The copper-containing membrane-bound monooxygenase enzyme family consists of enzymes facilitating the oxidation of methane (catalyzed by particulate methane monooxygenase, pMMO) and ammonia (catalyzed by ammonia monooxygenase, AMO), in both aerobic and anaerobic methanotrophs and nitrifiers, respectively, and the oxidation of C2-10 alkanes (catalyzed by particulate butane monooxygenase, pBMO). Despite catalyzing different substrates, pMMO, AMO and pBMO form catabolic enzymes related structurally and evolutionarily to each other, and are encoded by the genes pmoA, amoA and bmoA, respectively. It has been suggested that oxygen-dependent methane and ammonia monooxygenases evolved from a substrate-promiscuous ancestor after horizontal transfer(s) into new hosts, which eventually became methanotrophs and nitrifiers. However, no extensive studies have been conducted on molecular adaptation of the beta-peptide structure of pmoA, amoA and bmoA gene products, which form transmembrane polypeptides, and on selective pressures acting on them. Over 80 near-complete pmoA, amoA and bmoA gene from database were downloaded and analyzed to assess whether the combined amoA, pmoA and bmoA gene tree is congruent to the 16S rRNA gene tree for these microbes. The gene was separated into 15 segments and pairwise Ka/Ks values were calculated to assess the evolutionary and selection pressure exerted on these taxa, based on the hypothesis that they evolved from a methanotrophic ancestor, as well as calculate Ka/Ks values between members of each family. Our analyses indicated a high level of negative (or purifying) selection between and amongst all taxa. Ka/Ks values were highest between methanotroph pmoA and the anammox, and that the pmoA and amoA genes are under purifying selection their clusters, and supports the hypothesis that one of these genes likely arose from the other via horizontal gene transfer.