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Mutation in the Quinolone Resistance-Determining Region (QRDR) of the *gyrA* Gene in Ciprofloxacin-Resistant *Salmonella typhi*



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Abstract

The emergence of fluoroquinolone-resistant *Salmonella enterica* serovar Typhi poses a serious public health challenge, particularly in developing countries where ciprofloxacin is commonly used for treatment. This study investigated mutations in the quinolone resistance-determining region (QRDR) of the *gyrA* gene in ciprofloxacin-resistant *S. typhi* isolates obtained in Sokoto, Nigeria. Four previously identified ciprofloxacin-resistant clinical isolates were subjected to biochemical characterization, minimum inhibitory concentration (MIC) determination, polymerase chain reaction (PCR) amplification, and sequencing of the *gyrA* gene. MIC analysis revealed varying levels of resistance among the isolates, with values ranging from 2 µg/ml to 512 µg/ml. PCR amplification successfully detected the *gyrA* gene in all isolates, producing amplicons of approximately 318 base pairs. Sequencing analysis of the amplified gene showed 93% similarity with the reference sequence of *Salmonella enterica* serovar typhi strain CT18 from the NCBI database. A point mutation was identified at nucleotide position 249 within the QRDR, resulting in an amino acid substitution from Aspartate to Histidine. Structural analysis further indicated that this substitution occurs near the quinolone resistance-determining region, potentially affecting the interaction between DNA gyrase and ciprofloxacin. These findings suggest that mutations in the *gyrA* gene contribute to ciprofloxacin resistance in *S. typhi* isolates in Sokoto. Continuous surveillance and molecular characterization of resistant strains are essential to guide effective antimicrobial therapy and control the spread of resistant pathogens.

Keywords: Ciprofloxacin resistance; *Salmonella Typhi*; *gyrA* gene; Quinolone resistance-determining region (QRDR); Polymerase Chain Reaction (PCR).

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INTRODUCTION

Antimicrobial resistance has become one of the most serious global health challenges of the 21st century. It occurs when microorganisms develop the ability to withstand the effects of antimicrobial agents that were previously effective in treating infections. This phenomenon may arise through intrinsic resistance in certain bacteria, spontaneous genetic mutations, or through the acquisition of resistance genes from other microorganisms. The widespread emergence and dissemination of resistant pathogens threatens the effectiveness of modern medicine. Recent global estimates indicate that antimicrobial resistance was associated with millions of deaths worldwide, and without effective intervention the annual mortality could reach about 10 million by the year 2050 (Murray et al., 2022; O'Neill, 2016). Several factors contribute to the development and spread of antimicrobial resistance. The inappropriate and excessive use of antibiotics in both human and veterinary medicine, as well as their extensive application in agriculture, have accelerated the evolution of resistant microorganisms. In addition, the slow development of new antimicrobial agents by the pharmaceutical industry has further complicated the problem (Ventola, 2015; Laxminarayan et al., 2013). Among bacterial pathogens, increasing resistance has been reported in *Salmonella enterica*, an important cause of foodborne and systemic infections worldwide. Of particular concern is resistance to fluoroquinolone antibiotics such as Ciprofloxacin, which are widely used for the treatment of invasive salmonellosis (Fabrega & Vila, 2013). Quinolones constitute a large group of synthetic antimicrobial agents with broad-spectrum activity against many bacterial pathogens. The earliest member of this class, Nalidixic acid, served as the foundation for the development of newer quinolone derivatives. Over time, improved compounds known as fluoroquinolones were developed, offering enhanced antibacterial activity and better pharmacokinetic properties. These antibiotics have become widely used in clinical practice because of their effectiveness against a variety of Gram-negative and Gram-positive bacteria (Ball, 2000; Hooper & Jacoby, 2016). The antibacterial activity of quinolones is mainly directed against bacterial type II topoisomerases, particularly DNA gyrase and topoisomerase IV. DNA gyrase plays a crucial role in bacterial DNA replication and transcription by introducing negative supercoils into the DNA molecule, thereby maintaining proper DNA topology within the bacterial cell. Inhibition of this enzyme disrupts DNA replication and ultimately leads to bacterial cell death (Ruiz, 2003). Resistance to quinolones in *Salmonella* is most associated with mutations in the *gyrA* gene, which encodes the A subunit of DNA gyrase. These mutations are typically concentrated within a specific portion of the protein known as the quinolone resistance-determining region (QRDR). This region usually spans amino acid residues 67 to 106 of the *gyrA* protein. Mutations occurring within this region reduce the binding affinity of quinolone antibiotics to their target enzymes, thereby conferring resistance (Griggs et al.,

