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Phenotype-Genotype Analysis in a Cohort of Patients with Multiple Endocrine Neoplasia Type 1 (MEN1) Identifies a Novel Nonsense Mutation at Codon 554

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INTRODUCTION

MEN1 is characterised by parathyroid, pituitary and pancreatic tumours in association with neoplasia of intra-thoracic endocrine tissue, adrenal glands and cutaneous manifestations. Mutations of the tumour suppressor Menin are causative and affected patients possess heterozygous germline mutations in MEN1, with acquisition of a second hit in the wildtype allele initiating tumourigenesis. Phenotype-genotype correlations can provide insights into the molecular function of Menin and help guide management and surveillance. We therefore sought to analyse patients with MEN1 presenting to a tertiary centre.

METHODS

Case notes and electronic records were reviewed and those with a confirmed MEN1 phenotype were selected. Mutation loci and functional consequences were deduced using Ensembl and mutations were cross referenced with COSMIC and the Universal Mutation Database for MEN1. Chi-squared analysis was used to test for correlations between genotype and phenotype.

RESULTS

We identified 48 patients with MEN1. Of these 41 had confirmed mutations from either sequencing of exons 2-10 (62%) or targeted screening (38%). One patient underwent multiplex ligation dependent probe amplification but was found to be wild type. 23% of mutations were sporadic.

The functional consequences of the mutations were:

- **Missense (17%)**
- **Nonsense (23%)**
- **Frameshift (33%)**
- **Intronic regions (13%)**

All but one of these had been previously described to be pathogenetic.

One novel mutation was identified in exon 10, Q554X, which leads to a premature stop codon (Fig 3).

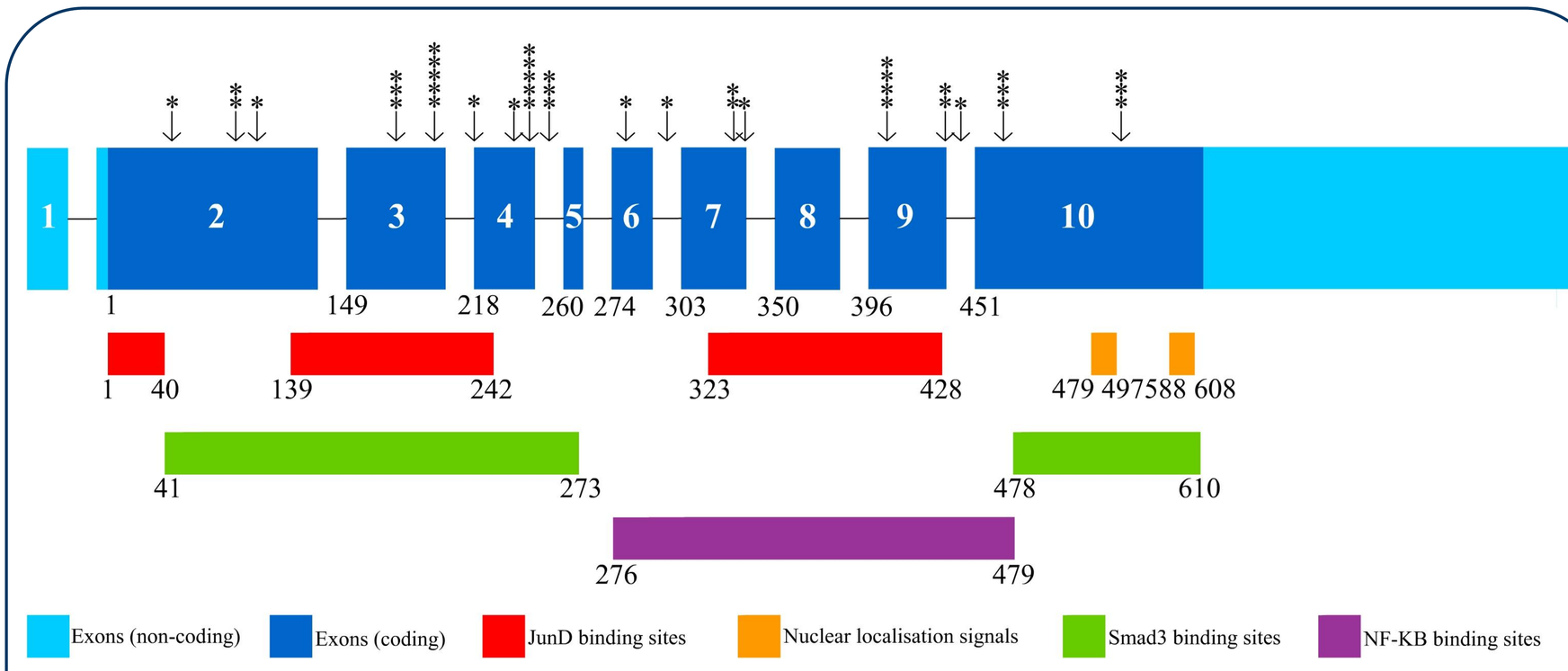

Fig 1. A schematic of the MEN1 gene depicting the sites of mutations identified in our cohort and their respective position within the domain structure of Menin
Numbers beneath bars indicate codons
*** indicates number of individuals with mutations at specified point**

