	2	0.41	0.21-0.81	6	0.014*
		DD	5	3	4.88	2.54-9.43	22.98	0.000*
	Oesophagus (Case n=6 and Control=6)	II	0	0	0	0-1.12	0.5	1
		ID	3	2	1.52	1.14-3.61	5.27	0.02*
		DD	3	4	0.73	0.29-0.91	9.61	0.03*
	Breast (Case n=3 and Control=3)	II	0	1	0	0-3.46	0.50	0.47
		ID	0	2	0	0-3.1	0.75	0.38
		DD	3	0	-1	0.6 - -1	1.28	0.27
	Liver (Case n=3 and Control=3)	II	0	3	0	0-1.69	1.36	0.24
		ID	2	0	-1	0.20- -1	0.75	0.38
		DD	1	0	-1	0.05- -1	0	1
	Lungs (Case n=5 and Control=5)	II	3	0	-1	0.2- -1	0.56	0.45
		ID	2	2	1	0.04-23	0	1
		DD	0	3	0	0-2.02	1.9	0.16
	Larynx (Case n=1 and Control=1)	II	0	0	-1	0-0	0.5	1
		ID	0	0	-1	0-0	0.5	1
		DD	1	1	-1	0-9233.6	0.5	1
	Oligodendrogina (Case n=2 and Control=2)	II	1	2	-1	0-39	0	1
		ID	0	0	-1	0-39	0	1
		DD	1	0	0	0.025- -1	0	1
	CAOf Unkwon Primary (Case n=2 and Control=2)	II	0	0	0	0.025- -1	0	1
		ID	2	1	0	0.025- -1	0	1
		DD	0	1	0	0-39	0	1
	Gall Bladder (Case n=11 and Control=11)	II	0	0	0	0-39	0	1
		ID	0	1	0	0-39	0	1
		DD	1	0	0	0-39	0	1
	Thyroid (Case n=1 and Control=1)	II	1	1	-1	0.025- -1	0	1
		ID	0	0	-1	0.025- -1	0	1
		DD	0	0	-1	0.025- -1	0	1
	Bone Marrow (Case n=1 and Control=1)	II	0	0	0	0-39	0	1
		ID	1	0	-1	0.025- -1	0	1
		DD	0	1	0	0-39	0	1
	Urinary Bladder (Case n=1 and Control =1)	II	0	0	0	0-39	0	1
		ID	1	0	-1	0.025- -1	0	1
		DD	0	1	0	0-39	0	1

Note: * Statistically significant. n: Sample size; ÷ 2 : Chi-square with 1 degree of freedom; OR: Odds ratio; CI: Confidence Interval; Ref: References

Table 3: Distribution of CD4 polymorphisms dominant and recessive model in patients of cancer and control

SNP	*Gender*	*Model*	*Test*	*Case% N=11*	*Control %n=11*	*OR*	*95% CI*	*P value*
CD4	ALL	II+ID VS DD	DOM	36 Vs 39	36 Vs 39	1	0.52-1.74	1.0
		II VS ID+DD	REC	06 Vs 69	12 vs 63	0.17	0.03-0.91	0.06

DOM: Dominant model: REC: Recessive model; n: sample size; OR: Odds ratio; CI: Confidence Interval: DOM model: Only when DD is present, the diseases would be caused, REC model: when D is in homozygous or heterozygous it will cause diseases. * Statistically significant

Table 4: Distribution of CD4 polymorphisms dominant and recessive model in patients of stomach cancer and control

SNP	*Gender*	*Model*	*Test*	*Case% N=11*	*Control %n=11*	*OR*	*95% CI*	*P value*
CD4	ALL	II+ID VS DD	DOM	13 VS 3	9 VS 6	2.84	1.498-5.45	0.0019*
		II VS ID+DD	REC	4 VS 12	6 VS 9	56.41	32.13-97.22	0.03*

Note: DOM: Dominant model: REC: Recessive model; n: sample size; OR: Odds ratio; CI: Confidence Interval: DOM model: Only when DD is present, the diseases would be caused, REC model: when D is in homozygous or heterozygous it will cause diseases. * Statistically significant

Table 5: Distribution of AluCD$_4$ polymorphisms dominant and recessive model in patients of oral cancer and control

SNP	*Gender*	*Model*	*Test*	*Case% N=11*	*Control %n=11*	*OR*	*95% CI*	*P value*
CD4	ALL	II+ID VS DD	DOM	5 VS 6	7 VS 4	0.48	0.27-0.84	0.015*
		II VS ID+ DD	REC	0 VS 11	1VS 10	0	0-0.37	0.006*