1996; Fabrega & Vila, 2013). Among the various mutations reported, substitutions at amino acid positions Ser-83 and Asp-87 are the most frequently observed in quinolone-resistant strains. Amino acid changes at Ser-83 may involve replacement with phenylalanine, tyrosine, or alanine, whereas substitutions at Asp-87 may include glycine, asparagine, or tyrosine. In some isolates of *Salmonella enterica* serovar Typhimurium, simultaneous mutations at both positions have been associated with high-level resistance to fluoroquinolone antibiotics (Giraud et al., 2006; Piddock, 2002). In Nigeria, *Salmonella* infections remain a major public health concern, contributing significantly to morbidity and occasionally mortality. Like many developing countries, treatment of salmonellosis in Nigeria largely depends on first-line antibiotics, particularly ciprofloxacin. However, the increasing emergence of ciprofloxacin-resistant strains poses a challenge to effective treatment and highlights the need for continuous monitoring of resistance mechanisms. Therefore, this study was conducted to investigate possible mutations in the *gyrA* gene of ciprofloxacin-resistant clinical isolates of *Salmonella enterica* serovar Typhi obtained from the bacterial reserve of microbiology Lab of Federal University Gusau, Zamfara State, Nigeria. Understanding the genetic basis of fluoroquinolone resistance will provide useful information for surveillance and management of antimicrobial-resistant *Salmonella* infections

Methodology

Sample Collection

Fifty (50) clinical strains of *S. typhi* previously isolated and utilized by our research team were used in this study. These strains had earlier been confirmed to be resistant to ciprofloxacin and were recovered from the Microbiology Laboratory of the Federal University Gusau. No direct patient sampling was conducted during this study. Subsequently, biochemical tests were performed to reconfirm the identity and resistance characteristics of the strains

Biochemical characterization and identification of *Salmonella typhi*

The following biochemical tests were carried out to characterize *Salmonella typhi*

Citrate test

A little portion of the isolate was inoculated into Koser citrate medium and incubated at 37°C for 72 hours. A positive citrate was confirmed by formation of bright blue colour while the initial green colour of the medium to donate negative test (Manga & Oyeleke, 2008).

Urease test

With the aid of a sterile wire loop, urea containing medium with phenol red indicator was inoculated with sample obtained from enrichment broth. A change in colour of the indicator from pink to red indicated a positive test for urease activity (Cheesbrough, 2000).

Indole test

Indole test was conducted using a method described by Manga & Oyeleke (2008). A little portion of the isolate was inoculated into 5ml peptone water enriched with 1% to tryptophan, then incubated for 48 hours at 37°C. While shaken gently, 0.5ml of Kovac's reagent was added. A positive test for indole was the formation of red layer on the surface of the medium. A yellow layer at the surface of the medium denotes a negative test for indole.

Methyl red (MR) and Voges-Proskauer (VP) test

These tests were carried out as described by Ochei & Kolhatkar (2000). A little portion of each isolate was inoculated into a glucose phosphate peptone water medium and was incubated at 37°C for 48 hours. Few drops of methyl red were added to the culture, MR positive test was indicated by red colour formation at the surface of the medium while no change denote negative test

Hydrogen sulphide production (H₂S) production

This was carried out as described by Cheesbrough, (2008). A little portion of each isolate was inoculated by streaking and stabbing into triple sugar medium and incubate at 37°C for 24 hours. Evolution of blackening on the medium indicated a positive test while no blackening indicated negative.

Motility test

This carried out as described by Singleton (1997). A little portion of each isolate are stabbed into a triple sugar iron agar and incubated at 37°C for 24 hours. Motility was observed by the spread of the organism outwards from the stabbed area.

