Characterization of *TMEM127*-related Tumor Predisposition in a Hereditary Cancer Cohort

Victoria Ellis, MS, CGC, June Mikkelson, MS, CGC, Jennifer Herrera-Mullar, MGC, CGC, DMA, Jamie Weyandt, PhD, Colin Young, PhD, Brittany Sears, PhD, MSPH, LCGC

BACKGROUND

- *TMEM127* pathogenic and likely pathogenic variants (PV) are associated with predisposition to pheochromocytoma (PCC).[1-3]
- Data on tumor prevalence for *TMEM127* PV heterozygotes are limited.
- Previous cohorts have ranged in size from case series to the largest cohort of 110.[1-3]
- This study aimed to aimed to characterize types and prevalence of tumors associated with PVs in *TMEM127* ascertained from a large multigene panel testing (MGPT) cohort.

METHODS

- 400 *TMEM127* PV heterozygotes were retrospectively identified via MGPT comprising 2-91 genes and single-site testing of *TMEM127* (n=18) at a single commercial diagnostic laboratory from 2015-2025.
- Individuals with PVs in other paraganglioma (PGL)/PCC genes were excluded.
- Tumor frequencies among *TMEM127* heterozygotes were compared to a pan-cancer MGPT-negative dataset using Fisher's exact test.

TAKE HOME POINTS

- This is the largest *TMEM127* PV cohort reported to date.[1-3]
- Results support the association of *TMEM127* with PGL/PCC and provide quantifiable odds of tumor frequency compared to a similarly selected cohort that is negative for PV in known PCC/PGL genes.
- This pan-cancer testing cohort reveals a lower frequency of PCC/PGL tumors in *TMEM127* PV heterozygotes compared to clinically ascertained cohorts.[1]
- Further studies on PGL, kidney, glioblastoma, and other tumor associations are needed to inform consensus surveillance guidelines.

RESULTS

- 400 internal *TMEM127* PV heterozygotes were identified (Fig 1)
- Personal history (Fig 2):
  - 5% (20/400) PCC (OR=31.49, p<0.001)
  - 0.5% (2/400) PGL (OR=5.8, p=0.058)
  - 1.75% (7/400) kidney cancer (NOS; p>0.05)
  - 0.25% (1/400) glioblastoma (NOS; p>0.05)
- Family history: 28.8% (62/363) positive family history of TMEM127-spectrum neoplasms: PCC (n=12), kidney (n=7), or brain tumors (n=5 glioblastoma, 28 unspecified) in first- or second-degree relatives

