Multiple endocrine neoplasia 4: genotype-phenotype association of germline *CDKN1B* variant type and site

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INTRODUCTION

- Multiple endocrine neoplasia type 4 (MEN4) syndrome is an autosomal dominant disorder caused by a germline mutation in the *CDKN1B* gene.
- *CDKN1B* codes p27, a tumor suppressor protein involved in cell cycle.
- MEN4 is characterized by occurrence of hyperparathyroidism (HPT), pituitary adenomas (PA), and neuroendocrine tumors (NET), similar to MEN1 syndrome.
- Possible genotype-phenotype correlation in MEN4 have not been thoroughly assessed.

OBJECTIVES

- Review the literature on MEN4 clinical course.
- Assess for possible genotype-phenotype association in MEN4.
- Describe new Israeli cases harboring a pathogenic variant in *CDKN1B.*

METHODS

A literature review on published and unpublished data from previously reported MEN4/*CDKN1B* cases (**Figure 1**).

Data gathered: clinical presentation, age of diagnosis and characteristics of each tumor, family history, *CDKN1B* variants reported.

Additional three families with *CDKN1B* pathogenic variant described.

Univariate analysis analysed time-dependent risks for developing PHPT, PitAd, or NET by variant type and position along the gene.

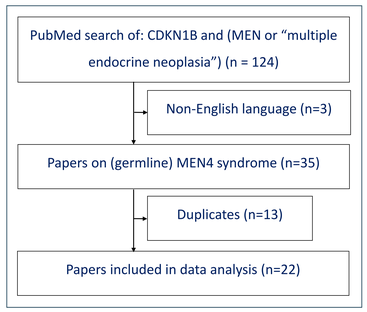

Figure 1. Literature search

RESULTS

A total of 74 cases of MEN4 were identified and analyzed

Three unrelated Ashkenazi Jewish families described, with identical *CDKN1B* mutation p.Q107fs in seven carriers

Family 1 (**Figure 2**), comprised one carrier with HPT, and one untested deceased family member with NET, family 2 had a patient with acromegaly and HPT, family 3 had no clinical symptoms

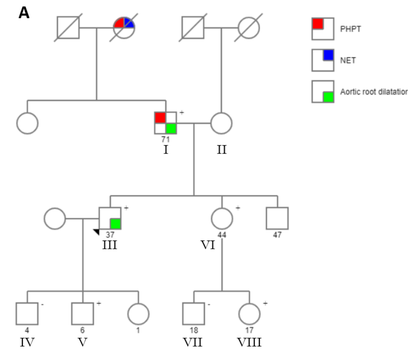

Figure 2. Family 1 lineage

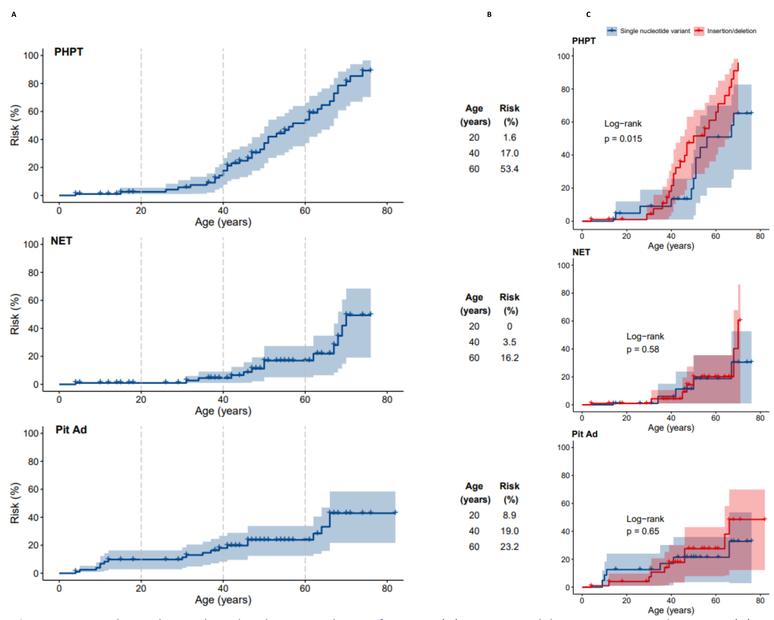

Figure 3. Time-dependent risk to developing each manifestation (A), percent risk by age 20, 40, and 60 years (B), variant type comparison (C)

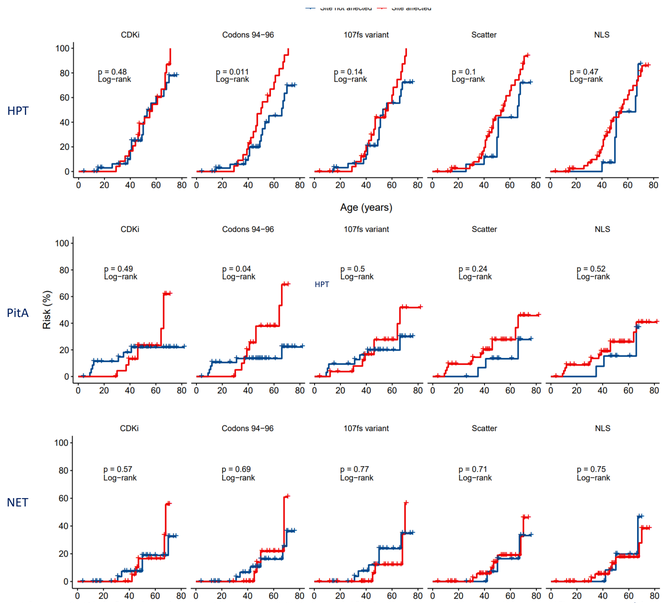

Figure 4. Risk for developing the main MEN4 manifestations over time with specific variants/domains

Overall cohort analysis (**Figure 3**)

HPT – age at diagnosis 50.6±13.9 years, risk was 53.4% by age 60 years.

PitAd - age at diagnosis 34.4±21.4 years, risk at age 60 was 23.2%.

NET – age at diagnosis 52.9±13.9 years, risk by age 60 was 16.2%

Patients with Indels had higher risk for PHPT vs. point mutations (Log-Rank, p=0.029).

Variant specific analysis (**Figure 4**)

Variants in codons 94-96 were associated with higher risk for PHPT (p<0.001) and PitAd (p=0.031).

The frameshift variant p.Q107fs was the most common variant identified (4/41 [9.7%] kindreds).

CONCLUSIONS

MEN4 is a rare syndrome, with 74 cases (including the presented case reports) described thus far

MEN4 is clinically distinct from MEN1, with lower risk and older age for HPT diagnosis and a relatively early presentation of PitA

We report possible genotype-phenotype correlations

REFERENCES

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Halperin et al, Endo Relat Cancer, in press

ACKNOWLEDGMENT

We thank Dr. Frederiksen and Dr. Nielsen for providing additional information on the cohort published on Frederiksen et al (JCEM, 2019)