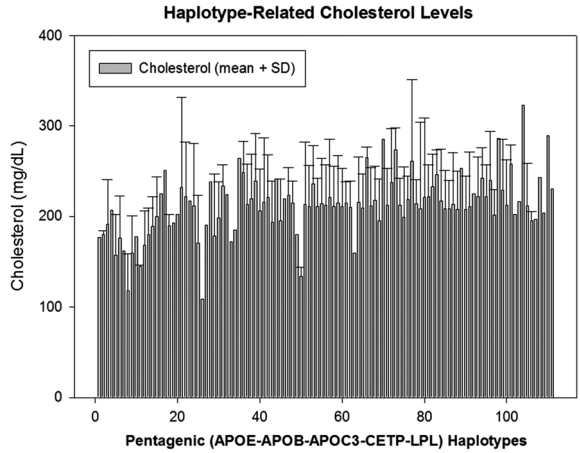

Figure 5.8 Pentagenic (APOE-APOB-APOC3-CETP-LPL) haplotype-related blood cholesterol levels in patients with Alzheimer's disease.

5.3 Pharmacogenomics

Pharmacogenomics accounts for 60–90% of the variability in pharmacokinetics and pharmacodynamics. The modest effect (and toxicity) of current AD and PD drugs (Tables 5.1 and 5.2) is in part due to their pharmacogenomic profile since over 70% of patients are deficient metabolizers.[6,11,18] The genes involved in the pharmacogenomic response to drugs in dementia fall into five major categories:

(i) Genes associated with disease pathogenesis: Mendelian mutations affect genes directly linked to AD, including >30 mutations in the amyloid beta precursor protein (*APP*) gene (21q21) (*AD1*); >160 mutations in the presenilin 1 (*PSEN1*) gene (14q24.3) (*AD3*); and >10 mutations in the presenilin 2 (*PSEN2*) gene (1q31-q42) (*AD4*).[53–57] *PSEN1* and *PSEN2* are important determinants of γ-secretase activity responsible for proteolytic cleavage of APP and NOTCH receptor proteins. Mendelian mutations are very rare in AD (1 : 1000). Mutations in exons 16 and 17 of the *APP* gene appear with a frequency of 0.30% and 0.78%, respectively, in AD patients. Likewise, *PSEN1*, *PSEN2*, and microtubule-associated protein Tau (*MAPT*) (17q21.1) mutations are present in less than 2% of the cases. Mutations in these genes confer specific phenotypic profiles to patients with dementia: amyloidogenic pathology associated with *APP*, *PSEN1* and *PSEN2* mutations and tauopathy associated with *MAPT* mutations representing the two major pathogenic hypotheses for AD.[53–59]

Multiple polymorphic risk variants can increase neuronal vulnerability to premature death. There are at least 695 genes potentially associated with AD,