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

Background: Pheochromocytomas (PCCs) and paragangliomas (PGLs) (PPGLs) are a genetically heterogeneous entity, with roughly 25-40% of cases found to harbor a pathogenic or likely pathogenic germline alteration. Existing practice guidelines advocating for the use of a sequential gene testing strategy to identify individuals with hereditary PPGL are driven by the presence of specific clinical features and predate the routine use of multigene panel testing (MGPT). However, increased adoption of MGPT represents a paradigm shift in hereditary cancer testing and may allow for updates to testing guidelines. 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. Individuals underwent MGPT of 10-12 genes depending on test order date. 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)*, and from May 2015 through December 2019, 1167 individuals had panel testing of 12 genes due to the addition of *MEN1* and *FH*.

Results: Overall, 27.5% of individuals had a pathogenic or likely pathogenic variant (PV), 9.0% had a variant of uncertain significance, and 63.1% had a negative result. Out of all PVs, most were identified in *SDHB* (40.4%), followed by *SDHD* (21.1%), *SDHA* (10.1%), *VHL* (7.8%), *SDHC* (6.7%), *RET* (3.8%), and *MAX* (3.6%). PVs in *FH*, *MEN1*, *NF1*, *SDHAF2*, and *TMEM127* collectively accounted for 6.5% of PVs. Clinical predictors of a PV included extra-adrenal location, diagnosis before the age of 45 years, multiple tumors, and positive family history of PPGL. Individuals with extra-adrenal PGL and a positive family history of PPGL were the most likely to have a PV (85.9%). The positive rate in nearly all clinical subgroups, with and without predictors of a PV, was above 10% (Table 1). Restricting genetic testing of hereditary PPGL to only *SDHB/C/D* genes misses a third (31.8%) of individuals with PVs. Among individuals with PVs in syndromic genes, over half (41.5%) did not have any additional syndromic features beyond PPGL reported by the ordering clinician.

Interpretation: Our data demonstrate a high diagnostic yield in individuals with and without established risk factors, a low inconclusive result rate, numerous individuals with syndromic PVs presenting with isolated PPGL, 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. Clinical predictors of positive results

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%)			