Interaction of HIV and the human innate immune system: Human Apolipoprotein B mRNA-editing Enzyme-catalytic Polypeptide-like 3G (APOBEC3G) alteration effect on HIV virus DNA sequence

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APOBEC3G is a protein family that interferes with the replication of the HIV virus by altering the genomic sequence of the virus. To combat this, the virus evolves a countermeasure in the form of a protein called Viral Infectivity Factor (*vif*) binds to APOBEC to reduce its effectiveness. In vitro, dilutions from zero to 1mg of APOBEC3G are injected into HIV infected cells. The cells' DNA sequences were analyzed to determine the nucleotide modification patterns cause by the protein. It was found that a hypermutation of guanine to adenine occurs in the cell. The modification was expanded to dinucleotides and trinucleotides. For dinucleotides, guanine preceded by guanine alters to guanine preceding adenine and adenine preceding guanine, and thymine precedes guanine the sequence modifies to thymine preceding guanine. Adenine preceding guanine preceding guanine, guanine preceding guanine preceding adenine and guanine preceding adenine preceding guanine converges from guanine preceding guanine preceding guanine to adenine preceding adenine preceding adenine and guanine preceding guanine preceding thymine alters to adenine preceding guanine preceding thymine for the trinucleotides transformation. More understanding of the effects of APOBEC3G modification on the virus' DNA sequences will lead to future development of an effective vaccine and drugs to cure and diminish the progression of AIDS.

1 Introduction

Of the 6.7 billion people worldwide around 33 million people are infected with the human immunodeficiency virus (HIV). This is one half of one percent of worldwide human population. Each year worldwide approximately 2.7 million people become infected with the disease and 2 million dies from Acquired Immunodeficiency Syndrome (AIDS) (13). Both HIV and AIDS disease are life limiting and altering disease that affects every ethnic group worldwide. Untreated, the virus limits the life expectancy of an infected individual to typically less than ten years. In 2007 1.7 million people in the sub-Sahara people Africa, 2.4 million people in Asia, 1.5 million people in Europe, and1.7million people in Latin America were infected and living with HIV. Based on UNAIDS 2006 data 1.2 million people in 2005 were living with the disease worldwide. World Health Organization (WHO) reports that an individual is infected with the virus in the United State every 9½ minutes. Worldwide, it is estimated that 16,000 individuals are infected daily (15). Immediate actions are necessary for reducing the increasing high rate of infection and spread of the disease, the cure vital the human society worldwide.

1.1 Past Research

Researchers have been trying to understand the disease with a hope of finding a cure for it. Work has been done on understanding the HIV virus through genotyping it genome, its and its interaction with the human immune system.

HIV-1 origin and Elite Controllers

Baker et al. and Dr. Bruce Walker have conducted research which studies elite controllers with anticipation of understanding the mechanisms of how they are able to control HIV virus in their immune system and use these mechanisms in developing and designing a vaccine (1,16). As define by Dr. Walker elite controllers are HIV infected individuals who have maintained HIV RNA levels below 50copies/mL for a least one year or longer in the absence of antiretroviral therapy. Unfortunately after examining recent literatures on the correlation between the viral and host immunology and host viral control ability the researchers were unable to determine the specific mechanisms that elite controllers immune system are using to maintain the viral counts. Some research along these lines, however the idea that T-cells can control HIV infection (5).

APOBEC

Various researchers have tried to understand APOBEC a protein family of cytidine deaminaases, and its role in the immune system and interacting with the HIV virus. APOAPOBEC superfamily of proteins is known for interfering with the replication of the HIV virus and other retroviruses by altering the genomic sequences of the virus. Although APOBEC3 (A, B, C, F, G) have been found by researchers to be effective in inhibiting HIV infections, APOBEC3G is found to be more potent inhibitor than the other four types of APOBEC3 (7, 8). HIV is known to deaminate cytidine to uridine in HIV DNA minus–strand causing hypermutation of guanine to adenine in the plus-strand of the viral DNA (15). Many researchers have confirmed and acknowledged that APOBEC3G causes a G to A hypermutation in HIV genomic DNA sequence (6, 8, 14).

