

Multiple-Variant *MEN1* Haplotypes Observed in Multiple Endocrine Neoplasia Type 1

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Introduction

Multiple endocrine neoplasia 1 (MEN1) is a tumor predisposition syndrome characterized by increased risk for numerous neoplasms, including those of the parathyroid, pituitary, and gastroenteropancreatic tract. Although most molecularly diagnosed cases carry a single pathogenic variant (PV) in *MEN1*, which encodes the protein menin, a commercial laboratory identified two families in which probands were found to carry multiple *MEN1* variants in *cis*. In isolation, each of these variants is currently classified as a variant of uncertain significance (VUS). However, the identification of these multi-variant haplotypes in probands meeting clinical diagnostic criteria suggests several non-exclusive potential mechanisms unusual for MEN1, including reduced penetrance variants and/or additive or synergistic effects of individual variants on menin function.

Methods

In the course of standard variant classification, two *MEN1* haplotypes with multiple variants in *cis* were incidentally identified by variant scientists. These variants underwent manual internal review, utilizing all available sources of evidence, such as population frequency data, *in silico* predictive tools, phenotypic information, and structural analysis.

Results

Haplotype 1 (*MEN1* c.[100C>A ; 311C>A] (p.[L34M,S104Y])) was first identified in a female with a personal history of pancreatic neuroendocrine tumor, multinodular goiter, pituitary microadenoma, and hyperparathyroidism. Her mother also tested positive for this haplotype and had a history of parathyroid and pancreatic neuroendocrine tumors and nephrolithiasis. The proband's daughter (age 18) and a maternal uncle (age 59) also tested positive for the haplotype but are clinically unaffected. Information about the individual variants in Haplotype 1 has not been reported in published literature and is limited in

ClinVar to one variant (*MEN1* c.100C>A), classified VUS by one other laboratory, or internal probands only. Internally, *MEN1* c.100C>A and *MEN1* c. 311C>A reach a VUS classification based on clinical data and *in silico* predictions.

Haplotype 2 (*MEN1* c.[1078A>T;1064G>A;1102G>A] (p.[I360F,R355Q,A368T])) was first identified in a female with a personal history of multiple parathyroid adenomas, hypercalcemia, and nephrolithiasis. Both parents tested negative for this haplotype, suggesting a *de novo* origin. The proband has two daughters, both of whom tested positive for the haplotype; they are currently age 6 and 14 with no clinical features of MEN1. Both of the proband's siblings, one of whom has a history of hyperparathyroidism, tested negative for the haplotype. Information about these individual variants has not been reported in published literature and is limited in ClinVar to one variant, classified VUS by two other laboratories (c.1064G>A). Internally, each is classified as a VUS due to deleterious *in silico* predictions; additionally, personal communication with an international laboratory indicates that c.1078A>T has been detected in a patient with recurrent hyperparathyroidism.

Given that each individual variant in the two haplotypes had evidence contributing to pathogenic points but did not exceed VUS classification, the haplotypes were classified internally according to evidence applying to the combined haplotypes (i.e., not their constituent variants individually). Due to the combination of phenotypes and *in silico* predictions, both haplotypes accrued enough evidence towards pathogenicity to be classified as likely pathogenic.

Conclusion

It is difficult to assess whether only one *MEN1* variant or an additive/synergistic effect of multiple variants contributes to the phenotype observed in the carriers of these haplotypes. Both scenarios suggest the potential for reduced penetrance variants in MEN1, a condition typically considered to have nearly complete penetrance. Identification of similarly ambiguous *MEN1* variants and haplotypes should prompt careful assessment by clinicians and diagnostic laboratories for clinical features consistent with MEN1 to ensure access to surveillance in affected individuals, for whom screening is recommended as early as age 5.