Somatic trinucleotide change encompassing codons 882 and 883 of the \textit{RET} proto-oncogene in a patient with sporadic medullary thyroid carcinoma

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Abstract

Objective: Restriction analysis is a straightforward procedure for mutational analysis. It is commonly used for screening \textit{RET} mutations. Incomplete digestion is a well-known cause of false results. Herein, we report another limitation of the method.

Design and Methods: Screening for somatic mutations in \textit{RET} exons 16, 13 and 15 was performed in a patient with a sporadic medullary thyroid carcinoma. Genetic study was carried out by both restriction analysis and direct sequencing.

Results: A somatic trinucleotide change encompassing codons 882 and 883 of the \textit{RET} proto-oncogene (GT\textsubscript{A} GCT to GT\textsubscript{T} TTT) was documented. Particular to this case is the silent mutation (GTA → GTT) at codon 882. Independently, both the novel silent mutation and the missense mutation at codon 883 may disrupt the same AluI restriction site. Based on the restriction pattern we were able to say that both mutations occurred in the same allele.

Conclusions: Restriction analysis is an easy approach for screening \textit{RET} mutations; however, it is not enough to assign a final diagnosis.

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in Fig. 1, the restriction pattern suggested the presence of the A883F mutation.

Sequence analysis not only confirmed the expected mutation but also documented a second sequence alteration involving codon 882 (Fig. 2). This last event is a silent mutation, GTA→GTT (Val→Val) which, by itself, also destroys the same restriction point for AluI. Since the restriction pattern corresponding to peripheral blood DNA was normal, as shown in lane 3 of Fig. 1, the second variant could not be interpreted as a polymorphism.

Discussion

No occult or de novo germline mutations in RET were found in this patient with an apparently sporadic MTC.

The frequency of germline mutations, either inherited or de novo, in sporadic MTC patients depends on the series ranging from 1.5% to 6% (6, 7).

Somatic mutations in RET have been described in 23–69% of sporadic MTCs. The most common occurs within codon 918 (8, 9). Mutations in codons 768 (10) and 883 (2) have been reported less frequently. In a few cases, MEN 2A-like somatic mutations (11, 12), as well as deletions in exons 10 and 11, have been identified. Furthermore, sporadic MTCs may have different cell subpopulations, some of which carry somatic mutations while others do not or, alternatively, different subsets of cells can carry different somatic mutations (13).

In the present case, in addition to the previously described codon 883 mutation, we found a second sequence variant at codon 882 (GTA→GTT) present in a heterozygous state. The A→T substitution, at the third position, disrupts one restriction site for AluI independently of the 883 mutation that also destroys the same restriction site. Moreover, based on the heterozygous AluI restriction pattern it is possible to say that both mutations occurred in the same allele (in cis). As a silent mutation, it can hardly be responsible for the aggressive behaviour of disease noticed in our patient. Nevertheless, it is necessary to be cautious in the interpretation of apparently neutral variants as these kinds of sequence variants can lead to an aberrantly spliced product (14, 15).

Most of the time, restriction analysis is an easy and reliable detection strategy for RET mutations. The present case points out one limitation of this method. Given the possible coexistence of different mutations associated with the same restriction pattern, only sequencing analysis will further clarify and definitely establish the diagnosis of exon 15 somatic mutations.

References


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