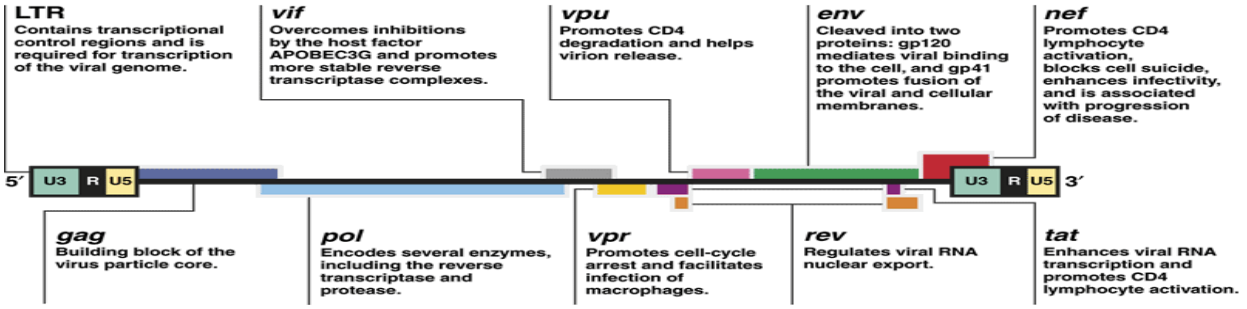
Viral Infectivity Factor (Vif)

The HIV protein Viral Infectivity Factor (vif) virus combat the hypermutation caused by APOBEC3G. Vif protects HIV from the hypermutation by preventing APOBEC3G from being incorporated into the virions that are being replicated in the host cells and transfer to the target cells (9,14).Since the interaction of vif with APOBEC3G from being incorporated into the virions that the host cell is producing. APOBEC3G antiviral action of mutating the HIV DNA is hindered and the HIV continues to proliferate from one cell to another. The proliferation ultimately causes T-cells count of patients to drop below 500 and above in HIV patient, who are said to develop AIDS when this count drops to 200. In comparison, a healthy individual, the T-cell count is 700 – 1000.

HIV-1

Research done by Santa Fe Institute Professor Tanmoy Bhattacharya and Santa Fe External Professor Bette Korber, stated that the origin of the main group of HIV-1 virus was between 1915 and 1941 (7). Along with the various research that have

been done on the HIV vif protein and its interaction with APOBEC3G and the human innate and adaptive immune system, work has also been done to study the virus structure, life cycle and its interaction with the human immune system. Researchers have found that HIV has nine genes gag, env, pol, tat, rev, nif, vif, vpr, and vpu. The gag, env, and pol gene products are used in the forming structural protein for new virus particles, while the remaining six genes tat, rev, nef, vif, vpr, and vpu determines the ability of the virus to infect cells and proliferate (6, 11).



www.gladstone.ucsf.edu/.../connections/fig1.html

Fig. 1. Summary of the HIV-1 genes alignment from 5'LTR to 3'LTR and the functions of the genes.

HIV particles are coated with fatty material known as viral envelope with approximately 72 protein gp120 and gp41 protein spikes projecting of the membrane. The inner layer of the viral envelope is a matrix formed from protein p17 and protein p24 forms the viral core. The viral core composes of two identical strands of RNA and three enzymes reverse transcriptase, integrase and protease which are essential for the replication of the virus (6, 11). The process by which HIV replicates and proliferates in CD4 T-cell goes as follows: The spikes of the protein gp120 and gp41 bind to CD4 protein and the viral envelope fuse to the T-cell membrane. The HIV particles RNA, reverse transcriptase and enzyme integrase and protease are released into the cell leaving behind the viral envelope. The HIV enzyme reverse transcriptase converts the HIV RNA particle into DNA and the DNA is integrated into the human cell's DNA by the HIV enzyme integrase. The cell converts the HIV gene into messenger RNA through transcription and new HIV proteins and enzymes are formed. The HIV enzyme protease catalyzes the protein into small pieces and the catalyzed proteins are used to construct a viral core for the virus. The newly developed virus is released from the cell (11).

HIV Vaccine

Designing and developing a vaccine to cure HIV continuously have been the goals of number of researches worldwide for over two decades. Although some researchers believe that that it's impossible to develop vaccination for the disease, other think otherwise but acknowledge that developing a vaccine is a daunting task. Based on data on HIV-1 infected chimpanzees researchers have agreed that antibody can prevent HIV infection, although when the vaccine was

produced in the monkey cell and implanted into a human cell the vaccine did provide the human cell with consistent protection against the virus (5). In September of 2007 Merck & Co Inc HIV vaccine MRK Ad5 HIV-1 gag/pol/nef trial and the trial was immediately halted because the vaccination showed no positive impact on the viral count of individuals who participated in the trial (2). These various vaccine trails show that many researches are determine in finding a solution that will end the HIV epidemic.

