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# Relationship of c-Kit Gene and Microsatellit Instability in the Pathogenesis of Wilms Tumors

Dear Editor,

Hereditary nonpolyposis colon cancer (HNPCC), known as Lynch syndrome (LS), is caused by germline mutations in one of five genes that function in the DNA mismatch repair (MMR) process involving MLH1, MSH2, MSH6 or PMS2 (1,2). Patients with mutations in MMR genes exhibit microsatellite instability (MSI), a phenomenon in which errors in replication of highly repetitive sequences cannot be repaired, resulting in alteration of the length of repeat sequences and eventually genomic integrity (2). Mutational spectra for genes with high MSI frequencies vary between different cancers. Therefore, only marker genes of MSI are analyzed for evaluation of MMR genes. It has been demonstrated that patients with LS almost always exhibit MSI due to underlying defects in MMR genes and especially MLH1 and MSH2 (3).

The importance of MSI and MMR has not been fully established in Wilms tumor (WT). In our earlier study, we evaluated MSI and MMR in 45 children with WT. Expressions of MLH1, MSH2, MSH6 and PMS2 were analyzed by immunohistochemistry of archival tissue sections. Real-time PCR melting analysis and fluorescence capillary electrophoresis (FCE) were performed to evaluate the MSI markers BAT25, BAT26, NR21, NR24, mono27, pentaD and pentaC genes in DNA extracted from tumor and normal tissues. MSI was observed in 6 cases but there was no association of MMR proteins and MSI with tissue expression. All MSIs were determined in the BAT-25 sequence of seven microsatellite marker genes (3). Interestingly, this microsatellite marker gene is localized in the human c-kit gene (4). We also found statistical significance between MSI and the size of the tumors (p=0.046). These findings were thought to indicate that the c-kit gene may play an important role in the development of WT. We therefore analyzed the c-kit gene in these six cases. Direct sequencing of PCR products for the c-kit gene was performed using the Beckman Genetic Analysis System. In three of the six cases, there were several genetic mutations in exon11 and exon17 of the c-kit gene (Table I, Figure1).

The KIT gene belongs to the family of class III receptor protein tyrosine kinases and KIT mutations have now been detected in several neoplasms (5,6). The use of tyrosine kinase receptor inhibitor has increasingly become a valuable therapeutic alternative in some KIT-related neoplasms (6).

**Table I:** C-kit mutation spectra of six cases

| | |
|---|---|
| **Case 1** | |
| Exon 9 | Wild type |
| Exon 11 | Wild type |
| Exon 13 | Wild type |
| Exon 17 | Wild type |
| **Case 2** | |
| Exon 9 | Wild type |
| Exon 11 | Wild type |
| Exon 13 | Wild type |
| Exon 17 | Wild type |
| **Case 3** | |
| Exon 9 | No PCR band |
| Exon 11 | No PCR band |
| Exon 13 | No PCR band |
| Exon 17 | No PCR band |
| **Case 4** | |
| Exon 9 | Wild type |
| Exon 11 | Wild type |
| Exon 13 | Wild type |
| Exon 17 | p.R804Q or c.2411G>A |
| **Case 5** | |
| Exon 9 | Wild type |
| Exon 11 | p.W557C or c.1671G>C; p.E562K or c.1684G>A |
| Exon 13 | Wild type |
| Exon 17 | Wild type |
| **Case 6** | |
| Exon 9 | Wild type |
| Exon 11 | p.P551H or c.1652C>A |
| Exon 13 | Wild type |
| Exon 17 | Wild type |

Hitherto it has been shown that KIT overexpression or KIT mutations are rare in WT, although they do appear to confer a worse prognosis (6,7). In our study, there were no statistically significant correlations between MSI positivity, and clinical prognostic factors such as bilateralism, stage and survival. However, MSI was correlated with the size of tumors. The mean diameter was 11.67±2.8cm in tumors with MSI and 8.92±2.85cm in tumors with microsatellite stability (MSS).

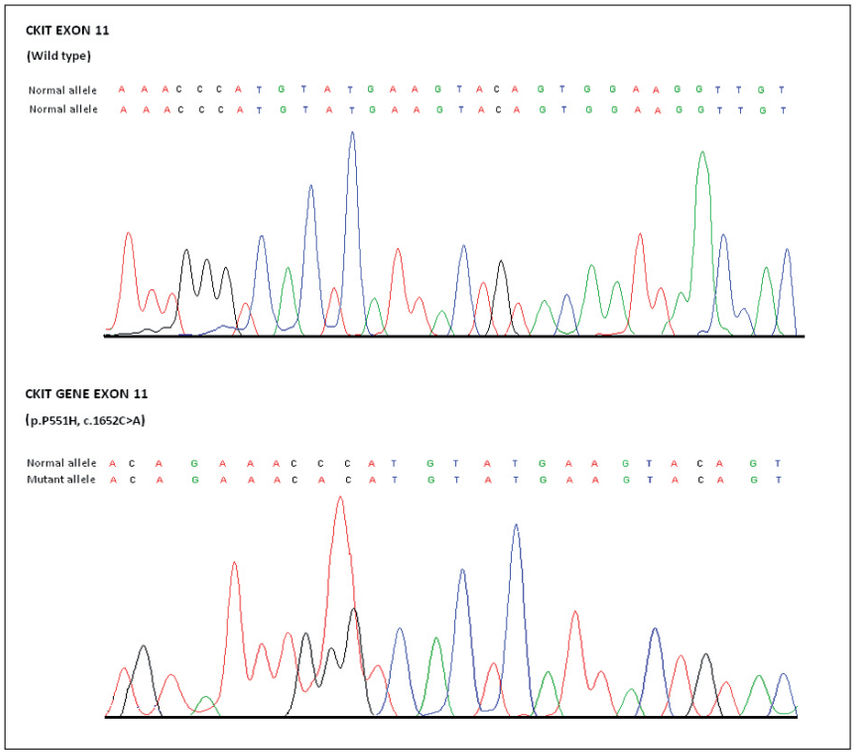


**Figure 1:** Curves of exon 11 in case 1 and case 6 (bottom).

In conclusion, the most characteristic features of MSI tumors associated with the defects of MMR genes in LS are now becoming clear, but the biological and clinical implications of MSI and the c-kit gene still remain unclear. More information related to the Bat25 marker gene of MSI and its connections to receptor protein tyrosine kinase pathways are essential to better understand the fundamental mechanisms of cancer development (3). Our findings suggest that it is important to determine whether molecular target genes function as a differentially regulated c-kit gene in the tumorigenesis of WT.

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