Triple sugar ion test

Triple sugar ion was prepared with a sterile needle, the culture from the solid medium was streak on the surface of the slant and butt are stabbed 3 times. Incubation is at 37°C for 24 hours, gas was formed by the appearance of one or several bubbles. TSI glucose fermenters were indicated by the butt becoming yellow. If both the butt and slope were yellow, it indicates the fermentation of glucose and sucrose, fermentation of lactose and sucrose but not that of glucose was detected with red butt and yellow slope (Manga & Oyeleke, 2008).

Microscopy of isolated ciprofloxacin resistant *S. typhi*

This was carried out as described by Cheesbrough (2000). All the Screen isolates were used for gram staining. A little portion of each of the colony was emulsified in few drops of sterile distilled water on a clean glass slide thereby making a thin smear. The smear was heat fixed by rapid passing about 3 times through the flame of spirit lamp. The smear was allowed to cool before staining. The fixed smear was flooded with crystal violet stain for 60 seconds then rapidly washed with distilled water, which was tipped off. The smear was treated with Lugol's iodine and allow for 30 seconds after which it was then rinse with clean water. The smear was decolorized with acetone and washed immediately with distilled water then stained with safranines and allow for 60 seconds before washing off again distilled water. The slide was then placed on a draining rack for the smear to air dry. The smear was then

examined microscopically to check for the shape of bacteria.

Minimum inhibitory concentration of ciprofloxacin

The minimum inhibitory concentration (MIC) of ciprofloxacin against the 4 test isolates was determined using the broth microdilution method in sterile 96-well microtiter plates. Briefly, 90 µL of Mueller-Hinton broth was dispensed into each well of the microtiter plate. Also, 90µl of ciprofloxacin of initial of concentration of 1024 µg/ml solution was added to the first well and serial two-fold dilutions were performed across the wells to obtain decreasing concentrations of the antibiotic. A fresh bacterial suspension was prepared from overnight cultures and adjusted to the 0.5 McFarland turbidity standard. Subsequently, 10 µL of the standardized bacterial inoculum was added to each well to give a final volume of 100 µL per well. Wells containing broth and bacterial inoculum without ciprofloxacin served as the positive control, while wells containing broth only served as the negative control. The plate was incubated at 37 °C for 18–24 hours. After incubation, the wells were examined for visible turbidity, and the MIC was recorded as the lowest concentration of ciprofloxacin that inhibited visible bacterial growth.

DNA extraction of ciprofloxacin resistant *S. typhi*

DNA was extracted using the phenol chloroform method. An aliquot (1 mL) of the sample was centrifuged at 2,000 rpm, for 4 minutes and the pellet are resuspended in 474 mL of TE, 25 mL 10% SDS and 1.25 mL of 20mg/mL proteinase K then incubated at 55°C for 30 minutes. Exactly 500 mL of 1:1 phenol-chloroform (pH 5) was added, mixed vigorously then centrifuged at 10,000 x g, for 4 minutes. The aqueous phase was aspirated and transferred to a fresh microtube and the DNA precipitated with 3M sodium acetate and ice-cold isopropanol. Samples were centrifuged at 16,000 x g, for 10 minutes, and the pellets are then washed with 80% ethanol. Finally, resuspended in 50 mL of TE buffer and store at 4°C

PCR amplification of *gyrA* gene using DNA Isolated from ciprofloxacin resistant *S. typhi*

The target *gyrA* gene was amplified using the following primers forward 5' TAC CGT CAT AGT TAT CCA CGA 3' and Reverse 5'GTA CTT TAC GCC ATG AAC GT 3'. The primer was obtained from NCBI database. Two microlitre of each of the primers were added in tubes containing PCR premix, and 2µL of extracted DNA samples, the volume was made up to 20µL by adding 14µL of deionised water, two drops of mineral oil were added to the mixture to prevent evaporation. Amplification is carried out using the following protocol: Predenaturation at 95°C for 5mins, Denaturation at 95°C for 30sec, Annealing at 57°C for 30sec, Extension at 72°C for 40sec, Final extension at 72°C for 5mins. The procedure was run for X35 cycles

Gel electrophoresis of PCR amplicons using DNA isolated from ciprofloxacin resistant *S. typhi*