1.2 Reason for Research

Due to the failures of many strategies that have been exerted in the hope of developing a treatment or a vaccine for the disease, the current researches have been modified from being data driven to knowledge driven. This current way of thinking calls for intervention that is focused on the interaction between the HIV and the human immune system.

Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) is a protein family that interferes with the replication of the HIV virus and other retroviruses by altering the genomic sequence of the virus. The virus, to combat this, has evolved a countermeasure in the form of a protein called Viral Infectivity Factor (*vif*) that can bind to APOBEC and reduce its effectiveness. Of course one possible outcome of APOBEC altering the genomic sequence of the HIV virus is that the immune system becomes unable to recognize the virus and therefore the virus cannot be eliminates by the immune system. Another outcome is that the severe genomic alteration of the virus causes the virus to become mutated making it incapable of producing proteins and leading to the virus' death. Thus, depending on the extent of the genomic sequence of the HIV virus that was altered by APOBEC, it can result in being beneficial or detrimental to the proliferation of the virus.

The purpose of this research is to determine the sequence alteration caused by APOBEC3G on HIV DNA sequence. In this research how HIV sequence alters with various APOBEC3G concentrations will be determine. The results of the research will determine if APOBEC3G does cause a hypermutation of guanine to adenine in HIV DNA sequence as stated by previous researchers and examine other nucleotide bases alterations cause by APOBEC3G. With data are available about the pattern of APOBEC hypermutation alteration of HIV genomic sequence, using bootstrap method and statistical techniques one can measure to what extent the HIV genomic sequence can be altered by APOBEC, and hence determine when the alteration can be beneficial or detrimental to the proliferation of the virus in the human organism. This research naturally has bearing on drugs that are designed to deactivate *vif* in an attempt to control the proliferation of the virus.

2 Experimental Design

The research is collaboration between, Steven M. Wilkonsky's, Michael H Malim's and Tanmoy Bhattacharya laboratories. The objective of the collaboration of the four researchers is to determine the relationship between APOBEC and Vif by holistically examining individuals who are high risk for

HIV infection and already infected individuals.

Data Source

The data that was used in this research came from both Wilkonsky's and Malim's laboratories. Malim did an in vitro experiment where seven various concentrations of APOBEC3G was implanted into various HIV infected cells. In six cases, each infected cell was given equal quantities of APOBEC3G solution, which contained different concentrations of APOBEC3G and a mutant – nonfunctional APOBEC. The seven concentrations dilution goes as follow:

Table 1. Summary APOBEC3G samples dilutions and amount of HIV DNA sequences obtained for each micrograms dilution.

Dilutions	**1**	**2**	**3**	**4**	**5**	**6**	**7**
APOBEC3G (mg)	0	0.01	0.033	0.1	0.33	1	0
Mutant (mg)	1	0.99	0.967	0.9	0.67	0	0
# of DNA seq.	25	24	29	28	35	30	28

The seven various dilutions were implanted into the individual cells and the HIV-1 gag protein of the virus was then sequenced by Wilkonsky's laboratory. The experiment was repeated several times with each concentration and the number of sequenced HIV DNA respectively to the dilution is shown in table1 above. The DNA sequences were aligned from base positions from 627 to 1779 because the beginning and the ending of the sequence HIV DNA varied. The DNA alignment resulted in a total 1153 for each sequenced DNA.

Data Analysis

Each DNA sequence was analyzed using C++ programming and Wilcox test in R program. The two analysis were used to determine p-value, parametric bootstrap statistic and slopes calculations. Bootstrapping is a statistical resampling method that allows the gathering of many alternative versions of a single statistic that would originally have been calculated as one sample. A 100 bootstrap samples were from the original number of DNA sequence.

