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GENETIC VARIATION AND MUTATIONAL DETERMINANTS OF RNASE L GENE IN GASTRIC CANCER PATIENTS

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ABSTRACT

Background: RNASE L acting as innate immune mediator have significant role in anti-pathogenic response.This present study is to identify RNASE and ANK domain mutation/s of RNASE L gene in gastric cancer patients.

Method: Total 120 blood samples were collected in this study and stratified as Gastric carcinoma patients, GC with H.pylori and H.pylori positive patients. After DNA extraction RNASE-L gene was amplified using PCR and gel-electrophoresis was performed.Amplified samples of RANSE-L were sent to Macrogen, Korea for sequencing. Sequencing results were analysed using Bio Edit and MEGA11 software.Mutations of RNASE-L gene in H pylori with gastric cancer were reported.

Result: Out of 120 collected blood samples, 5% were of GC, 50% of GC alongside with H pylori, and residual samples were of H-pylori positive individuals. Of these, 58.3% are men and 41.6% are women. Sequence examination revealed that only one sample had SNV (single nucleotides variant) G>A in domain of RNASE, and no any sample had SNV in domain ARD.

Conclusion: The study identified low frequency of genetic variation in RNASE L gene among gastric cancer patients in Pakistani population. Only a single detected synonymous mutation in RNase domain suggest that genetic mutations might not be common culprit behind gastric tumours in Pakistan.However, the study highlights potential role of host immune response genes Pylori infection and biological role of RNASE gene in gastric cancer.

KEYWORDS: RNASE L, GC, H- Pylori, RNase.

INTRODUCTION

Gastric carcinoma (also known as stomach cancer) is one of most common and deadly diseases worldwide (1, 2). According to Global data 2022, Gastric cancer is the fourth main reason of dying following lung, colorectal and liver carcinoma. Around one in 12 of all oncological deaths are caused by gastric cancer. It has fifth highest occurrence amongst cancers, 5.7% of all young people are infected with the disease. Gastric cancer is considered as one of the most behaviourally influenced hence preventable cancer (3).

Stomach dysfunction is one of the predisposing factor associated with pathophysiology of Gastric cancer leading to cirrhosis which often develops gastric cancer. Gastric carcinogenesis is regarded as a complex event arising as result of accumulation of genetic as well as epigenetic variations. Up-regulation of different factors are also involved in the cancer cell survival by regulating cell cycle and inhibition of apoptosis (4) .

There are different risk factors involved in gastric cancer pathogenesis such as smoking, tobacco, vinyl chloride, heavy alcohol intake, obesity, diabetes and diet. H pylori is main culprit of gastric cancer specially in the endemic regions where it is found in 80% of the Gastric cancer cases (1). Recent evidence by Raghav Sundar et al. (2025) highlights that environmental, microbial and genetic factors with *H. Pylori* being a major modifiable factor, emphasizing on role of molecular profiling, immunotherapy and precision medicine in improving patient outcome.

Cellular immune response occurs in bacterial/viral infection through the initiation of natural killer (NK) cells and cytotoxic T lymphocytes and production of neutralizing antibodies. Different cytokines and chemokines are also involved in immune response such as type 1 IFNs are most important cytokines involved in antiviral response which are produced by T-cells while adaptive immune system is activated by NK (5, 6). They also up-regulate some intrinsic gene including the 2-5` OLIGOADENYLATE SYNTHETASE (OAS) and induce the apoptosis of viral infected cells (7, 8).

RNASE L/ OAS 2-5 first pathway is the antiviral response studied in 1970s (9). The initiation and activation of RNASE L throughout the bacterial infection also occurs by interferon (IFN) action against the bacterial infection (10). In activation pathway of RNASE L, when interferon binds to receptor it leads to the modification and transcription of oligo adenylate syntheses (OAS). The binding of bacterial dsRNA to OAS leads to production of OAS 2'-5'. This formation induce the initiation of the RNASE L by dimerization (11).

RNase L is endoribonuclease protein naturally present in inactive state and gets activated when bacterial/viral infections occur (12) to eliminate the bacterial-infected cells through the apoptosis (13). The breakdown of various cellular RNAs, for example rRNA binding to ribosomes contributes to the antiviral activity of RNase L (14, 15) .

