Schimke immunoosseous dysplasia (SIOD), which is characterized by prominent spondyloepiphyseal dysplasia, T-cell deficiency, and focal segmental glomerulosclerosis, is a panethnic autosomal recessive multisystem disorder with variable expressivity. Biallelic mutations in switch/sucrose nonfermenting (swi/snf) related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1 (SMARCAL1) are the only identified cause of SIOD. However, among 72 patients from different families, we identified only 38 patients with biallelic mutations in the coding exons and splice junctions of the SMARCAL1 gene. This observation, the variable expressivity, and poor genotype-phenotype correlation led us to test several hypotheses including
modifying haplotypes, oligogenic inheritance, or locus heterogeneity in SIOD. Haplotypes associated with the two more common mutations, R820H and E848X, did not correlate with phenotype. Also, contrary to monoallelic SMARCAL1 coding mutations indicating oligogenic inheritance, we found that all these patients did not express RNA and/or protein from the other allele and thus have biallelic SMARCAL1 mutations. We hypothesize therefore that the variable expressivity among patients with biallelic SMARCAL1 mutations arises from environmental, genetic, or epigenetic modifiers. Among patients without detectable SMARCAL1 coding mutations, our analyses of cell lines from four of these patients showed that they expressed normal levels of SMARCAL1 mRNA and protein. This is the first evidence for nonallelic heterogeneity in SIOD. From analysis of the postmortem histopathology from two patients and the clinical data from most patients, we propose the existence of endophenotypes of SIOD.