3 Results

Based on the high p values of the dilution 1 and 7 for the mononucleotides 0.2539 (cytosine), 0.7853 (guanine), 0.5861 (thymine), and 0.918 (adenine), that as expected, dilution 1 and 7 are the same. The sequence alteration pattern was determined for mononucleotides, dinucleotides and trinucleotides. The correlation the ration of mononucleotides guanine, adenine, cytosine and thymine over the total concentration of the four nucleotides with each of the APOBEC3G dilutions is depicted in Fig. 1. In figure 2, the nucleotide ratio mean was obtained from the following equations:

$$NRM = \frac{W}{W*X*Y*Z} \qquad \mu = \frac{\mu}{n*\ 100}$$

μ is the ration mean for a nucleotide sequence for one HIV-1 DNA sequence. W, X, Y, Z is the different nucleotide hence A, C, G, and T. The ratio mean of a nucleotide divided by n the number of sequenced HIV-1 DNA per a dilution time 100 bootstrap samples is equivalent to the nucleotide ratio mean (NRM).

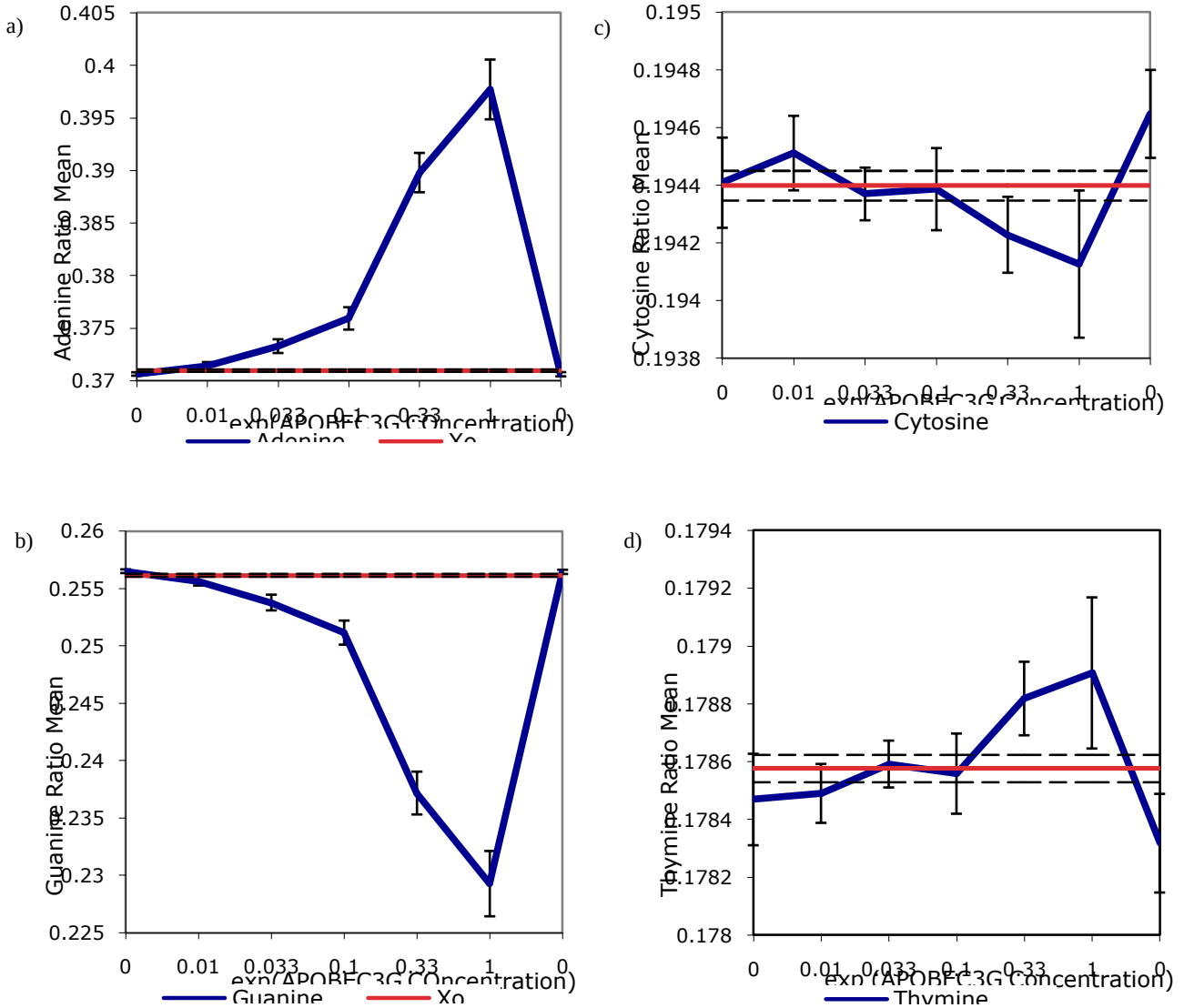


Fig. 2. The correlation of the four mononucleotides displays that with increase APOBEC3G about Xo the weighted mean and Xo standard deviation S_o (+) and S_o (-) of determine if there is base concentration alternation with increase of APOBEC3G.