RNASE L has three Domains: Ankyrin domain repeat N –terminal, Terminal C (catalytic) domain Ribonuclease (RNASE), and homology domain (PK) protein kinase (16). The single feature of the ANK repeats in RNase L is that they interact with a nucleic acid and 2-5 OAS. ANK repeats 2 and 4 are involved in 2-5A binding. 2-5A binding to Ankyrin-region of RNase L transforms enzyme from inactive to the active dimers (17). The RNASE L activation in cells causes cleavage and degradation of viral nucleic acid causing cell death. PK and RNASE domains have kinase and endoribonuclease activities and they are also activated in response to unfolded protein (9, 18).

RNASE L activity produces OAS and 2-5A which reveals that initiation of RNASE L during viral infections increases autophagy even though the RNase L has a pro apoptotic activity (19). It has been considered lately that RNASE L also has a tumour suppressor action due to this one pro-apoptotic activity (20). RNASE L have been shown to have significant impact on the pathogenesis and metastasis of Prostate cancer. It has also been identified as a strong candidate for hereditary prostate cancer 1 (HPC1) allele. Several mutations have been also observed in RNASE L gene in Prostate cancer that is related with reduced enzyme activity, increased risk of high grade tumours as well as increased expression of inflammatory biomarkers (21). Another study has also reported RNASE L mutation associated with greater load of virus XMRV in prostate cancer. Madsen *et. al.* have also expected the germline mutation RNASE L association with improved threat of cancer Neck and Head , cancer of Cervical and the cancer of breast (22, 23). These studies mainly highlighted kinase-like and catalytic domain activities. Ankyrin repeat domain remains mainly un-explored despite its crucial role in 2-5 A binding, enzyme activation and conformational change.

In this study, we aim to understand host immune dysregulation in gastric tumorigenesis by investigating the genetic mutations in RNASE L in gastric cancer patients because of its strong connection with chronic inflammation linked with *H. Pylori,* which remains largely unexplored in gastric cancers.

MATERIAL AND METHODS

Study Design and Setting: It was an observational analytical cross-sectional study, conducted at Gastro-oncology department of Jinnah Postgraduate Medical Centre, Karachi.

Participants: The study enrolled members in three groups: *Helicobacter pylori* positive individuals (n=76), patients diagnosed with gastric cancer (GC) along with *H. pylori* infection (n=40), and patients diagnosed with Gastric Cancer only (GC only n=4) because few patients with gastric cancer came to be negative for *H. Pylori* infection status.

Written Informed consent was achieved from all contributors, and complete information about the study was conveyed to every single patient incorporated in the study. The research was conducted after approval from the Institutional Review Board (IRB) and was carried out from 12 October 2023 to 12 September 2024.

Study included patients with diagnosed *H. Pylori* infection and/or gastric cancer, with age ≥10 years and given informed consent. All persons suffer with co-infection (HBV, HIV, CMV or EBV) or with inadequate clinical data have been excluded from the study. A sample size of 120 blood samples was determined. Sample size estimation was based on standard formulas for observational studies. A prevalence of 6% was considered as reported in previous studies using 98% confidence interval (24, 25) however subgroup analyses were exploratory due to unequal group distribution. Sample collection done via non-probable convenient sampling technique. Blood samples were obtained from patients following aseptic techniques.

Blood samples were collected in EDTA tubes and subsequently centrifuged. The buffy coat was then carefully separated and used for DNA extraction.

DNA Extraction and PCR: Genomic DNA turned into extracted by the QIAamp Mini kit DNA (Qiagen, Germany) consistent with the manufacturer's instructions. The purity and concentration of DNA changed into decided by a spectrophotometer through calculating absorbance at 260 nm and 280 nm wavelengths. Samples having concentration more than 20µg were used for further processing.

Polymerase Chain Reaction (PCR) has been done of extracted DNA with housekeeping primers gene i.e. β-globin. This was followed by amplification of the ankyrin repeat domain (ARD) and RNASE domain of the RNASE L gene. The primer sequences used included ARD forward (5'-CGAAGATGTTGACCTGGTCC-3') and reverse (5'-CATACACAGCGGCTTCCATG-3') producing a 302 bp product for Ankyrin domain, as well as RN1 forward (5'-GATTTATTTTGTGTTGCTACCAC-3') and reverse (5'-GTAGGAATGAAAACAATACTTAC-3') producing a 208 bp product for RNASE domain (Table 1).

