

## Mutation and Polymorphism Report

**Authors:** M.E. Sáez<sup>1</sup>, A. Ruiz<sup>1</sup>, A. Cebrián<sup>2</sup>, F. Morales<sup>3</sup>, M. Robledo<sup>2</sup>, G. Antiñolo<sup>1</sup>, and S. Borrego<sup>1</sup>

**Affiliations:** <sup>1</sup> Unidad de Genética Médica y Diagnóstico Prenatal, Hospitales Universitarios Virgen del Rocío, Sevilla, Spain

<sup>2</sup> Departamento de Genética, Fundación Jiménez Díaz, Madrid, Spain

<sup>3</sup> Sección de Endocrinología, Hospital Universitario Infanta Cristina, Badajoz, Spain

**Corresponding Author Address and E-mail:** Salud Borrego MD, PhD

E-mail: gantinolog@nexo.es

**Title :** A new germline mutation, R600Q, within the coding region of *RET* proto-oncogene: a rare polymorphism or a MEN 2 causing mutation?

**Keywords:** *RET* proto-oncogene; medullary thyroid carcinoma; molecular analysis

**Species:** Human

**Change is:** Unknown

### Gene/Locus

**Name:** *RET* proto-oncogene

**Symbol:** *RET*

**Genbank accession number:** M57464

**OMIM accession number:** 164761

**Locus specific database:**

**Chromosomal location:** 10q11.2

**Inheritance:** Germinal

### Mutation / polymorphism name

**Nucleotide change–Systematic name:** (nt) c1730G |A

**Amino acid change–Trivial name:** R600Q

**Mutation / polymorphism type:** Missense

**Polymorphism frequency:**

**Detection method:** Fluorescent SSCP.

**Detection conditions:** 10F: gcgccccaggaggctgagtg / 10R: ggtggtggtcccggccgcc

5'-95°C→[(30"-95°C→1'-68°C) x 25]→7'-68°C

MDE 0.5X; TBE 0.6X; glycerol 5%

10 W

**Diagnosis method developed:** PCR followed *Msp* I digestion.

**Evidence for existence and effect of mutation:**

|                                                          | Yes | No | Don't know |
|----------------------------------------------------------|-----|----|------------|
| 1. Base change found on repeat PCR sample                | x   |    |            |
| 2. Base change segregates or appears with trait          |     | x  |            |
| 3. Base change affects conserved residue                 |     | x  |            |
| 4. Expression analysis supports hypothesis for causation |     |    | x          |
| 5. Normals tested (50 required)                          | x   |    |            |

**Ancillary data**

1. **Haplotype association :** Unknown.
2. **Ethnic background/Population association :** South of Spain.
3. **Geographic association :** Unknown.
4. **Frequency (of mutation) in population:** 0/150.
5. **Clinical phenotype of proband :** Medullary Thyroid Carcinoma.
6. **Homologous allele** (if recessive trait):
7. **PIC:** (if microsatellite)
8. **Other:**
9. **Present in HGMD listing:** Yes: No:X

**Comments**

We present a new mutation, namely R600Q, within the coding region of *RET* proto-oncogene detected in a female patient (46 yr of age) with medullary thyroid carcinoma (MTC). This variation has been also found in the mother (73 yr of age), three out of five siblings (52, 50 and 45 yr of age) and one nephew (19 yr of age) of the index patient. No other change has been found after direct sequencing of the entire coding region of *RET* proto-oncogene.

The R600Q mutation lies near 609-620 cysteine rich region localized at exon 10 of *RET* proto-oncogene. Nevertheless, this residue is not conserved among mammals and is not close to any functional domain related to tyrosine-kinase activity. In addition, the three siblings and the nephew were available for biochemical screening whose results were within the normal range. All these data would suggest that R600Q could be a harmless variation.

However, R600Q has been found only in the index patient and her relatives and has not been detected in any of the 300 control chromosomes analysed so far. For that reason it can not be ruled out that R600Q may be a rare low penetrance allele contributing to the development of the disease. Further studies, specially functional assays, may help to elucidate this issue.

**Acknowledgments**

This work was supported by grants 97/0339 and 98/0898 from the Fondo de Investigaciones Sanitarias (Spain).