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DETECTION OF 16S *rRNA* AND 23S *rRNA* GENE MUTATIONS IN MULTIDRUG RESISTANT *SALMONELLA* SEROVARS ISOLATED FROM DIFFERENT SOURCES USING RNA SEQUENCING METHOD

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SUMMARY

The rapid emergence of resistant bacteria is occurring worldwide. Antibiotic resistance is a serious problem for human beings because pathogenic microorganisms that acquire such resistance void antibiotic treatments. Bacterial antibiotic resistance mechanisms include efflux, reduced influx, modification and degradation of the drug, as well as mutation, modification or overexpression of the target. However, our knowledge as to how bacteria acquire antibiotic resistance is still fragmented, especially for ribosome-targeting drugs. *Salmonella* is a leading cause of foodborne salmonellosis in the world. The number of antibiotic resistant isolates identified in humans is steadily increasing, suggesting that the spread of antibiotic resistant strains is a major threat to public health. *Salmonella* is commonly identified in a wide range of animal hosts, food sources, and environments, but our knowledge as to how *Salmonella* resistance to antibiotics is still fragmented in this ecologically complex serovar. Therefore, the aim of this study was to support for finding novel mechanisms that render bacteria resistant to the ribosome targeting antibiotics, we screen for antibiotic resistant 16S and 23S ribosomal RNAs (rRNAs) in multidrug resistant *Salmonella* serovars isolated from raw retail meats isolated from Hanoi, Vietnam. Bioinformatic analysis identified 193 unknown novel mutations (64 mutations in 16S rRNA and 129 mutations in 23S rRNA genes). These mutations might play a role in streptomycin resistant in *Salmonella* serovars. These results suggest that uncharacterized antibiotic resistance mutations still exist, even for traditional antibiotics. This study is only a preliminary kind, further validation before they are applied in *Salmonella* or other closely related species are required.

Keywords: MDR *Salmonella*, mutation, 16S rRNA gene, 23S rRNA gene, RNAsequencing

INTRODUCTION

Aminoglycosides are used in treating a wide range of infections caused by gram-negative bacteria and has been classified by the World Health Organization as critically important antimicrobial drugs. They inhibit bacterial protein synthesis by binding to the 16S ribosomal subunit, leads to bacteria death. Resistance to these antimicrobial agents usually results from the production of aminoglycoside-modifying enzymes, reduced intracellular antibiotics accumulation, or mutation of ribosomal proteins or rRNA. An additional mechanism, methylation of the aminoacyl site of 16S rRNA, confers high level resistance to clinically crucial aminoglycosides such as streptomycin and gentamicin (Bonomo, Szabo, 2006; Fair, Tor, 2014; Katie *et al.*, 2010; Kohanski *et al.*, 2010). Exogenously acquired 16S rRNA methyltransferase (16S-RMTase) genes responsible for a really high level of resistance to various aminoglycosides have been widely distributed among *Enterobacteriaceae* including *Salmonella* serovars. This genetic apparatus may thus contribute to the rapid worldwide dissemination of the resistance mechanism among pathogenic bacteria. The worldwide dissemination of 16S-RMTases is becoming a global concern and this implies the necessity to continue investigations on the trend of 16S-RMTases to restrict their further worldwide dissemination (Wachino, Arakawa, 2012).

The ribosome is functionally critical sites exist mainly on RNAs, many antibiotic target sites exist on rRNAs, as several resistant point mutations (Moazed, Noller, 1987; Yassin *et al.*, 2005). This is because ribosomes play a crucial role in protein biosynthesis, translating messenger RNA encoded genetic information into proteins, which consists of sequential multistep reactions such as initiation, elongation, termination, and recycling. Owing to these extremely elaborate reaction dynamics, there are different sorts of inhibitors targeting each step of the translation process (Wilson, 2013). Acquisition of mutations in target sites of the antimicrobial mechanism is often observed for ribosome targeting drugs such as aminoglycosides (e.g., streptomycin, gentamycin), tetracycline, chloramphenicol, macrolides, lincomycins, streptogramin A, and oxazolidinones; the former three are known to target the 30S subunit that contains the 16S rRNA as its main component, whereas the others are known to attack the 50S subunit that contains the 23S rRNA as its main component (Wilson, 2006).

