Universal Multi-Gene Panel Testing for Individuals with Pheochromocytomas and Paragangliomas

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BACKGROUND

- Existing practice guidelines to identify individuals with hereditary pheochromocytomas (PCCs) and paragangliomas (PGLs) (PPGLs) advocate for sequential gene testing strategy guided by specific clinical features and predate the routine use of multigene panel testing (MGPT).
- Here we describe results of MGPT for hereditary PPGL in a clinically and ancestrally diverse cohort from a diagnostic laboratory.

METHODS

- Demographic and clinical information of individuals undergoing targeted MGPT for hereditary PPGL were collected from test requisition forms and supporting clinical documents provided by the ordering clinician and retrospectively reviewed.
- From August 2013 through May 2015, 560 individuals had targeted MGPT that included 10 genes (*NF1, MAX, SDHA/B/C/D/AF2, RET, TMEM127*, and *VHL*). From May 2015 through December 2019, 1167 individuals had panel testing of 12 genes due to the addition of *MEN1* and *FH*.

RESULTS

- Pathogenic variant (PV) and variant of uncertain significance (VUS) rates are shown in Figures 1 and 2.
- Affected individuals with a family history (fhx) of PPGL were the most likely to have a PV. The positive rate in nearly all clinical subgroups even without predictors of a PV remained over 10%, including individuals with a single tumor and those without a fhx (Table 2).
- Restricting genetic testing of hereditary PPGL to only *SDHB/C/D* genes misses a third (31.8%) of individuals with PVs (Figure 3).

TAKE-HOME POINTS

- Our data demonstrate a high diagnostic yield in individuals with and without established risk factors, a low inconclusive result rate, and a substantial contribution to diagnostic yield from rare genes when included in testing.
- These findings support updating practice guidelines to incorporate universal testing of all individuals with PPGL and the use of concurrent MGPT as the ideal platform.

Table 1. Cohort Description

Characteristic	Cohort Total n=1727
Sex	
Female	1019 (59.0%)
Male	708 (41.0%)
Ethnicity	
African American	194 (11.2%)
Ashkenazi Jewish	34 (2.0%)
Asian	80 (4.6%)
Caucasian	1016 (58.8%)
Hispanic	97 (5.6%)
Other/Unknown	306 (17.7%)
Personal History	
Affected	1338 (77.5%)
Affected at least one PGL	649 (37.6%)
Affected PCC only	689 (39.9%)
Unaffected	127 (7.3%)
Not provided	106 (6.1%)
Average Age	
All	46.8 (SD 17.0)
Affected	46.9 (SD 17.0)
Unaffected	46.7 (SD 17.1)
Age at PPGL Dx	41.8 (SD 17.1)

Figure 1. Overall Results

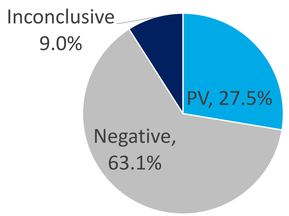

Figure 2. PV and VUS by Gene

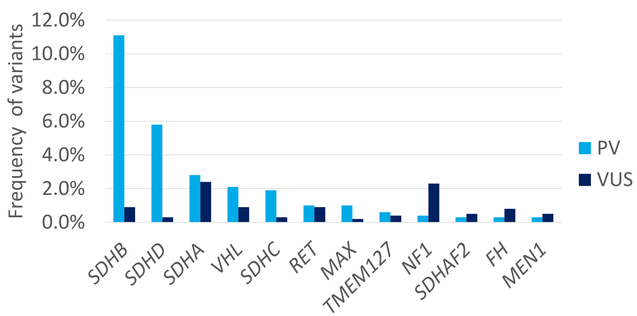

Figure 3. Increased Yield by Gene Inclusion

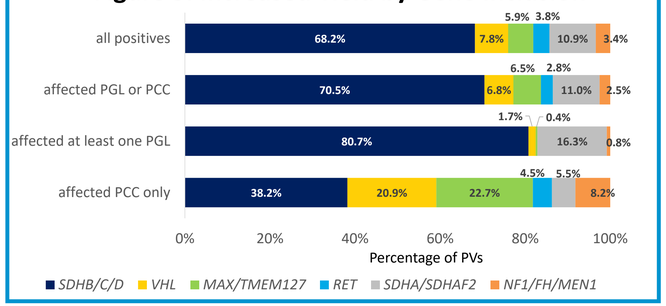

Table 2. Clinical Predictors of Positive Result

Clinical Feature	Total	Number positive (%)	OR	95% CI	p-value
At least one PGL +/- PCC	588	284 (48.3%)	4.1	3.1-5.2	<0.001
PCC Only	629	118 (18.8%)			
PCC Only Dx <45y	341	96 (28.2%)	5.3	3.0-9.3	<0.001
PCC only Dx ≥45y	232	16 (6.9%)			
Multiple PCC	30	18 (60.0%)	7.5	3.5-16.0	<0.001
Single PCC	599	100 (16.7%)			
PCC + Fam Hx PPGL	34	24 (70.6%)	12.8	5.9-27.7	<0.001
PCC - Fam Hx PPGL	596	94 (15.8%)			
PGL Dx <45y	315	203 (64.4%)	5.5	3.8-8.0	<0.001
PGL Dx ≥ 45y	233	58 (24.9%)			
PGL + PCC or PGL	57	36 (63.2%)	2.0	1.1-3.6	0.02
Single PGL	531	248 (46.7%)			
PGL + Fam Hx PPGL	64	55 (85.9%)	7.9	3.8-16.3	<0.001
PGL - Fam Hx PPGL	524	229 (43.7%)			

REFERENCES

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