Genotyping-Phenotypic correlation of S Typhi isolates provide insights for the design of novel anti microbial agents

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Abstract

Anti-microbial multidrug resistance is currently a major roadblock for the treatment of enteric fever. This is a major health problem in various different endemic regions and also extends to the travellers returning from the developing countries. Ceftriaxone has emerged as the drug of choice for fluoroquinolone resistant strains of *Salmonella* Typhi with azithromycin being used generally for uncomplicated cases of typhoid fever.

A genotypic - phenotypic analysis was conducted to identify resistance mechanisms linked to specific mutations in clinical isolates from the Indian subcontinent. Whole genome sequencing (WGS) was conducted for 133 clinical isolates from blood culture of typhoidal patients to predict antimicrobial resistance genes. DNA was extracted from each isolate and subjected to whole-genome sequencing (WGS) on the Illumina Mi-Seq platform. The possible genes were identified from the assembled sequences. The antimicrobial susceptibility of *S.* Typhi isolates against the 1st, 2nd and 3rd line-antibiotics were tested using the disc diffusion method and E-Test. A high genotype-phenotype correlation for chloramphenicol, ampicillin, co-trimoxazole, ciprofloxacin and ceftriaxone was observed in the studied isolates of *S.* Typhi. The conformational changes occurring due to the mutations in the *gyrA*/*gyrB* were further explored in the DNA gyrase protein. Further Quinazoline derivatives were designed and synthesized using structure-based drug design approach. The synthesized compounds were evaluated for their in vitro antimicrobial activity against multi-drug resistant S. Typhi strains. The DNA gyrase was cloned, expressed and purified to assess the inhibitory action of the designed compounds on the ATPase activity of the enzyme. Two of the developed compounds showed promised and can be explored for developing more effective therapeutic options.