Germline mutations of the MSR1 gene in prostate cancer families from Germany.

Abstract:
The MSR1 gene at 8p22 has been suggested as a candidate gene for hereditary prostate cancer because germline variants have been found to be associated with the disease. Aside from a single nonsense mutation (R293X) that was found repeatedly at low frequencies in several samples, little evidence has been gained by follow-up studies to confirm the gene's relevance for prostate cancer. Prompted by reasonable support for a linkage to 8p22, we sought to determine the mutation spectrum of MSR1 in our family sample. Screening of 139 probands (representing 139 prostate cancer families) revealed 15 novel and a total of 20 sequence variants within the 10 coding exons and their intronic proximities. Aside from the known mutation c.877C>T (R293X) present in two of our families, we identified a second nonsense allele (c.251C>G; S84X) and a splice-site mutation (c.818-1G>A) that results in mRNA instability (each in a single pedigree). The novel missense alleles were c.703C>T (H235Y), c.856C>T (P286S), c.905C>T (P302L), c.1193C>G (A398G), and c.1289A>G (K430R). Of the eight variants that affect the encoded protein (splice site, nonsense, and missense), only R293X as well as the polymorphism c.823C>G (P275A) were additionally present at remarkable frequencies in further samples of sporadic prostate cancer and controls. Of note, carriers of R293X were equally frequent in 367 sporadic prostate cancer cases (1.9%)
and in 197 controls (2.0%). To our knowledge, our study is the first to demonstrate further loss of
function variants of MSR1 apart from R293X. Nevertheless, the low frequencies of deleterious alleles,
in addition to an apparently moderate penetrance, does not support MSR1 as a major susceptibility
gene in this family sample.