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BACKGROUND & METHODS

- Multiple endocrine neoplasia 1 (MEN1) is a high-penetrance tumor predisposition syndrome characterized by increased risk for parathyroid, pituitary, gastroenteropancreatic (GEP) neoplasms, and other endocrine and non-endocrine tumors.
- Clinical diagnosis is achieved in a proband with two or more endocrine tumors of the parathyroid, anterior pituitary, and/or GEP tract.¹
- Molecularly diagnosed cases typically carry a single pathogenic variant (PV) in *MEN1*, which encodes the protein menin, a multifaceted regulator of cell proliferation.
- During standard variant classification, two *MEN1* haplotypes with multiple variants in *cis* were incidentally identified by variant scientists at a commercial laboratory.
- Due to their presentation in probands meeting clinical diagnostic criteria, these variants underwent manual internal review, utilizing all available sources of evidence.

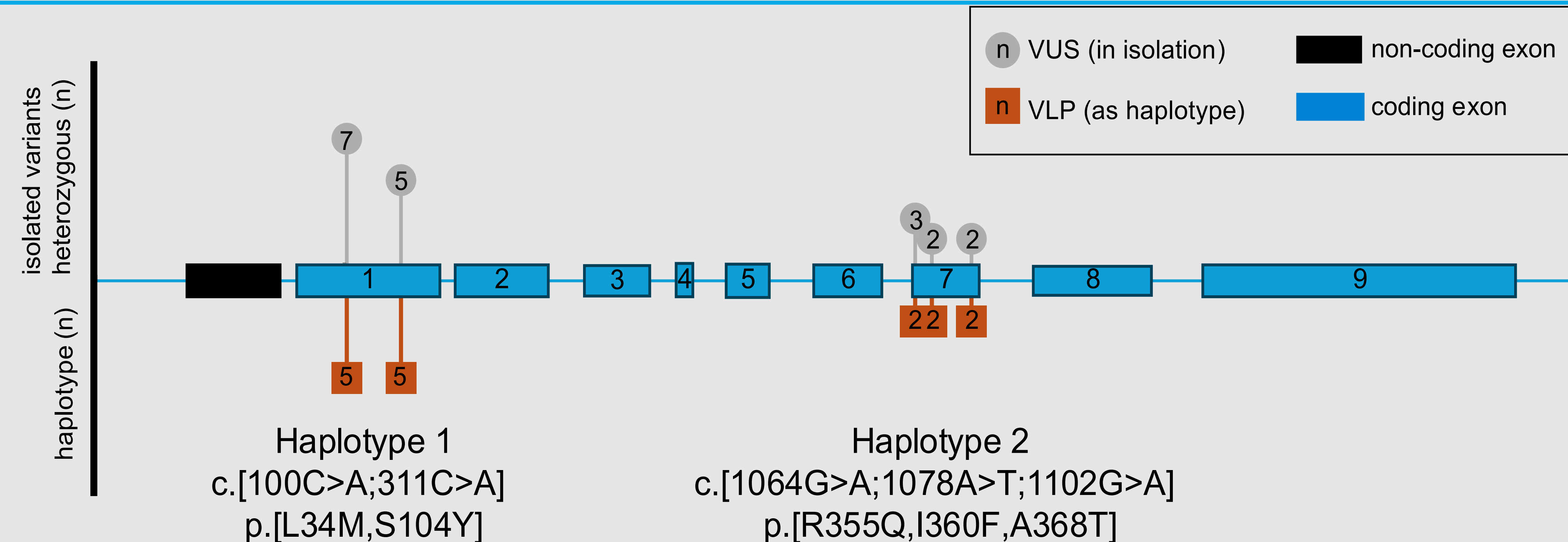


Figure 1. Internal allele frequencies in single-variant heterozygotes (top), where each variant in isolation is classified as a VUS, and frequencies seen in Haplotypes 1 and 2 (bottom), where each haplotype has been observed in multiple relatives within one family each.

TAKE HOME POINTS

- Identification of multi-variant haplotypes in probands meeting clinical diagnostic criteria suggests mechanisms unusual for *MEN1*, including reduced penetrance variants and/or additive effects of individual variants on menin function.
- Pending structural studies may clarify the mechanism of these haplotypes.