The thermal cycling conditions for PCR included an initial denaturation at 95°C for 10 minutes, followed by 35 cycles of denaturation at 95°C for 60 seconds, annealing at 56°C for 60 seconds, and extension at 72°C for 30 seconds, with a final extension at 72°C for 6 minutes. For *Helicobacter pylori* quantification, PCR conditions included an initial incubation at 50°C for 30 minutes, followed by denaturation at 95°C for 15 minutes, and 50 cycles consisting of 94°C for 30 seconds, 50°C for 60 seconds, and 72°C for 30 seconds.
The products of amplified by PCR were examined through 2% agarose electrophoresis gel ready with (0.2–0.5 µg/mL) ethidium bromide. PCR products were sent to Macrogen Korea for sanger sequencing. Raw Sequences were carefully analysed and high quality sequences were aligned using BioEdit and MEGA11 and compared with reference sequence. Visual inspection of electropherograms was done to check peak clarity and absence of background noise.

Statistical Analysis: Data was analyzed through statistical software SPSS version 19. All data, containing demographic variables (age, marital status, and clinical characteristics), were collected and analyzed to define their association with RNASE L gene expression and gastric cancer (GC). Descriptive statistics, containing mean (±SD), frequencies and graphical representations, were used to summarize the data. Chi-square test was used for categorical data while Fischer exact test was applied where expected cell counts were <5.

RESULTS

The study involved a total of 120 members, with mean age of 60.86 ± 15.85 with males 58.3% and females 41.7%. Among them, 10 participants (8.3%) were aged 10–30 years, 40 participants (33.3%) were aged 31–50 years, another 40 participants (33.3%) were aged 51–70 years, and 30 participants (25%) were aged 71–77 years (Table 2). These findings indicate a slightly higher representation of middle-aged participants and a predominance of male participants in the study population.
A total of 116 samples, comprising 76 *H. pylori* positive and 40 gastric cancer patients with *H. pylori* infection, the distribution of bacterial load was categorized into increasing range as follows: low(180-22200IU/mL),moderate(22400-44620IU/mL),High (44720-66840IU/mL),and very high (66940-89160IU/mL).The majority of samples were observed into moderate to high load categories. The median bacterial load was of 280, 419 IU/mL. Bacterial load characterization was done on basis of data distribution rather than predefined clinical threshold (26). Chi-square goodness-of-fit analysis indicated significantly non-uniform distribution of bacterial loads ($p < 0.001$), with most samples concentrated in the intermediate load ranges and very few at the lowest or highest ranges (figure 1).
Visualization of the amplified product after PCR amplification of the RNASE L gene's RNase domain against a DNA ladder by gel electrophoresis consistently revealed a single, robust band at the expected molecular weight of 302 bp. A total of 70 samples successfully produced this 302 bp amplicon with sufficient purity and yield, all of which were subsequently processed for downstream sequencing to facilitate genetic mutation analysis of the domain (Figure 2).
The genetically study of the Ankyrin Repeat Domain (ARD) and RNase inside the *RNASEL* gene was directed to find the potential Single Nucleotide Variants (SNVs) across 70 samples of study. Sanger sequencing and electropherogram analysis revealed a high degree of sequence conservation within the cohort. Within the RNase domain, only a single sample 1.71% (1/70) exhibited a genetic variation, identified as a heterozygous g.15666G>A SNV (reference genome NG_009024.2). Notably, this transition did not result in an amino acid substitution, indicating a synonymous (silent) mutation. In contrast, the ARD domain showed no evidence of SNVs or allelic variations in any of the analysed samples, as demonstrated by the consistent wild-type traces in the electropherograms. Multiple sequence alignment further confirmed that the nucleotide sequence of the *RNASEL* gene remains highly stable across the majority of the tested population. The RNase domain analysis revealed a high degree of sequence stability, with only one identified variation in the entire cohort (1.71%) (Figure 3).

