Hypermutable Pseudomonas aeruginosa isolates (hypermutators) have been identified in patients with cystic fibrosis (CF) and are associated with reduced lung function. Hypermutators display a greatly increased mutation rate and an enhanced ability to become resistant to antibiotics during treatment. Their prevalence has been established among patients with CF, but it has not been determined for patients with CF in Australia. This study aimed to determine the prevalence of hypermutable P. aeruginosa isolates from adult patients with CF from a health care institution in Australia and to characterize the genetic diversity and antibiotic susceptibility of these isolates. A total of 59 P. aeruginosa clinical isolates from patients with CF were characterized. For all isolates, rifampin (RIF) mutation frequencies and susceptibility to a range of antibiotics were determined. Of the 59 isolates, 13 (22%) were hypermutable. Whole-genome sequences were determined for all hypermutable isolates. Core genome polymorphisms were used to assess genetic relatedness of the isolates, both to each other and to a sample of previously characterized P. aeruginosa strains. Phylogenetic analyses showed that the hypermutators were from divergent lineages and that hypermutator phenotype was mostly the result of mutations in mutL or, less commonly, in mutS. Hypermutable isolates also contained a range of mutations that are likely associated with adaptation of P. aeruginosa to the CF lung environment. Multidrug resistance was more prevalent in hypermutable than nonhypermutable isolates (38% versus 22%). This study revealed that hypermutable P. aeruginosa strains are common among isolates from patients with CF in Australia and are implicated in the emergence of antibiotic resistance.