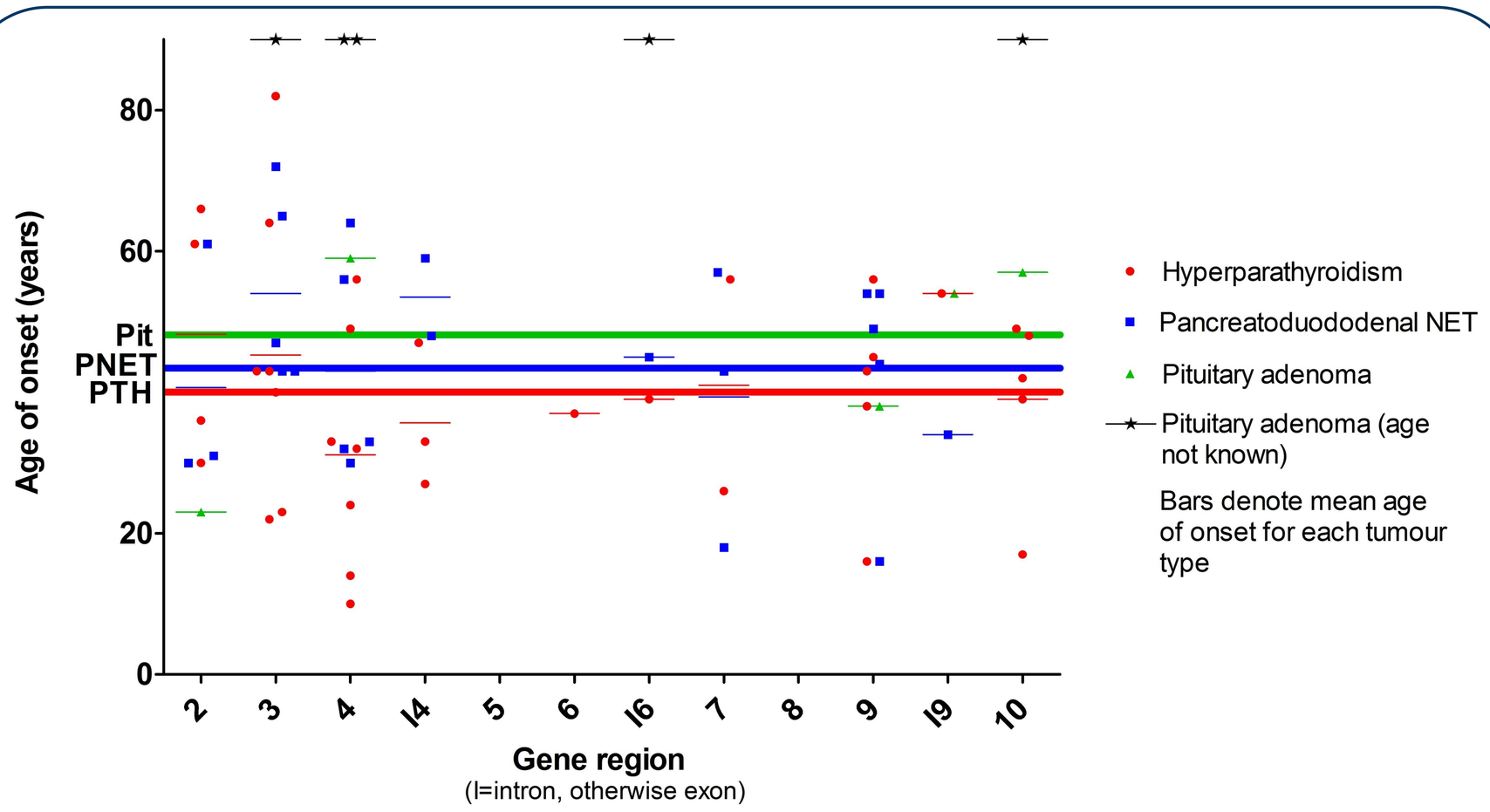

Fig 2. A graph showing age of onset of disease by location of mutation in MEN1 gene regions

- **Correlation analyses of age of onset and clinical manifestations versus site of mutation within the MEN1 gene did not demonstrate any statistically significant associations**

DISCUSSION

Our results reflect findings from previous studies suggesting that there are no obvious MEN1 phenotype-genotype correlations (Fig 2). Indeed, the disease is variable even between members of the same family bearing identical mutations.

A novel mutation, Q554X (Fig 3), was found in a patient with primary hyperparathyroidism and a gastrinoma. Deletion of 13 nucleotides in exon 10 is predicted to cause truncation at codon 554 resulting in loss of a nuclear localisation signal and the C terminus. This area is thought to be critical for DNA binding and the pathogenicity of this mutation emphasises the importance of this region in Menin function.

NOVEL MUTATION Q554X

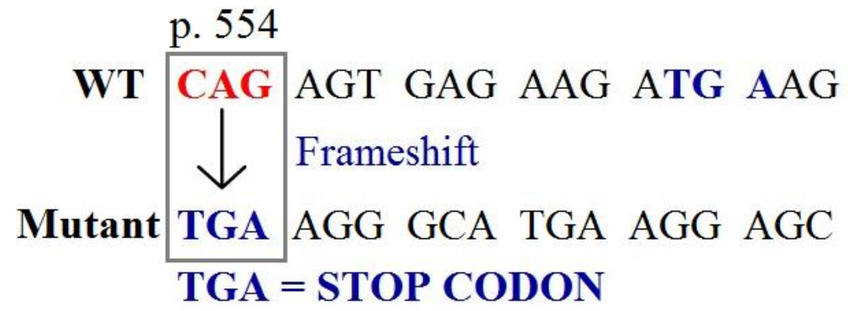

Fig 3. Q554X frameshift mutation

REFERENCES

Wautot, V. *et al*. "Germline Mutation Profile of MEN1 in Multiple Endocrine Neoplasia Type 1: Search for Correlation Between Phenotype and the Functional Domains of the MEN1 Protein" *Human Mutation* 20:35-47 (2002)