DISCUSSION

Gastric cancer (GC) is a multifactorial disease that generates due to combination of environmental exposures, biological risk factors, and genetic pre-dispositions. Each patient's pathophysiology encompasses complex intracellular mechanisms modulated by microbial pathogens and the patient's unique genetic characteristics. In Pakistan, a South Asian country, with population exceeding 190 million people, the burden of gastric cancer is expected to increase due to a large number of individuals (approximately 24 million) being between 0 to 24 years of age who have limited access to adequate healthcare services, potentially increasing future risk and delaying early diagnosis.
cancers is one of the main reason of demise in Pakistan, with gastric most cancers being one of the maximum not unusual cancers within the united states; but, there isn't an up-to-date and centralized most cancers registry in Pakistan up to date achieve authentic incidence and prevalence statistics for gastric most cancers, which makes improvement of an effective and sustainable healthcare plan up to date. Most available records for GC patients come from local population registries (e.g., Karachi and Punjab) or from institutional databases (e.g., Jinnah Postgraduate Medical

Centre). Very few studies related to gastric cancer risk factors in Pakistan have been carried out, but one of the consistently reported risk factors for gastric cancer in Pakistan is the association of gastric cancer with Helicobacter pylori infection (27).

In our study, most of the patients were males of younger age groups, a finding consistent with Yousaf, Tasneem et al. 2021 but middle aged males were also found to be commonly involved in our study as also highlighted by Raghav Sundar et al. (2025).

In the present study, RNASE L gene shows high sequence conservation. Similar findings were reported for RNase domain by Madsen, Ramos et al. 2008 who described conservation of sequences for RNase domain but contrary to our study reported several mutations in ankyrin and kinase like domain in cervical cancer (28). Studies on prostate cancer widely while also on breast and uterine cancers and melanomas have reported RNase L variants which leads to increased risk of carcinogenesis (29-33) yet in our study we find no such association. One possible explanation for absence of significant RNase L mutations might be that RNase role has been strongly implicated in viral associated malignancies while gastric carcinomas have so far significant association with bacterial infection i.e. *H. Pylori* which may have involved different pathways as compared to virus associated tumours (34, 35). These findings imply that RNase L sequence and hence changes in protein structure does not play significant role in gastric cancers but there might be other contributors. Dysregulation of immune pathways, gene expression changes or environmental factors already reported are hence more critical contributors (36, 37). It is also important to note that absence of RNase L mutations does not completely exclude the potential role of RNase L in gastric carcinoma. Epigenetic modifications, altered gene expression or post translational modifications need to be evaluated as well (20, 38, 39).

CONCLUSION

This study concludes that RNASE L gene is highly conserved in gastric cancer patients in Pakistan with no mutation identified in ankyrin and kinase like domain while only a single synonymous variant (g.15666G>A) detected in RNase domain. A dire need to explore other pathways like gene expression analysis and immune mediated response need to be evaluated in larger study cohort.

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Conflict of Interest: None.

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Table 1: Primer sequence and PCR conditions for RNASE L domains amplification

Genes amplified	**Primers sequence**		**Product Size**
Ankyrin domain of RNASE L	Forward 5'-CGAAGATGTTGACCTGGTCC-3'		302 bp
	Reverse 5'-CATACACAGCGGCTTCCATG-3'		
RNase domain of RNASE L	Forward 5'-GATTTATTTTGTGTTGCTACCAC-3'		208 bp
	Reverse 5'-GTAGGAATGAAAACAATACTTAC-3'		
PCR Settings for RNASE L domains			
Initial denaturation	95°C	10 minutes	1 cycle
Denaturation	95°C	60 seconds	35 cycles
Annealing	56°C	60 seconds	
Extension	72°C	30 seconds	
Final Extension	72°C	6 minutes	1 cycle

Table2: Distribution of Age and Gender

Demographic Information		
Age Group (Years)	**Frequency**	**Percentage (%)**
10–30	10	8.33
31–50	40	33.33
51–70	40	33.33
71–77	30	25.00
Gender		
Male	70	58.33
Female	50	41.66

Total	**120**	

Note: Note: Demographically Data are presented

Table 3: Genetic analysis of RNASE and ARD domain of RNASE L gene

S.No	NO	Mutation Genomic	Change A.A
1	46RNASE	g.15666**G>A (Heterozygous)** NG_009024.2:	None

Note: Nucleotide Numbering is based on the RNASEL genomic reference sequence NG_009024.2