Our knowledge as to how bacteria acquire antibiotic resistance is still fragmented, especially for the ribosome targeting drugs. Therefore, tremendous effort is being made to identify the mechanisms and mutations that lead to bacterial resistance to antibiotics. There are many unfound and uncharacterized antibiotic resistance point mutations in rRNA genes. Understanding this can help ensure we can effectively treat bacterial infections such as *Salmonella* serovars. Researchers have long tried to list as many resistant point mutations in rRNAs as possible (Miyazaki, Kitahara, 2018). There is limited information about point mutations in 16S rRNA and 23S rRNA genes in *Salmonella* isolated from retail meats in Vietnam. Thus, this study aims to detect point mutations in 16S rRN*A* and 23S rRNA genes, which is one of keys to prevent the spread of multidrug-resistant *Salmonella* serovars.

MATERIALS AND METHODS

Collection and preparation of samples

A total of 25 *Salmonella* serovars were serotyped and received from laboratory in Institute of Genome Research, Vietnam Academy of Science and Technology, including 2 *S. warragul*, 1 *S. london*, 4 *S. derby*, 2 *S. indiana*, 1 *S. meleagridis*, 1 *S. give*, 2 *S. rissen*, 11 *S. typhimurium* and 1 *S. assine*. The originated strains from pork, beef and chicken meat at retail markets in Hanoi, Vietnam.

Antibiotic susceptibility tests

The antimicrobial susceptibility test was performed according to the Clinical and Laboratory Standards Institute (CLSI-2015) and used the disk diffusion method as Kirby-Bauer's description. Drug susceptibility was tested on the Muller Hinton agar plates. Cultures were grown at 37^{o}C for 18-24 h in Brain Heart Broth Infusion (Biolife-Italia) and prepared on Mueller-Hinton agar. The antibiotic disks were placed aseptically on it and plates were incubated at 37^{o}C for 16-18 h.

The eight tested antimicrobials were often used in husbandry and treatment of animal farms as well as human diseases in Vietnam such as ampicillin (AMP) 10 µg, ceftazidime (CAZ) 30 µg, gentamicin (GEN) 10 µg, streptomycin (STR) 10 µg, ciprofloxacin (CIP) 5 µg, chloramphenicol (CHL) 30 µg, tetracycline (TET) 30 µg, and trimethoprim/sulfamethoxazole (SXT) 1.25/23.75 µg (BD Diagnostics).

RNA sequencing and virulence gene detection

Total RNA was extracted from *Salmonella* spp. according to the manufacturer's instructions (TRIzol Reagent, Life Technologies Inc.). RNA was concentrated and purified with an RNA MinElute kit (Qiagen). mRNA-seq libraries were produced from 1 µg of genomic RNA libraries, following the TruSeq Nano DNA Sample Preparation Guide, Part # 15041110 Rev. Library preparations were sequenced on a HiSeq4000 (Illumina) platform (Next Generation Sequencing Div. MACROGEN, Inc., Daejeon, Korea) using TruSeq Nano DNA Kit. The trimmomatic program was used to remove adapter sequences. The trimmomatic program was used to remove adapter sequences. All subsequent analyses were based on high quality, clean data. Transcriptome *de novo* assembly using automated parameters in Geneious R11 software (Kearse *et al.*, 2012). The 16S rRNA gene mutations were analyzed using ResFinder (Center for Genomic Epidemiology) (Zankari *et al.*, 2012).

RESULTS

Antibiotic resistance of *Salmonella* isolates

Twenty-five *Salmonella* spp. were tested for

antibiotic resistance against 8 antibiotics. All strains were susceptible to CAZ, and 52% of the isolates were resistant to at least one antibiotic (data not showed). Total 9 *Salmonella* isolates were shown the multi-antimicrobial resistance, including one *S. meleagridis*, one *S. derby*, one *S. give*, three *S. typhimurium*, one *S. warragul*, one *S. indiana*, and one *S. rissen*). In addition, *S. indiana* isolate from chicken showed resistance to 8 antibiotics (Table 1).

In silico 16S rRNA and 23S rRNA gene mutation analysis

Six out of nine multidrug resistance samples were selected for mRNA sequencing, including *S. indiana* (Sal 4), *S. derby* (Sal 6), *S. give* (Sal 7), *S. typhimurium* S360 (Sal 8), *S. typhimurium* S384 (Sal 11), and *S. typhimurium* S181 (Sal 12). A total of 193 point mutations were identified (64 point mutations in 16S rRNA and 129 point mutations in 23S rRNA). A listing over the mutations among isolates was presented in Table 2.

Table 1. Susceptibility results of multidrug-resistant *Salmonella* isolates.

