in clinical isolates of *Enterococcus faecium* (Fiedler et al. 2016). A systematic approach to evaluate the potential of tetracycline resistance genes to evolve tigecycline resistance was attempted with the mutants of *tet*(A), *tet*(K), *tet*(M), and *tet*(X) (Linkevicius et al. 2015). All mutants selected were capable to decrease the susceptibility of *E. coli* host toward tigecycline. The authors predicted that *tet*(X) could become the most problematic since mutations can improve the weak intrinsic activity of *Tet*(X) against tigecycline without collateral loss of activity toward other tetracyclines (Linkevicius et al. 2015). Thus, the existing pool of resistance genes conferring resistance to the earlier tetracycline generations may serve as building blocks for the emergence of resistance to newer tetracyclines such as glycylcyclines.

23.11 Evolutionary Aspect of *tet*(X)

Another aspect that makes *tet*(X) even more problematic is the dynamic of its dissemination. These ecological aspects have been discussed by us earlier (Aminov 2009, 2013a). In our initial phylogenetic analyses, we established that TetX belongs to flavoprotein monooxygenases that hydroxylate specific regions in organic molecules and present in many metabolic pathways of the Bacteria, Archaea, and Eukarya (Harayama et al. 1992). Based on amino acid sequence and three-dimensional structure, they are distributed into six classes (A–F) (van Berkel et al. 2006). TetX belongs to the class A monooxygenases, which are involved in the microbial degradation of aromatic compounds by *ortho* or *para* hydroxylation of the aromatic ring (Moonen et al. 2002). Our phylogenetic analysis of class A monooxygenases uncovered the high diversity of these enzymes as well as their incongruence with the phylogeny that is based on standard markers such as the 16S rRNA gene (Aminov 2009). The latter may suggest extensive HGT processes during the evolution of class of flavoprotein monooxygenases. Another prominent feature of the genes encoding flavoprotein monooxygenases is frequent duplication events that accompanied their evolution. These genes are present in genomes of many bacterial species, with a wide-ranging ecological presence, including terrestrial, aquatic, and intestinal ecosystems, while some of these bacteria are opportunistic pathogens. These enzymes perform a broad range of biochemical reactions, which, interestingly, also include modification of various aromatic polyketide antibiotics other than tetracyclines such as rifampin (Andersen et al. 1997), mithramycin (Prado et al. 1999), griseorhodin (Li and Piel 2002), chromomycin (Menendez et al. 2004), and auricin (Novakova et al. 2005). Thus, TetX belongs to the class of enzymes that are ubiquitous in environmental microbiomes and perform many biochemical functions including modification of many antibiotics as concomitant functions.