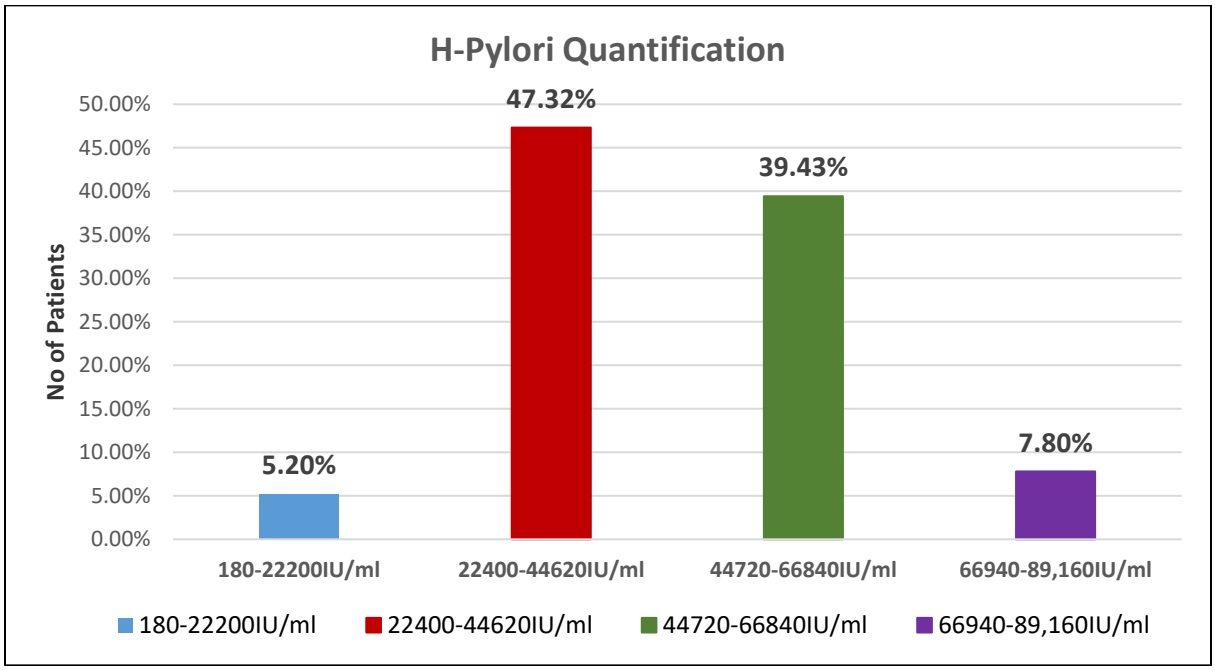

Figure 1: Show the proportion of H pylori patients presenting different ranges

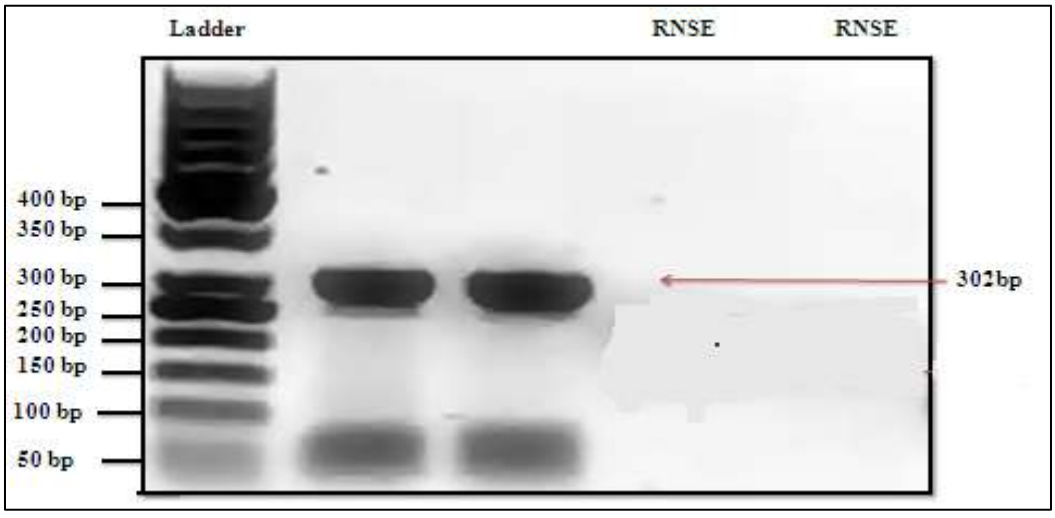

Figure 2:RNASE L gene PCR

Agarose gel 2% showing are 4, 5 product amplified of domain RNase of the gene RNASE L, besides DNA ladder base pair 50 of LD.