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Agarose gel 1.5 % was prepared by weighing 0.5 g of agarose powder in a conical flask, 50mL of triacetate EDTA was added, the solution was dissolved by heating in a microwave for 5 mins at 60 °C and allowed to cool. Later 4µL of ethidium bromide was added and the gel was allowed to cast after carefully placing the comb to create loading wells. Loading dye (2 µL) was mixed with 8 µL PCR amplicon using a pipette after which the mixture was loaded into the well, the first well contained 100bp DNA ladder. The gel was finally placed in TAE tank buffer and allowed to run for 30 minutes at 81 Volts. Electrophoresed amplicon bands were excised from the gel and dissolved in GB buffer (pH 7.5), and incubated at 50°C for 8mins, with gentle tapping of the tube until completely dissolved. Then 100µL of isopropanol was added, mixed and transferred into a DNA extracted and eluted with ethanol mini column, then centrifuged at 11 rpm for 60 secs. The flow through was discarded and the column was put back to the column tube, 750 µL of DNA washing powder was added and centrifuge at 11 rpm for 1 min, the flow through was discarded again. Residual ethanol was then removed by centrifuging the empty column at 11 rpm for 1 min. The column was placed in a clean 1.5 ml microcentrifuge tube, 30 µL of the elution buffer was added to the column and centrifuge at 11 rpm for 1min, and the DNA was then eluted.

Sequencing of ciprofloxacin resistant *S.typhi gyrA* gene amplicon

Extracted amplicon from electrophoresed gel as previously described was sequenced using DNA sequencer (ABI sequencing Machine, USA). The principle is based on the Sangers dideoxy method. Dye terminator cycles sequencing with quick start kit sequence reaction is prepared in 2.0 ml tube, all the reagents were kept on ice

while preparing the sequence reaction mixture according to the following protocol respectively. Exactly 4 µL of deionised water was added to the tube, 6 µL and 2 µL of DNA template and primers was then added to the tube respectively. Lastly 8 µL of DTSC quick start mix [containing dNTPs, ddNTPs, Trus-HCl, MgCl2, Reaction buffer (pH 8.9) and sequence DNA polymerase 1], were added to the mixture this was then placed in the PCR machine which was set as follows for optimization: Denaturation 95 °C for 20secs, Annealing 50 °C for 30secs, Extension 60 °C for 4mins. This procedure was run for X30 cycle. Immediately after the completion of the cycle, 10 µL of deionised water was added, 5 µL EDTA, 125 Mm EDTA, (pH 8.0) was also added to the mixture, followed by addition of 65 µL of 100% ethanol the mixture was vortexed gently then incubated at room temperature for 15 mins, after which the sample was centrifuged at 14000rpm at °C for 15mins. The supernatant was removed. 70% ethanol was added and centrifuge at 14000 rpm at 4 °C for another 2 mins. The supernatants were discarded with a micropipette. The sample was centrifuged at 30 °C for 7 mins to dry the pellet. Lastly the sample mixture was loaded in 96 well trays of sequencer and run. The result was then displayed on a computer monitor, the displayed colours represent distinct nucleotide base.

Results

Minimum inhibitory concentration of *S. typhi* Isolates

The bacterial isolates from **Sample 1** showed susceptibility to ciprofloxacin with MIC of 2 µg/ml **Sample 2** showed high susceptibility to this drug with an MIC of 512 µg/ml while **Isolates 3** and **4** showed an MIC of 256 µg/ml.

