Mutational Screening of RET, HRAS, KRAS, NRAS, BRAF, AKT1, and CTNNB1 in Medullary Thyroid Carcinoma

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Abstract: Background: Screening medullary thyroid carcinomas (MTCs) for rearranged during transfection (RET) mutations becomes increasingly important for clinical assessment of the disease. The role of mutations in other genes including RAS (i.e. HRAS, KRAS, and NRAS), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), v-akt murine thymoma viral oncogene homolog 1 (AKT1), and CTNNB1 (P-catenin) is unknown or not fully explored yet for this disease. Materials and Methods: Formalin-fixed and paraffin-embedded (FFPE) material was the primary source for screening 13 sporadic and inherited MTCs and matched non-tumor specimens. Multiplex PCR was included in the PCR protocol. Sequence analysis encompassed mutational hotspot regions in RET exons 5, 8, 10, 11, and 13 to 16; HRAS exons 1 and 2; KRAS exons 1 and 2; NRAS exons 1 and 2; BRAF exon 15; AKT1 exon 2, and CTNNB1 exon 3. Results: We identified RET mutations in seven of 13 MTCs: five RET-positive cases revealed a mutation in exon 16 (M918T) and two a mutation in exon 10 (C618S and C620S). In four of the RET-positive cases, the mutation was inherited, out of which three were reportedly associated with a multiple endocrine neoplasia type 2 (MEN2) syndrome, i.e. MEN2A (C618S), MEN2A/familial MTC (FMTC) (C620S), and MEN2B (M918T). These cases reflect the known MEN2 genotype-phenotype

correlation. Three of the five stage IVc MTCs were inherited RET-positive cases. Mutational screening in HRAS, KRAS, NRAS, BRAF, AKT1, and CTNNB1 disclosed one sporadic RET-negative MTC (stage III) with mutation in HRAS codon 13 (G13R). Conclusion: Our study supports the clinical relevance of screening MTC patients for RET mutations. The role of RAS mutations, in particular HRAS mutations, in sporadic RET-negative MTC has not been fully explored yet. Mutations in BRAF, AKT1, and CTNNB1 are likely not to play a role in MTC.

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