***Salmonella* serovar**	**Antibiotics**							
	AMP	**CAZ**	**GEN**	**STR**	**CIP**	**CHL**	**TET**	**SXT**
Indiana	R	S	R	R	R	R	R	R
Rissen	S	S	S	R	S	R	R	R
Warragul	S	S	S	S	S	R	R	R
Typhimurium S384	R	S	R	R	S	R	R	R
Give	R	S	S	R	S	R	R	R
Meleagridis	R	S	S	R	S	R	R	R
Derby	R	S	S	R	S	S	R	S
Typhimurium S181	R	S	S	R	S	S	R	S
Typhimurium S360	R	S	S	R	S	R	R	R

Abbreviations: R (resistant); S (sensitive)

Table 2. Mutations in 16S *rRNA* and 23S *rRNA* genes among isolates.

Sal 4	**Sal 6**	**Sal 7**	**Sal 8**	**Sal 11**	**Sal 12**
16S_rrsD r.45A>G	16S_rrsD r.54A>G	16S_rrsD r.54A>G	16S_rrsD r.54A>G	16S_rrsD r.45A>G	16S_rrsD r.45A>G
16S_rrsD r.54A>G	16S_rrsD r.642G>T	16S_rrsD r.248C>A	16S_rrsD r.636T>A	16S_rrsD r.54A>G	16S_rrsD r.54A>G
16S_rrsD r.248C>T	16S_rrsD r.744T>C	16S_rrsD r.642G>T	16S_rrsD r.645G>A	16S_rrsD r.702T>C	16S_rrsD r.702T>C
16S_rrsD r.260A>G	16S_rrsD r.756G>C	16S_rrsD r.726T>C	16S_rrsD r.648C>T	16S_rrsD r.756G>C	16S_rrsD r.756G>C
16S_rrsD r.891C>T	16S_rrsD r.1164T>C	16S_rrsD r.756G>C	16S_rrsD r.891C>T	16S_rrsD r.1047C>T	16S_rrsD r.1047C>T
16S_rrsD r.933G>A	16S_rrsD r.1272G>C	16S_rrsD r.900G>T	16S_rrsD r.1047C>T	16S_rrsD r.1095T>G	16S_rrsD r.1095T>G
16S_rrsD r.1017C>T	16S_rrsD r.1441T>C	16S_rrsD r.921G>A	16S_rrsD r.1095T>G	16S_rrsD r.1128C>T	16S_rrsD r.1128C>T
16S_rrsD r.1047C>T	16S_rrsD r.1650A>G	16S_rrsD r.1095T>G	16S_rrsD r.1164T>C	16S_rrsD r.1164T>C	16S_rrsD r.1164T>C
16S_rrsD r.1050C>T	16S_rrsD r.1749G>A	16S_rrsD r.1161G>A	16S_rrsD r.1212A>G	16S_rrsD r.1212A>G	16S_rrsD r.1212A>G
16S_rrsD r.1095T>G	16S_rrsD r.1836C>T	16S_rrsD r.1218A>G	16S_rrsD r.1281T>C	16S_rrsD r.1293T>C	16S_rrsD r.1293T>C
16S_rrsD r.1164T>C	16S_rrsD r.1860T>C	16S_rrsD r.1254C>T	16S_rrsD r.1287T>C	16S_rrsD r.1344T>C	16S_rrsD r.1344T>C
16S_rrsD	16S_rrsD	16S_rrsD r.1281T>C	16S_rrsD	16S_rrsD r.1356G>A	16S_rrsD r.1356G>A

