To Include or Not to Include: RASopathy Genes in Cardiomyopathy Genetic Testing

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Background

Cardiomyopathy, particularly hypertrophic cardiomyopathy, is a common feature of a group of disorders known as the RASopathies. Many disorders within the RASopathy spectrum have variable phenotypic presentation and cardiomyopathy may be the presenting clinical feature. When additional recognizable features are mild or absent, making a clinical diagnosis is more complicated. For this reason, some clinicians choose to test genes associated with RASopathies as part of the diagnostic evaluation for patients presenting with an indication of cardiomyopathy. Currently, it is unclear how often clinicians include RASopathies in the differential diagnosis when evaluating individuals with a presentation or family history of cardiomyopathy. At Invitae, clinicians ordering genetic testing for cardiomyopathy have the option of including appropriate RASopathy genes or limited evidence genes along with the primary panel genes.

○	02261	Invitae Hypertrophic Cardiomyopathy Panel	24	ACTC1, ACTN2, BAG3, CAV3, CSRP3, DES, ELAC2, FHL1, GLA, LAMP2, MTO1, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTR, VCL
		Gene(s) that can be added to the panel at no additional charge		
	○	02261.1 Limited-evidence genes	12	ANKRD1, CALR3, GATA4, JPH2, LDB3, MYH6, MYLK2, MYOM1, MYOZ2, MYPN, NEXN, PDLIM3
	○	02261.2 RASopathy genes	16	A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NF1, NRAS, PTPN11, RAF1, RASA1, RIT1, SHOC2, SOS1, SPRED1

Figure 1. Invitae Cardiology Requisition Form

Methods

Ordering behavior regarding the addition of a panel of curated RASopathy genes (A2ML1, BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NF1, NRAS, PTPN11, RAF1, RASA1, RIT1, SHOC2, SOS1, and SPRED1) to curated cardiomyopathy panel orders at Invitae was examined. Genetic testing results were reviewed to determine how often variants in RASopathy genes were identified. Ordering clinician specialty was determined and any test ordered by a physician geneticist or genetic counselor, or that documented a consult by a genetics specialist, was considered to have had a genetics consult.

Results

Of 168 sequential cardiomyopathy panel tests, 38 (23%) included genes related to RASopathy. The primary panels ordered for cardiomyopathy included 88 for a hypertrophic cardiomyopathy panel, 44 for a cardiomyopathy comprehensive panel, and 36 for an arrhythmia and cardiomyopathy comprehensive panel. Specifically, RASopathy genes were included in 18 (21%) of hypertrophic cardiomyopathy panel tests, 11 (25%) of cardiomyopathy comprehensive panel tests, and 9 (25%) of arrhythmia and cardiomyopathy comprehensive panel tests.

Primary panel	Total ordered	RASopathy included
HCM	88	18 (21%)
Cardiomyopathy	44	11 (25%)
Arrhythmia and cardiomyopathy	36	9 (25%)
TOTAL	168	38 (23%)

Table 1. Number of test orders

Four Variants of Uncertain Significance were identified in a RASopathy gene. None of these tests contained an additional Pathogenic variant, however, additional Variants of Uncertain Significance in primary panel and limited evidence genes were identified. In general, this compares to 28 tests that identified at least one Variant of Uncertain Significance in a primary gene related to hypertrophic cardiomyopathy.

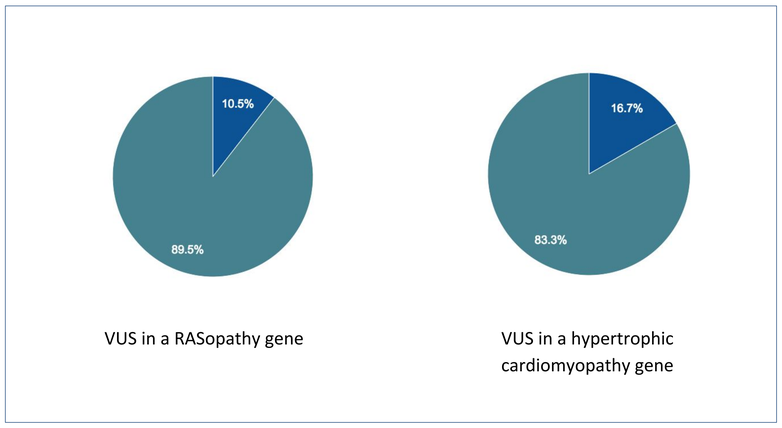

Figure 2. Percentage of tests returning at least one Variant of Uncertain Significance

The median age of patients for whom RASopathy genes were included was 38 years old, compared to 50 years old for the entire cohort.

Overall, 148 (88.1%) of tests had a documented genetics consult prior to ordering. The remaining tests were ordered by a cardiologist and did not include documentation of clinical genetics involvement. Of orders orders including RASopathy genes, 95% (n=36) documented a genetics consult for the patient prior to the test order compared to 86.2% (n=112) of cardiomyopathy orders not including RASopathy genes.

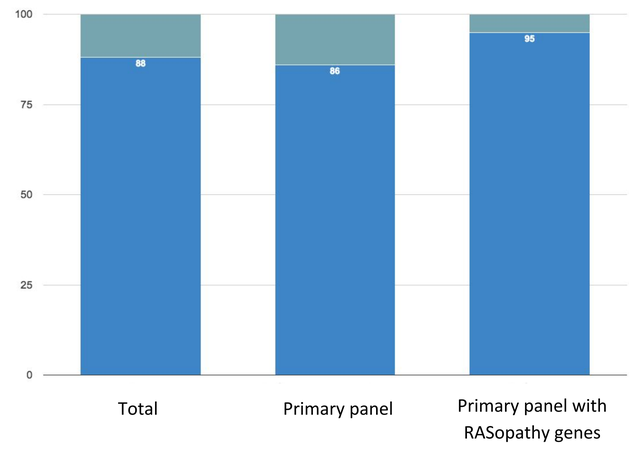

Figure 3. Percentage of test ordered with a documented genetics consult

Conclusion

These results indicate that some clinicians, particularly those with a genetics background, view analysis of RASopathy genes as a valuable addition for patients with cardiomyopathy. Additionally, these results suggest that including RASopathy genes as part of the diagnostic evaluation allows a broader evaluation for the genetic basis of cardiomyopathy and may uncover genetic variants that could be related to the patient's phenotype. The median age of the patients tested for RASopathy genes suggest that the evaluation of these genes is not isolated to pediatric populations. Further evaluation of ordering behaviors and outcomes will be valuable in helping clinicians determine best practices for ordering RASopathy gene testing for patients with cardiomyopathy.