The linear regression slope and R^2 values were used to determine farther alteration pattern beside mononucleotide. As shown in fig. 3 based on the slope and the R^2 values it was determined which HIV DNA nucleotides are being altered with the increase of APOBEC3G concentration resulting in positive or negative or constant slope. If the nucleotides had a positive slope infers that the concentration of the nucleotide is increase and negative slope meant that the nucleotide quantity was

decreasing while constant slope- a slope less than ±1 surmise the nucleotide quantity remained relatively the same with the increase of APOBEC3G concentration.

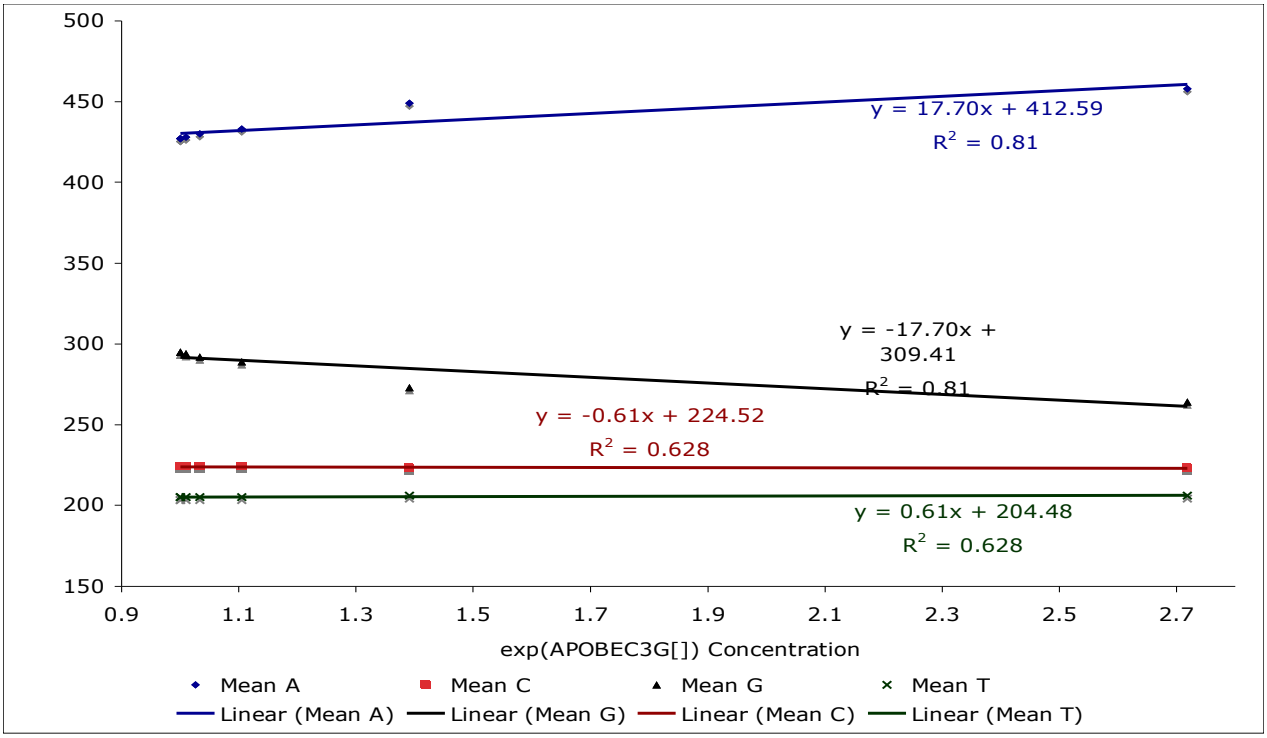


Fig. 3. Adenine, cytosine guanine and thymine slope correlation in relation to the increase of APOBEC3G concentration. The quantity of adenine in

This method was used in determining the dinucleotides and trinucleotides sequences alteration. The summary of the mononucleotides, dinucleotides, and trinucleotides are illustrated in the tables 2, 3 and 4.