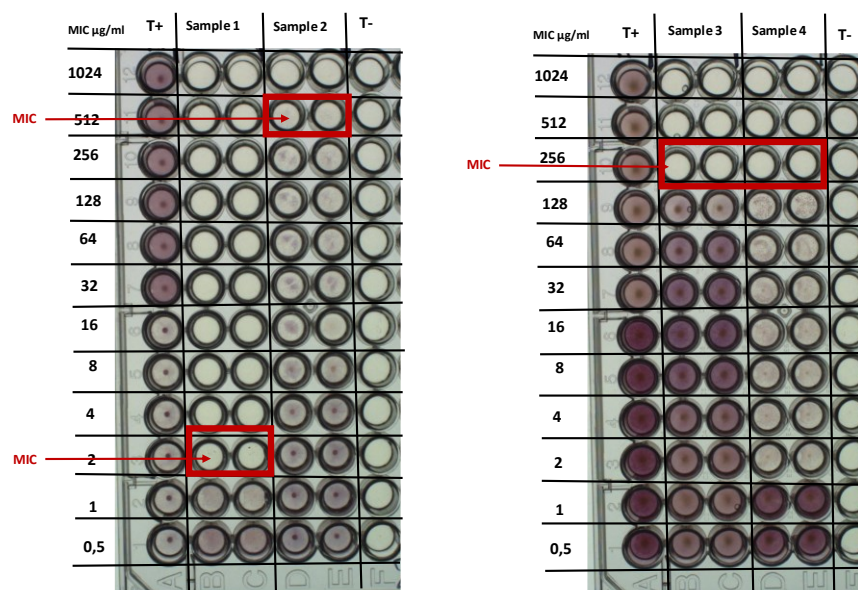


Figure 1: Minimum Inhibitory Concentration of *S. typhi* Isolates collected from the Microbiology Lab of Federal University Gusau

gyr A Gene Amplification by PCR

Presented in Figure 3 is the result of the polymerase chain reaction targeting *gyrA* gene present in DNA of isolated *S. typhi*. Bands in wells 1, 2, 3 and 4 are samples which were resistant to the antibiotics as shown in the MIC test. All the amplicon corresponds to the expected band size of our primer which is 318 base pairs

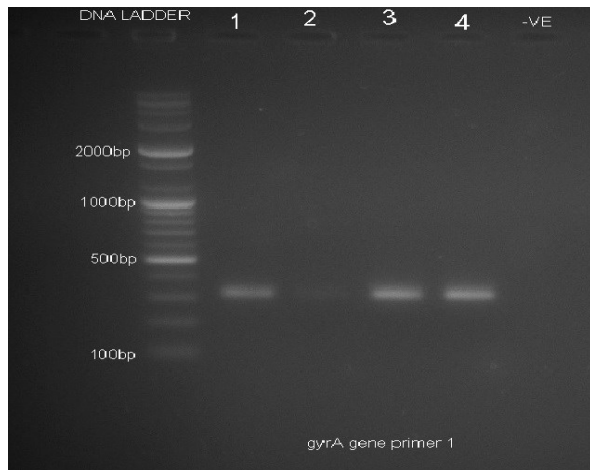


Figure 2: PCR Amplicons of *gyrA* Gene of Ciprofloxacin Resistant Strains of *S. typhi* Isolated

Sequence of the *gyrA* gene of *S. typhi* Sample 1

The result from sanger’s sequencing of the *gyrA* gene of Sample 1 gave a nucleotide sequence of 271 base pairs with the following 5’ – 3’ sequence:

5’CCGTATAAAAAATCTGCCCGTGTCGTTGGTGAC
GTAATCGGTAAATACCATCCCCATGGTGA CTGGC
GGTCTATGACACGATCGTCCGCATGGCGCAGCCAT
TCTCGCTGCGTTATATGCTGGTAGACGGTCAGGGT
AACTTCGGTTCTATCGACGGCGACTCTGCGGCGG
CAATGCGTTATACGAAATCCGTCTGGCGAAAATT
GCCCATGAACTGATGGCCGATCTCGAAAAAGAGA
CGGTTCGATTCGTGGATAACTATGACGGTA-3’

The nucleotide sequence showed 93 % BLAST alignment with the reference sequence of *S. enterica serovar typhi* strain CT18 *gyrA* gene deposited in the NCBI data base after the nucleotide BLAST in NCBI. After the BLAST point mutation were observed between the nucleotide sequence of reference and amplicon *gyrA* gene at position 249 of the nucleotides this region fall within a region called nucleotide resistance determining region which is a region on *gyrA* between amino acid 67 to 106, The observed mutation showed a nucleotide substitution from guanine (G) to cytosine (C) at the first position of the codon (GAT → CAT), resulting in a missense mutation that caused a change in the encoded amino acid from aspartate to histidine.

