Registry and Genetic Testing for Hereditary Non-polyposis Colorectal Cancer in Taiwan

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Hereditary nonpolyposis colorectal cancer (HNPCC) is caused by a deficiency in DNA mismatch repair in consequence of germline mutations mainly in the genes MSH2 and MLH1. The identification of mutations in germline mismatch-repair genes at the time of diagnosis of colorectal cancer is important in the management of the disease. From 2002 to 2005 a total of 100 Taiwanese un-related HNPCC families fulfilling the Amsterdam criteria (I or II) were registered at the NHRI. Searching for mutations the hMSH2 and hMLH1 genes has been completed in the 93 Taiwanese HNPCC families by using denaturing high performance liquid chromatography (DHPLC) analysis, DNA sequencing for the aberrant chromatograms, and multiplex ligation-dependent probe amplification (MLPA) analysis to determine the occurrence of large genomic deletions of MLH1 and MSH2.

Pathogenic mutations in MSH2 or in MLH1 were identified in 63 of 93 index patients (68%). In 15 patients, a pathogenic MSH2 mutation, and in 46 patients, a pathogenic MLH1 mutation was identified. Double mutations were identified in two index patients (one with a mutation each in MLH1 and MSH2; the other with two discrete mutations in MSH2 (Table 1). Overall we identified 14 large genomic deletions in 14 families and 29 point mutations in 49 families. Among the 29 point mutations, 19 mutations (found among 22 families) were novel, 12 in MLH1 and 7 in MSH2, while 10 mutations (found among 29 families) have been reported in the HNPCC database (http://www.insight-group.org) or elsewhere. Noteworthy is that most the mutations were identified in 1 index patients and some in 2 index patients except for two mutations that were significantly over-represented and accounted for 29% of all cases with pathogenic mutations: the mutation MLH1, c.793C>T was found in 13 index patients, and the mutation MLH1, c.1846_1848delAAG, was found in 5 patients. Thirteen families harbored a MLH1 c.793C>T mutation. A total of 81 cancers were noted in these families: 57 colon cancers, six rectal cancers, one endometrial cancer, five gastric cancers, and 12 other non-HNPCC related cancers. The 13 families are all living in the western Taiwan. Documented family histories indicated that the traceable ancestors of these families were not related to one another. All the seemingly unrelated families were native of Taiwan instead of Hakka, Aborigines, or the new-comer recently migrated from Mainland China in the 20th centuries. Thus, MLH1 c.793C>T could be a founder mutation in Taiwan.