Table 2. Summary of the mononucleotides slopes and correlation of determination R^2.

Mononucleotide	Slope	R^2
A	17.70	0.810
C	-0.61	0.628
G	-17.70	0.810
T	0.61	0.628

For the mononucleotide, adenine had a slope 17.70 and a R^2 value of o.81 meaning that the quantity of adenine in the HIV-1 DNA is increased with enhance concentration of ApoBEC3G. The quantity of guanine (slope = -17.70,

R^2= 0.81) decreased as APOBEC3G concentration rises. The quantity of both cytosine and thymine, which had slopes with less values than 1 (slope = $\pm$0.61) remained constant as the concentration changes. Hence guanines are being altered to adenine (G to A) as the concentration of APOBEC3G increases. Since only Gs and As and neither cytosine (C) nor thymine (T) are converging, for determining the alternation pattern of dinucleotides and trinucleotides sequences the two converging nucleotides G and A were the prime focus.

In table 3 is the list of the all possible dinucleotides sequences based on mononucleotides conclusion that the guanines are being altered to adenine.

Table 3. Summary of the dinucleotides' slopes and correlation of determination R^2. Ex: ApG = A precede G

Dinucleotides	Slope	R^2
ApG	5.91	0.582
CpG	-1.20	0.922
GpG	-16.44	0.774
TpG	-6.42	0.718
ApA	11.70	0.906
CpA	1.20	0.922
GpA	-1.07	0.731
TpA	6.56	0.710
GpC	-0.13	0.048
GpT	-0.09	0.023
ApC	0.60	0.172
ApT	0.46	0.359

For the dinucleotides, ApG (slope = 5.91, R^2= 0.582) and GpA (slope = -1.07, R^2 = 0.731) are altered to ApA (slope = 11.70, R^2 = 0.906) with an increase in APOBEC3G concentrations. Neither GpC (slope = -0.13, R^2 = 0.048) nor GpT (slope = -0.09, R^2 = 0.023) converge to ApC (slope = 0.60, R^2 = 0.172) or ApT (slope = 0.46, R^2 = 0.359) respectively. CpG (slope = -1.20, R^2 = 0.922) and TpG (slope = -6.42, R^2 = 0.718) converge to CpA (slope = 1.20, R^2 = 0.922) and TpA (slope = 6.56, R^2 = 0.710) respectively. And GpG can converge to ApG (slope = 5.91, R^2= 0.582) and GpA (slope = -1.07, R^2 = 0.731). A summary the dinucleotides alteration is NG $\rightarrow$ NA where N is [A or C or G or T], GpG (guanine precede guanine) $\rightarrow$ (alters to) either GpA or ApG, ApG $\rightarrow$ APA, and GpA $\rightarrow$ ApA. The slope of GpC, GpT, ApC, ApT are less than 1 hence GpC and GpT respectively does not converge to ApC and ApT.

The trinucleotides sequences variation pattern is summarized in table 4.

Table 4. Summary of the HIV DNA trinucleotides slopes and correlation of determination R^2. Ex: ApGpA = A precede G precede A

Trinucleotides	Slope	R^2
ApGpA	5.02	0.765
ApGpC	0.48	0.324
ApGpG	0.77**	0.411
ApGpT	1.59	0.753
ApApA	5.80	0.877
ApApC	0.61	0.628
ApApG	5.64	0.931
ApApT	0.62	0.628
GpGpA	-5.61	0.817
GpGpC	-0.52	0.380
GpGpG	-9.38	0.722
GpGpT	-1.72	0.797
GpApA	1.10	0.537
GpApC	-0.36	0.182
GpApG	-1.65	0.872
GpApT	-0.26	0.110

**The only except to the rule that if the slope is less than 1 there is no alteration effect is ApGpG and this exception is supported by the dinucleotides GpG $\rightarrow$ ApG patterns. Although the slope is less than 1 ApGpG does alter and this is supported by the dinucleotides GpG $\rightarrow$ ApG patterns.

GpGpC (slope = -0.52, R^2 = 0.380) does not convert to neither GpApC (slope = -0.36, R^2 = 0.182) nor ApApC (slope = 0.61, R^2 = 0.628) and neither does GpApC (slope = -0.36, R^2 = 0.182) alter to ApApC (slope = 0.61, R^2 = 0.628). GpGpT (slope = -1.72, R^2 = 0.797) does not alters to GpApT (slope = -0.26, R^2 = 0.110) but it does alter to ApGpT (slope = 1.59, R^2 = 0.753).

