Title: Characterization of *TMEM127*-related tumor predisposition in a multigene panel testing cohort

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Introduction:

Loss of function variants in *TMEM127* are associated with predisposition to pheochromocytomas (PCC), and the *TMEM127* tumor spectrum may also include paragangliomas (PGL) and renal cell carcinoma (RCC). Due to the rarity of reported *TMEM127* pathogenic and likely pathogenic variants (PVs), data on tumor prevalence and corresponding surveillance recommendations remain limited. This study aimed to characterize tumor types associated with PVs in *TMEM127* from a cohort of 400 patients tested at a commercial laboratory and compare them with tumor frequencies in *SDHA* and *SDHB* heterozygotes.

Methods:

We conducted a retrospective clinical data review of patients heterozygous for a PV in *TMEM127* who underwent hereditary cancer predisposition testing at a single diagnostic testing laboratory from 2015-2025. *TMEM127* PVs were detected in 382 probands who underwent multi-gene panel testing (MGPT) of 2-91 genes; an additional 18 had single-site analysis for familial *TMEM127* variants. Individuals with PVs in other PGL/PCC-associated genes were excluded from analysis. Tumor frequencies among individuals with *TMEM127* PVs were compared to a MGPT-negative dataset using Fischer's exact test. Additionally, tumor frequencies among internally identified, panel-tested *SDHA* and *SDHB* heterozygotes were compared to the MGPT-negative dataset.

Results:

Among 400 probands with *TMEM127* PVs, 215 had a personal history of cancer (53.75%). *TMEM127*+ probands were significantly more likely to have a personal history of PCC than MGPT-negative probands (OR=31.49, CI 16.4-60.5, $p<0.001$). The majority of probands diagnosed with PCC (n=18), were diagnosed before age 50 (67%) and ranged from (23-68). Eight probands were diagnosed with renal cancer; none were diagnosed before age 50, and there was no significant difference between RCC prevalence in *TMEM127*-positive vs

MGPT-negative cohorts (OR=1.44, CI 0.67-3.10, p=0.35). The frequency of PGL development (n=2) in *TMEM127* PVs relative to MGPT-negative patients approached but did not meet statistical significance (OR 5.8, CI 1.3-26.3, p=0.058). Only one patient had two *TMEM127*-spectrum primaries, both of which were PGL. The frequency of glioblastoma (n=1) was not significantly different between *TMEM127* PVs and MGPT-negative group (OR=1.99, CI 0.26-15.04, p=0.41).

Family history was provided for 363 probands. Sixty-two (28.8%) reported a family history of PCC, PGL, brain cancer/tumor, or renal cancer, including 20 first-degree relatives (FDR) and 36 second-degree relatives (SDR). The most common tumor reported in FDRs was PCC (N=12). Renal cancers were reported in 7 FDR and SDRs, and, surprisingly, brain cancer/tumors were reported in 37 of these relatives (including 1 FDR and 4 SDRs reported to be diagnosed with glioblastoma specifically). No PGL diagnoses were reported in FDR or SDRs.

Relative to MGPT-negative probands, PCC risk for *TMEM127* carriers fell between that of *SDHA* and *SDHB* (OR 14.39, CI 7.2-28.8, p<0.0001; OR 110.7, CI 65.3-187.9, p<0.0001; respectively).

Conclusions:

With the inclusion of this gene in multigene panel testing (MGPT) for hereditary cancer risk, these individuals are being identified at an increased frequency. This retrospective cohort corroborates previously published data that PCC is the most frequent tumor type in *TMEM127* heterozygotes and, importantly, demonstrates that the risk of developing PCC in *TMEM127* heterozygotes falls between that of *SDHB* and *SDHA* PV carriers. Our findings support screening for PCC similar to that recommended for *SDHB* carriers and highlight the need for consensus guidelines to support patient access to these screenings. Further studies to evaluate the association with PGL, RCC, glioblastoma, and other tumor types are warranted.