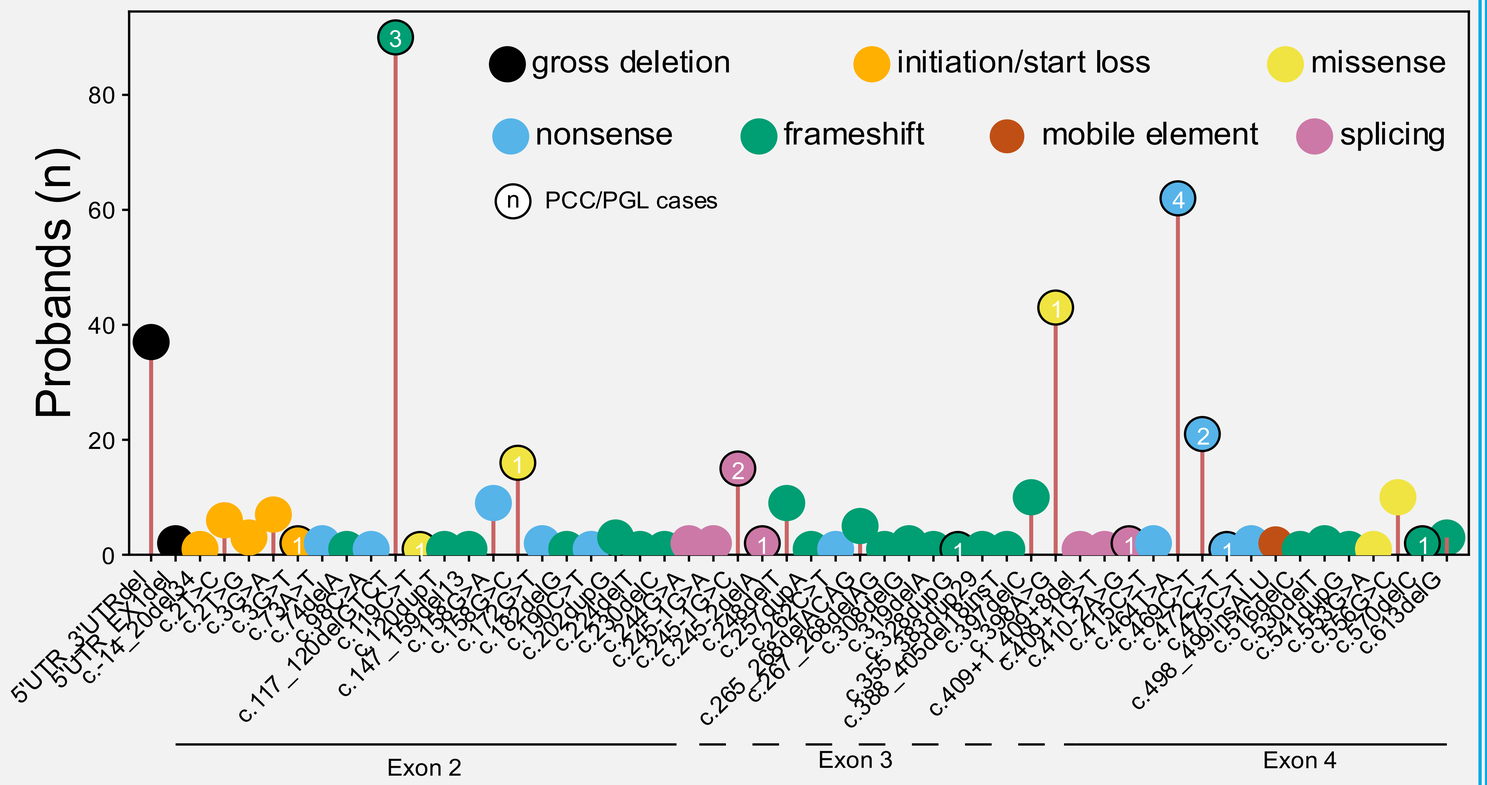

FIGURE 1: Frequency of *TMEM127* PV and LPVs identified internally at a commercial laboratory, coded by variant type (e.g., nonsense vs splice site) and presence of PCC/PGL in probands.