Sal 4	Sal 6	Sal 7	Sal 8	Sal 11	Sal 12
r.1173C>T	r.1863C>T		r.1293T>C		
16S_rrsD r.1197C>T	16S_rrsD r.1866G>A	16S_rrsD r.1293T>C	16S_rrsD r.1344T>C	16S_rrsD r.1441T>C	16S_rrsD r.1441T>C
16S_rrsD r.1212A>G	16S_rrsD r.1917A>G	16S_rrsD r.1344T>C	16S_rrsD r.1356G>A	16S_rrsD r.1462C>T	16S_rrsD r.1462C>T
16S_rrsD r.1218A>G	16S_rrsD r.2103T>C	16S_rrsD r.1356G>A	16S_rrsD r.1455T>C	16S_rrsD r.1665G>A	16S_rrsD r.1665G>A
16S_rrsD r.1281T>C	16S_rrsD r.2424A>T	16S_rrsD r.1506C>T	16S_rrsD r.1833C>T	16S_rrsD r.1752C>T	16S_rrsD r.1752C>T
16S_rrsD r.1287T>C	16S_rrsD r.2442C>A	16S_rrsD r.1650A>G	16S_rrsD r.1836C>T	16S_rrsD r.1819T>C	16S_rrsD r.1819T>C
16S_rrsD r.1293T>C	23S r.78T>C	16S_rrsD r.1836C>T	16S_rrsD r.1860T>C	16S_rrsD r.1860T>C	16S_rrsD r.1860T>C
16S_rrsD r.1344T>C	23S r.137T>A	16S_rrsD r.1860T>C	16S_rrsD r.1917A>G	16S_rrsD r.1917A>G	16S_rrsD r.1917A>G
16S_rrsD r.1356G>A	23S r.142A>T	16S_rrsD r.1881C>G	16S_rrsD r.1932C>G	16S_rrsD r.1920C>T	16S_rrsD r.1920C>T
16S_rrsD r.1506C>T	23S r.264C>G	16S_rrsD r.1917A>G	16S_rrsD r.2196C>A	16S_rrsD r.2424A>T	16S_rrsD r.2424A>T
16S_rrsD r.1710G>A	23S r.284T>C	16S_rrsD r.1926A>G	16S_rrsD r.2424A>T	16S_rrsD r.2442C>A	16S_rrsD r.2442C>A
16S_rrsD r.1740C>T	23S r.285G>A	16S_rrsD r.2298T>C	16S_rrsD r.2442C>A	23S r.451T>C	
16S_rrsD r.1836C>T	23S r.348A>G	16S_rrsD r.2352C>T		23S r.562A>T	
16S_rrsD r.2424A>T	23S r.349T>C	16S_rrsD r.2355T>C		23S r.569T>C	
16S_rrsD r.2442C>A	23S r.353C>T	16S_rrsD r.2367A>G		23S r.577A>G	
23S r.138T>C	23S r.544C>G	23S r.149C>G		23S r.1165delC	
23S r.142A>T	23S r.547A>T	23S r.169T>C		23S r.1167_1168insT	
23S r.264C>G	23S r.548G>A	23S r.170G>A		23S r.1170T>G	
23S r.284T>C	23S r.549G>C	23S r.651T>C		23S r.1178C>T	
23S r.285G>A	23S r.550_551insT	23S r.762A>T		23S r.1567T>C	
23S r.348A>G	23S r.613A>T	23S r.769T>C		23S r.1888T>G	
23S r.349T>C	23S r.626A>C	23S r.777A>G			
23S r.353C>T	23S r.646T>C	23S r.1272A>G			
23S r.354A>G	23S r.766T>C	23S r.1285T>C			
23S r.504A>C	23S r.877A>T	23S r.1597T>C			
23S r.543G>C	23S r.884T>C	23S r.1599T>C			
23S r.547A>C	23S r.892A>G	23S r.1608G>A			
23S r.550C>G	23S r.1171G>A	23S r.1611C>G			
23S r.626A>C	23S r.1174T>G	23S r.1612C>A			
23S r.646T>C	23S r.1175delA	23S r.1613C>T			
23S r.766T>C	23S r.1178C>T	23S r.1615C>T			
23S r.877A>T	23S r.1211C>T	23S r.1616G>A			
23S r.884T>C	23S r.1219T>G	23S r.1618G>T			
23S r.892A>G	23S r.1220G>C	23S r.1619G>C			
23S r.1171G>A	23S r.1229C>G	23S r.1631A>G			
23S r.1174T>C	23S r.1230A>T	23S r.1750T>C			
23S r.1176T>G	23S r.1392A>G	23S r.1767T>C			
23S r.1178C>T	23S r.1405T>C	23S r.2088T>G			
23S r.1219T>G	23S r.1719T>C	23S r.2096A>G			
23S r.1220G>C	23S r.1730G>A	23S r.2678C>G			
23S r.1229C>G	23S r.1733C>G	23S r.2679C>A			
23S r.1230A>T	23S r.1734C>A	23S r.2683T>A			
23S r.1387A>G	23S r.1735C>T	23S r.2687G>T			