For the trinucleotides it is assumed that single and not multiple alterations happen at the same time. Hence GpGpG (slope = -9.38, R^2 = 0.722) alters either ApGpG (slope = 0.77, R^2 = 0.411) or GpApG (slope = -1.63, R^2 = 0.872) or GpGpA (slope = -5.61, R^2 = 0.817). Both GpApG and ApGpG converge to ApApG (slope = 564, R^2 = 0.913). GpApG and ApGpG also proceed to GAA (slope = 1.10, R^2 = 0.537) and AGA (slope = 5.02, R^2 = 0.765) respectively. ApGpA, GpApA and ApGpG all alters to ApApA (slope = 5.80, R^2 = 0.877).

A network diagram of the trinucleotides sequences that does alter with the increase of APOBEC3G concentration is displayed below fig. 5 and a list of nucleotide patterns that does not alter is summarized in fig 4.

GC ⇒X AC
GT ⇒X AT
GGC⇒X AAC
GGC ⇒X GAC
GGT ⇒X GAT
GGT ⇒X AAT

Fig. 4. List of nucleotides sequences that remained unaltered with an enlargement in the APOBEC3G concentration. .

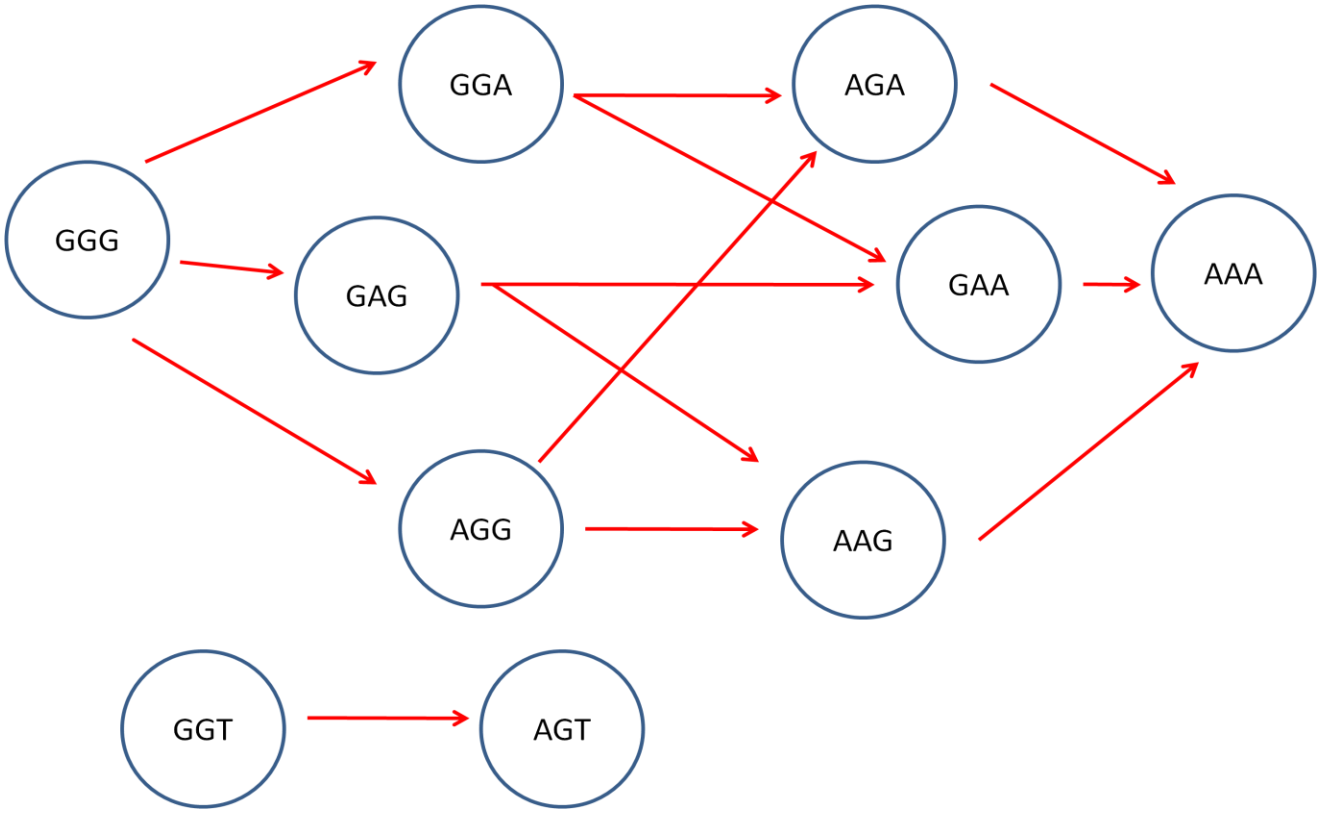


Fig. 5. A network summary of the HIV DNA trinucleotides pattern alteration causes by APOBEC 3G.

4 Discussion

The results from this research also support that previous researchers have concluded that APOBEC3G causes a hypermutation of guanine to adenine in the HIV DNA sequence (6, 8, 14). As depicted in figure 2 the Xo value intercept all the

standard deviation the points for both thymine and cytosine, hence the APOBEC3G concentration does not have an alteration affect on neither cytosine nor guanine. The Xo line of adenine and guanine only intercept two of the standard deviated point on each of the nucleotide hence adenine and guanine are altering with the increase of APOBEC3G concentration. From analysis of the nucleotides alteration about Xo it was concluded that APOBEC3G cause an alteration in the HIV-1 DNA sequence of converging guanine to adenine.

The results also reveal alteration patterns that researches are unaware of. From the dinucleotides results it was determined that GpG → ApG, GpG → GpA, GpD → ApD where D is A or G, and DpG → DpA where D is A or G or T. The GpG → ApG was previous discovered by researchers. Researchers believed that a guanine preceding a guanine was the only alteration pattern that will led to the hypermutation of guanines to adenines (9). The dinucleotide alteration pattern of GpG → ApG disproves previous researchers' findings. Hence GpG can alter to either GpA or ApG. It has also been found that guanine preceded by either adenine or guanine can alter to ApA or ApG. If adenine or guanine or thymine is followed by a guanine, the sequence will converge to ApA, GpA, or TA respectively with the increase of APOBEC3G concentration. When a guanine is followed by either a thymine of cytosine, the dinucleotide remains the same and does not alter.