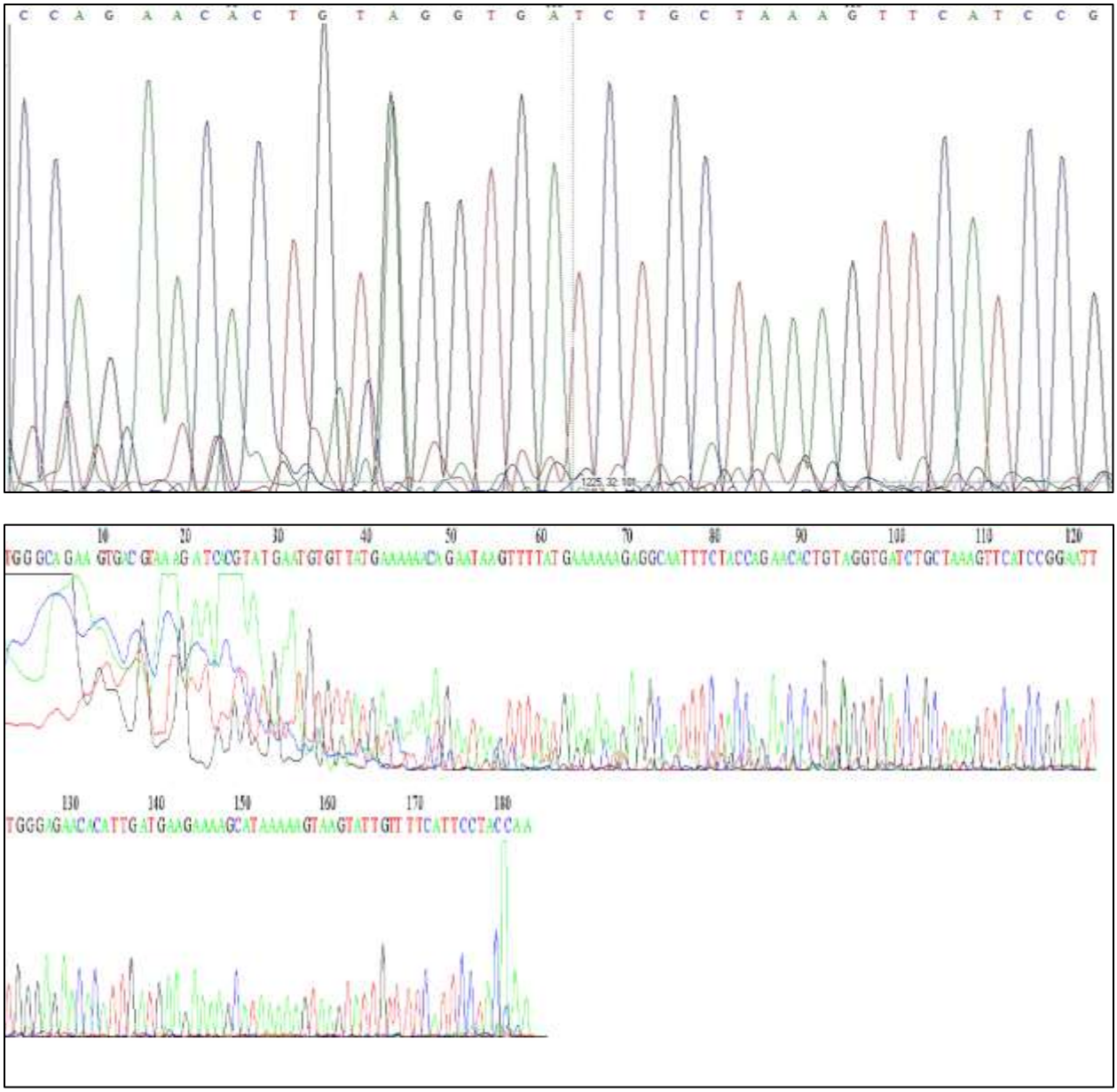

Figure 3: Electropherogram represents the sequence of RNASEL Gene Represents the Nucleotide alignments of DNA Sequences The arrow shows the G>A base substitution in RNASE Domain of RNASE L gene corresponds to genomic position NG_009024.2:g.15666.

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