Sal 4	Sal 6	Sal 7	Sal 8	Sal 11	Sal 12
23S r.1400T>C	23S r.1737C>T	23S r.2688G>C			
23S r.1523T>C	23S r.1738G>A				
23S r.1712T>C	23S r.1740G>T				
23S r.1723G>A	23S r.1741G>C				
23S r.1726C>G	23S r.1753A>G				
23S r.1727C>A	23S r.1872T>C				
23S r.1728C>T	23S r.1889T>C				
23S r.1730C>T	23S r.2210T>G				
23S r.1731G>A	23S r.2800C>G				
23S r.1733G>T	23S r.2801C>A				
23S r.1734G>C	23S r.2805T>A				
23S r.1746A>G	23S r.2809G>T				
23S r.1865T>C	23S r.2810G>C				
23S r.1882T>C					
23S r.2203T>G					
23S r.2793C>G					
23S r.2794C>A					
23S r.2798T>A					
23S r.2802G>T					
23S r.2803G>C					
23S r.56A>G					
23S r.78T>C					
23S r.113T>A					
23S r.114T>C					
23S r.137T>A					
23S r.142A>T					
23S r.146T>C					
23S r.147G>A					
23S r.210A>G					
23S r.211T>C					
23S r.215C>T					
23S r.216A>G					

DISCUSSION

The rRNA is the most commonly exploited RNA target for antibiotics. The bacterial ribosome comprises 30S and 50S ribonucleoprotein subunits, contains a number of binding sites for antibiotics and is an target for novel antibacterial agents (Howard *et al.*, 1996). Bacterial ribosomes have two ribonucleoprotein subunits. The bacterial rRNA includes 5S, 16S and 23S rRNA, the smallest (5S rRNA) being an approximately 120 nt RNA. The smaller 30S subunit contains a single approximately 1500 nt RNA (16S rRNA) and about 20 different proteins while the larger 50S subunit contains an approximately 2900 nt RNA (23S rRNA) and about 30 different proteins (Moore, 2001). Aminoglycosides are a group of well-known antibiotics that have been used successfully for more than half a century. Streptomycin and gentamycin are typical antibiotics which function by binding to specific sites on bacterial rRNA and affecting the fidelity of protein synthesis. The rRNA aminoacyl-tRNA site (rRNA A-site) is a major target for aminoglycosides which selectively kills bacterial cells. Binding of drug to the 16S subunit near the A-site of the 30S subunit leads to a decrease in translational accuracy and inhibition of the translocation of the ribosome (Thomas, Hergenrother, 2008).

There are three main mechanisms for microorganisms to acquire antibiotic resistance such as (i) enzymatic inactivation or modification of antibiotics (e.g. β-lactamases inactivate penicillin) (Li, Nikaido, 2009); (ii) acquisition of mutations in target sites of the antibiotics; and (iii) decreasing the

net drug concentration in the cell by reducing drug permeability via cell wall or by increasing the activity of efflux pumps (e.g. tetracycline resistance) (Bassetti *et al.*, 2017). Among these, acquisition of mutations in target sites of the antibiotics is often observed for ribosome targeting drugs such as streptomycin, gentamycin; the former three are known to target the 30 S subunit that contains the 16 S rRNA as its main component, whereas the others are known to attack the 50 S subunit that contains the 23 S rRNA as its main component (Wilson, 2006). There are a large number of antibiotics that target the ribosome. This is because ribosomes play a crucial role in protein biosynthesis, translating messenger RNA-encoded genetic information into proteins, which consists of sequential multistep reactions such as initiation, elongation, termination, and recycling. There are different kinds of inhibitors targeting each step of the translation process (Lambert, 2012; Wilson, 2006; Wilson, 2014). As the ribosome is RNA-rich, and functionally critical sites exist mainly on RNAs (the decoding center in 16S rRNA and peptidyl transferase center in 23 S *rRNA*), many antibiotic target sites exist on rRNAs, as do several resistant point mutations (Hong *et al.*, 2014; Noller, Yassin *et al.*, 2005).

Many antibiotics inhibit the growth of bacteria by targeting protein biosynthesis. Streptomycin has been shown to interact directly with the small ribosomal subunit. The ribosome accuracy center is a highly conserved component of the translational apparatus, comprising an rRNA domain and several polypeptides of the small subunit. Mutations within rRNA genes have been found to confer drug resistance; for some of these mutations experimental proof for a cause-effect relationship has been provided (Andersson, Hughes, 2011; Cocozaki *et al.*, 2016; Smith *et al.*, 2013; Springer *et al.*, 2001).