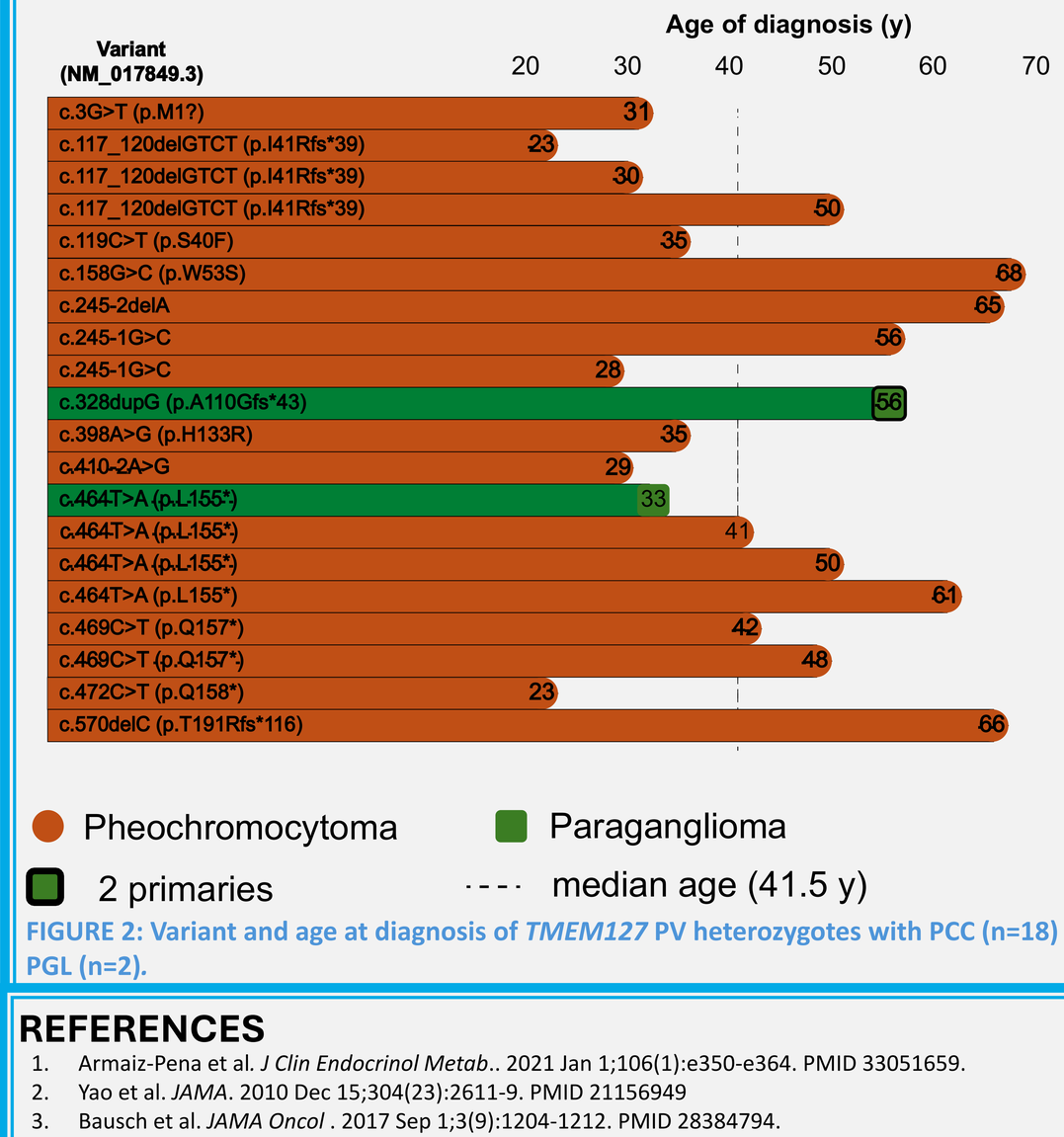

FIGURE 2: Variant and age at diagnosis of *TMEM127* PV heterozygotes with PCC (n=18) and PGL (n=2).

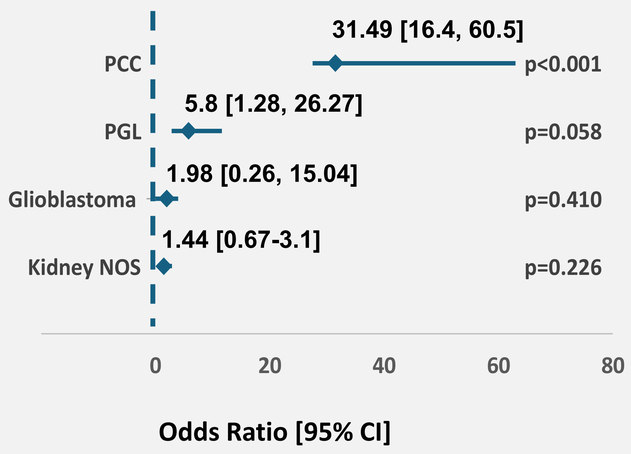

FIGURE 3: Odds ratios among *TMEM127* PV heterozygotes compared to MGPT-negative cohort.

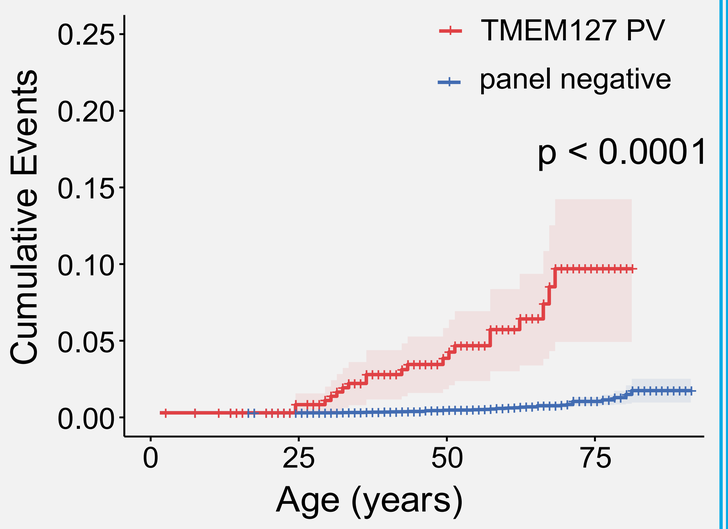

Figure 4: Kaplan-Meier plot comparing age and event frequency of PCC or PGL occurrence in *TMEM127* PV vs MGPT-negative cohorts.

REFERENCES

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