Table 1: NCBI BLAST Analyses of Point Mutations in *S. typhi gyr A* Gene Amplicon and CT18 Strain NCBI Reference Sequence

Percentage Identity	Nucleotide Mutation (Ref→Amp)	Amino Acid Mutation (Ref→Amp)
93%	249(GAT→CAT)	Aspartate-Histidine

Key: Ref = References Sequences of *S. enterica serovar typhi* Strain CT18 Obtained NCBI, USA (NC-003198.21)
Amp = Amplicon for Isolate *S. typhi*.

Three-dimensional structures of the *gyrA* gene amplicon of this study and reference sequence in NCBI CT18 strain sequence

Presented in Plates 4.2 and 4.3 are the three-dimensional protein ribbon structures of sequenced *gyrA* gene amplicon of this study and reference sequence in NCBI CT18 strain sequence. Superimposition of both structures shows region Aspartate-Histidine substitution lies in the vicinity of the quinolone resistance determining region (QRDR) indicated using purple dots.



Figure 3: Three-Dimensional Structure of *gyr A* Gene Amplicon of DNA Isolated from *S. typhi* of this study



Figure 4: Three-Dimensional Structure of Reference *S.typhi* CT18 Strain NCBI Reference Sequence obtain from NCBI

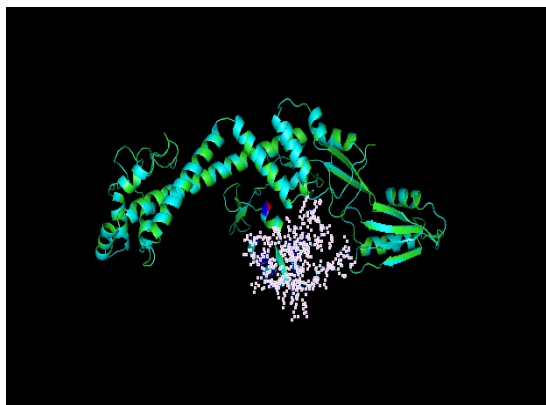


Figure 5: Superimposed 3D Protein Structure of CT18 Strain NCBI Reference Sequence and Isolated *S. typhi gyrA* Gene Amplicon

Discussion

This study investigated mutations in the quinolone resistance-determining region (QRDR) of the *gyrA* gene in ciprofloxacin-resistant *Salmonella enterica* serovar Typhi isolates obtained in Sokoto, Nigeria. Fluoroquinolones such as ciprofloxacin inhibit bacterial DNA replication by targeting DNA gyrase and topoisomerase IV, which are essential enzymes involved in DNA supercoiling and replication (Hooper & Jacoby, 2016; Ruiz, 2003). The MIC results showed high levels of resistance among the isolates, with values ranging from 2 µg/ml to 512 µg/ml. High MIC values indicate reduced susceptibility to ciprofloxacin and suggest that fluoroquinolone therapy may be less effective in treating infections caused by these strains. Similar findings have been associated with mutations in the QRDR region of the *gyrA* gene in *Salmonella* species (Fabrega & Vila, 2013; Piddock, 2002). PCR amplification successfully detected the *gyrA* gene in all isolates with the expected amplicon size of 318 base pairs, confirming the presence of the target gene. Sequence analysis revealed a point mutation at nucleotide position 249 within the QRDR, resulting in an amino acid substitution from aspartate to histidine. Mutations in this region are known to reduce the binding affinity of quinolone antibiotics to DNA gyrase, thereby contributing to antibiotic resistance (Griggs et al., 1996; Giraud et al., 2006). Three-dimensional protein structural analysis also indicated that the mutation occurred close to the QRDR, suggesting possible structural changes that may affect drug–enzyme interactions. These findings support previous reports that mutations in the *gyrA* gene play a key role in fluoroquinolone resistance in *Salmonella*. Overall, the results highlight the presence of ciprofloxacin-resistant *Salmonella Typhi* strains in Sokoto and emphasize the need for continuous surveillance of antimicrobial resistance and responsible antibiotic use to prevent further spread of resistant pathogens.

Conflict of Interest

The authors declare that there are no conflicts of interest associated with this study. This research was conducted independently, and the authors have no financial, personal,

or professional relationships that could have influenced the outcomes or interpretation of the results

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