The trinucleotides alteration pattern followed the patterns of the mononucleotide and dinucleotide. GpGpD → GpApD, which is D is A or G or T is the same the dinucleotide pattern of GpD→ ApD. There was a network of alteration for GpGpG trinucleotide, the trinucleotide can be altered to ApGpG and GpApG and GpGpA which can alter to ApApG and ApGpA and GpApA and all can alter to ApApA with an increase in APOBEC3G concentration.

5 Conclusion

The data collected from the result support researchers previous finding that APOBEC3G cause a hypermutation of guanine to adenine. Previous researchers also concluded that a GpG dincleotide pattern was needed for the alteration to occur. Based on the finding that both a GpA and ApG alteration are results of GpG modifications, and also ApGpG , GpGpA and GpApG converges from GpGpG trinucleotides. Hence guanine does not need to precede a guanine to result in the G to A alteration. Other alteration pattern caused by APOBEC3G are GpD → ApD where D is A or G, and DpG → DpA where D is A or G or T. And when guanine is follow by a cytosine or thymine there is no alteration.

In knowing the DNA modification cause by APOBEC3G on HIV DNA sequence can be used to measure to what extent the sequence is beneficial or detrimental to the proliferation to the virus in the immune system. Therefore, if the unfavorable of the nucleotides effect signified, new drug can be produced to imitate the alteration effects hence eliminating the virus from the human immune system. Understanding effects of APOBEC3G modification on the HIV sequence will lead to the development of an

effective vaccine or drug to cure or diminish the progression of AIDS.

5.1 Future Research

Research ideas for the continuation of this research are to determine the sequence alteration position in the HIV DNA. Knowing the alteration position in the gag gene of the virus will lead to research that study how these positions participate in the proliferation of the virus. And in knowing significant of the positions in the virus one can then determine if the alterations at these locations is an advantage or disadvantage to the proliferation of the virus in the immune system. Another future work is to better understand why the alterations happens at one specific position and not another by analyzing the interactions of the protein and the virus molecular structure. Having a better understanding of the relationship between APOBEC3G and the HIV virus will lead to the development drugs or vaccine that will deactivate *vif* and control the proliferation of the virus.

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