Note: DOM: Dominant model: REC: Recessive model; n: sample size; OR: Odds ratio; CI: Confidence Interval: DOM model: Only when DD is present, the diseases would be caused, REC model: when D is in homozygous or heterozygous it will cause diseases. * Statistically significant

Table 6: Distribution of CD4 polymorphisms dominant and recessive model in patients of cervical cancer and control

SNP	*Gender*	*Model*	*Test*	*Case% N=11*	*Control %n=11*	*OR*	*95% CI*	*P value*
CD4	FEMALE	II + ID VS DD	DOM	5 VS 6	7 VS 4	0.48	0.27-0.84	0.015*
		II VS ID + DD	REC	0 VS 11	3 VS 8	0	0-0.089	0.000*

Note: DOM: Dominant model: REC: Recessive model; n: sample size; OR: Odds ratio; CI: Confidence Interval: DOM model: Only when DD is present, the diseases would be caused, REC model: when D is in homozygous or heterozygous it will cause diseases. * Statistically significant

sistent and linked to an increased risk of lung cancer, according to their analysis of the association between these variants and risk of lung cancer in the enormous TRICL GWAS dataset. Their study found that smokers with a high genotype for CYP2A6 activity are more likely to get lung cancer.

In the low-risk Chinese population, Wu et al. (2010) discovered links between IL-17A and IL-17F gene polymorphisms with stomach cancer. The IL-17F 7488GA and GG genotype was found to significantly increase the risk of developing gastric cancer, however the IL-17A 197 polymorphism was not associated with susceptibility to the disease. After stratification by clinic pathological traits, the associations between the IL-17F 7488GA genotype and gastric cancer seemed to vary with

tumour locations and histological types. Different intestinal or diffuse histological subtypes, as well as tumours arising from the cardia or noncardiac, have been observed to exhibit different clinical, epidemiological, and genetic characteristics (Correa 2004; Kim et al. 2005). Interleukin (IL)-17A and interleukin (IL-17F), two inflammatory cytokines that are crucial for inflammation and probably contribute to cancer, are expressed by a distinct subset of CD4+ Th cells (Leyla et al. 2013).Th17 cells, a newly discovered lineage of CD4+ T helper cells that subverts the Th1 and Th2 lineages, are an unique subgroup of effector T helper cells (Harrington et al. 2005; Park et al. 2005). Particularly Th17 cells have been found to produce IL-17A and IL-17F, which makes them generally proinflammatory. Their emergence has been associated with an increase in autoimmune and inflammatory diseases, such as psoriasis, inflammatory bowel conditions, and rheumatoid arthritis.

The relationship between CD4 gene polymorphisms and human malignancies has not yet been studied. For the first time in our case-control study, we looked into links between CD4 and various malignancies among the Naga tribes.

CONCLUSION

The II allele was discovered to be the most common genotype overall, and this study indicated a strong relationship between the II genotype and cervical cancer, stomach cancer, oral cancer, and ovarian cancer. The II Genotype has demonstrated a substantial value in the case of Cervical Cancer ($p=0.000^{*}$).While stomach cancer has been significantly associated with all three Genotypes II, ID, and DD (p=0.03, p=0.000, and p=0.0019, respectively). Oral cancer has been significantly associated with the Genotypes II and DD (p=0.006 and p=0.015, respectively). Ovarian cancer has been significantly associated with all three Genotypes II, ID, and DD (p=0.00, p=0.014, and p=0.00, respectively). Oesophageal Cancer shows Significant Value in the Genotypes ID and DD (p=0.02 and p=0.03 respectively). Other cancers, such as those with an unknown source, those of the gallbladder, thyroid, bone marrow, urinary bladder, nasal cavity, breast, larynx, liver, and lungs, as well as oligodendrogina, had not demonstrated any substantial usefulness. To further broaden and clarify these linkages, future research with larger cohorts is predicted by this work.

RECOMMENDATIONS

Up to this point, the Naga Tribes have not been investigated on the genetics of cancer. According to the data gathered, the Naga population has been affected by a number of cancers, thus it is important to comprehend the genetics of the illnesses afflicting the indigenous population. As a result, the current study will aid in spreading enlightened information about cancer among the tribal community, which in turn will shed light on the disease's pathophysiology and suggest preventive measures.

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