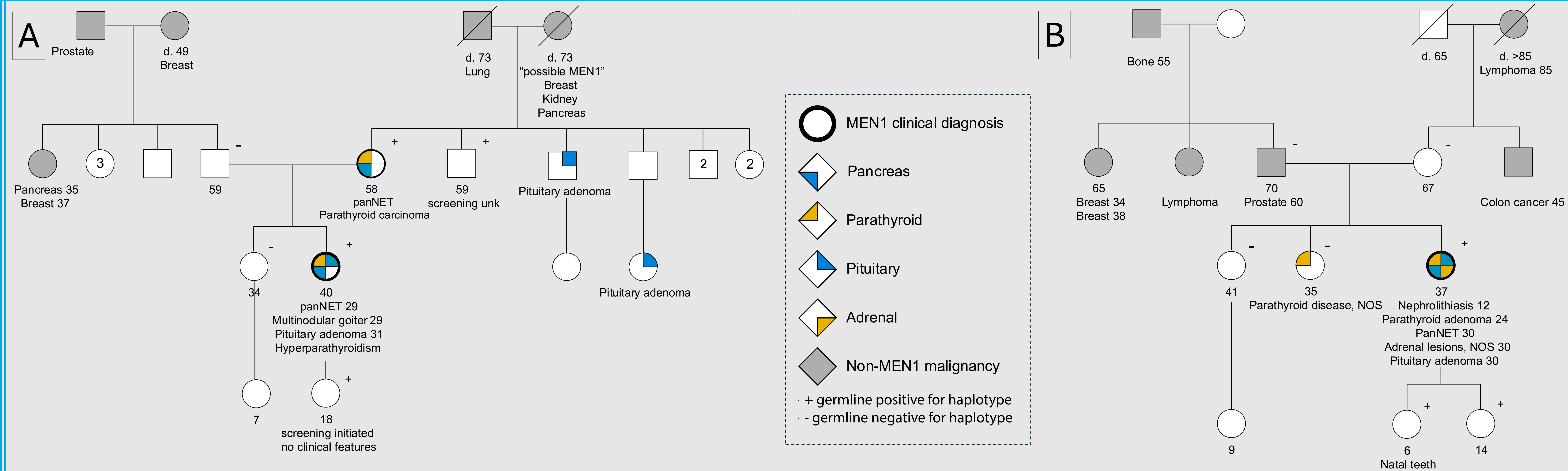


Fig 2. A) Haplotype 1, *MEN1* c.[100C>A; 311C>A] (p.[L34M,S104Y]). Variant segregates with clinical diagnosis in proband and mother. B) Haplotype 2, *MEN1* c.[1064G>A;1078A>T;1102G>A] (p.[R355Q, I360F, A368T]). Haplotype is apparently *de novo* in the proband, who meets clinical diagnostic criteria. The children of both probands are receiving age-appropriate screening and have no MEN1 features currently.

RESULTS

Haplotype 1: *MEN1* c.[100C>A; 311C>A] (p.[L34M,S104Y])

Clinical diagnosis

- Proband: pancreatic neuroendocrine tumor (29 y), multinodular goiter, pituitary adenoma, and hyperparathyroidism.
- Mother: PanNET, parathyroid carcinoma; haplotype segregates with maternal MEN1 features.
- Maternal uncle positive for haplotype and reportedly unaffected but history is limited.
- Additional maternal relatives with reported pituitary adenomas (Fig 2A) but histories and genetic statuses are unavailable.

Classification

- Internally, *MEN1* c.100C>A and *MEN1* c. 311C>A reach a VUS classification based on clinical data and *in silico* predictions; no individual-variant probands meet clinical criteria for MEN1. ClinVar reporting limited to VUS for c.100C>A; both variants absent from published literature.
- However, as a haplotype they are classified as Likely Pathogenic (VLP) based on the affected status of the proband.

Haplotype 2 (*MEN1* c.[1064G>A;1078A>T;1102G>A] (p.[R355Q, I360F, A368T]))

Clinical diagnosis

- Proband: history of nephrolithiasis beginning age 12, multiple parathyroid adenomas identified prior to age 24, and pancreatic and adrenal tumors between age 24-37.
- Both parents and all siblings 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.

Classification

- Internally, each variant is classified as a VUS due to deleterious *in silico* predictions; no individual-variant probands meet clinical criteria for MEN1. ClinVar reporting limited to VUS for c.1064G>A, all variants absent from published literature.
- However, as a haplotype they are classified as Likely Pathogenic (VLP) based on the affected status of the proband. ClinVar and published literature is limited or absent.