We have provided a comprehensive summary of the point mutations in 16S rRNA and 23S rRNA genes expression across the multidrug-resistant *Salmonella*. The mRNA-seq of *Salmonella* isolates showed the collective expression of 193 point mutations genes conferring resistance to gentamycin and streptomycin. The presence of these genes could contribute to the pathogenicity of these *Salmonella* isolates and also indicates the potential for these isolates to resist various antibiotics. In this study, point mutations detected in Sal 4 and Sal 11 exhibited 100% concordance, with all isolates displaying phenotypic resistant to gentamycin and streptomycin and all containing point mutations typically associated with resistance to these antimicrobials (Table 1 and Table 2). Likewise, all of six streptomycin resistant strains carried point mutations. Despite the concordance between genotypic and phenotypic in Sal 4 and Sal 11, there were some examples of disagreement. Most notably, there were four isolates (Sal 6, Sal 7, Sal 8, and Sal 12) that possessed point mutation genes (Table 2) but were not resistant to gentamycin (Table 1). A blast search released that these novel point mutation has not been reported previously in any organism. This result suggested that these point mutations are associated with resistance to streptomycin, and mutations expression in Sal 4 and Sal 11 are involved with gentamycin and streptomycin resistance in our isolates. Further studies are necessary in order to conclude association between these point mutations and gentamycin and streptomycin resistant in six isolates.

CONCLUSION

Antibiotic resistance is a serious problem, more and more pathogenic bacterial are developing immunity to widely used antibiotics, rendering them useless. Tremendous effort is being made to identify the mechanisms and mutations that lead to bacterial resistance to antibiotics. Understanding this can help ensure we can effectively treat multidrug *Salmonella* resistant infections. Our results suggest that there are many unfound and uncharacterized antibiotic resistance point mutations in rRN*A* genes. These mutations might contribute to streptomycin resistant in *Salmonella* serovars. This result is only a prediction, further validation is required.

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PHÁT HIỆN ĐỘT BIẾN GEN *16S rRNA* VÀ *23S rRNA* TRONG CÁC CHỦNG *SALMONELLA* ĐA KHÁNG THUỐC ĐƯỢC PHÂN LẬP TỪ CÁC NGUỒN KHÁC NHAU BẰNG PHƯƠNG PHÁP GIẢI TRÌNH TỰ RNA-SEQ

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TÓM TẮT

Sự gia tăng của vi khuẩn kháng thuốc đang xảy ra trên toàn thế giới. Kháng kháng sinh là một vấn đề

nghiêm trọng đối với con người, vì các vi sinh vật gây bệnh có khả năng kháng thuốc sẽ làm mất tác dụng của kháng sinh. Cơ chế kháng thuốc ở vi khuẩn bao gồm các kênh bơm thải thuốc, cải biến và làm thoái biến thuốc, đột biến, thay đổi đích tác động của thuốc. Tuy nhiên, hiểu biết của chúng ta về cách vi khuẩn kháng kháng sinh vẫn còn rời rạc, đặc biệt là đối với các thuốc có đích tác động là ribosome. *Salmonella* là một nguyên nhân hàng đầu gây ô nhiễm thực phẩm trên thế giới. Số lượng vi khuẩn kháng kháng sinh này phân lập được ở người đang tăng lên, cho thấy sự lây lan của các loài vi khuẩn kháng kháng sinh là mối đe dọa lớn đối với sức khỏe cộng đồng. *Salmonella* thường có mặt trong một lượng lớn các loài động vật, trong thức ăn, và môi trường, nhưng kiến thức của chúng ta về cách *Salmonella* kháng thuốc vẫn còn chưa rõ ràng. Do đó, mục đích của nghiên cứu này là hỗ trợ trong việc nghiên cứu các cơ chế mới giúp vi khuẩn các kháng kháng sinh có đích tác động là ribosome. Chúng tôi sàng lọc biểu hiện đột biến của các gen 16S rRNA và 23S rRNA ở các loài *Salmonella* đa kháng kháng sinh phân lập được từ thịt bán lẻ ở khu vực Hà Nội, Việt Nam. Kết quả đã xác định được 193 đột biến điểm (64 đột biến ở gen 16S rRNA và 129 đột biến ở gen 23S rRNA). Những đột biến này có thể có vai trò trong đề kháng kháng sinh streptomycin. Kết quả này cho thấy rằng còn nhiều đột biến kháng kháng sinh vẫn còn chưa được biết đến, ngay cả đối với các kháng sinh cổ điển. Nghiên cứu này chỉ là kết quả sơ bộ, việc đánh giá thực nghiệm cần được tiến hành trước khi được áp dụng ở *Salmonella* và các loài vi khuẩn khác.

Từ khóa: *Salmonella* đa kháng thuốc, đột biến điểm, 16S rRNA, 23S rRNA, giải trình tự mRNA