Ambry Genetics®
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Research For Your Practice

Advancing Gene Characterization in Hereditary Cancer: Lessons and a Real-World Example

Rigorous, standardized gene characterization

Expertly curated panels

Actionable results you can trust

BUILDING A FOUNDATION FOR GENE-DISEASE VALIDITY (GDV)

The expansion of hereditary cancer testing has created opportunities and challenges for clinical labs and providers to strike the right balance. While larger panels increase the chance of detecting clinically relevant findings, they also raise the risk of reporting ambiguous results, especially if gene-disease relationships are not well vetted.

The importance of rigorous gene characterization is demonstrated in **two recent studies from Ambry**: a large-scale evaluation of GDV across hereditary cancer genes, and a case-based investigation that established *RPS20* as a cancer predisposition gene.[1,2]

In a comprehensive assessment of 85 genes frequently used in hereditary cancer testing, investigators found that GDV scoring rubrics—which were originally designed for rare disease —required calibration when assigning evidence for more commonly observed phenotypes with variable penetrance, such as cancer (Figure 1).[1] Use of scoring criteria validated for hereditary cancer **prevents premature characterization of genes** with preliminary evidence from small studies that are not reproducible. The analysis also showed that limited evidence genes had disproportionately high VUS rates and were unlikely to be upgraded to moderate, strong, or definitive categories. This demonstrates the clinical and operational burden of limited evidence genes in routine testing.

These findings emphasize the value of applying evidence thresholds and performing regular re-curation to maximize yield while minimizing ambiguity.

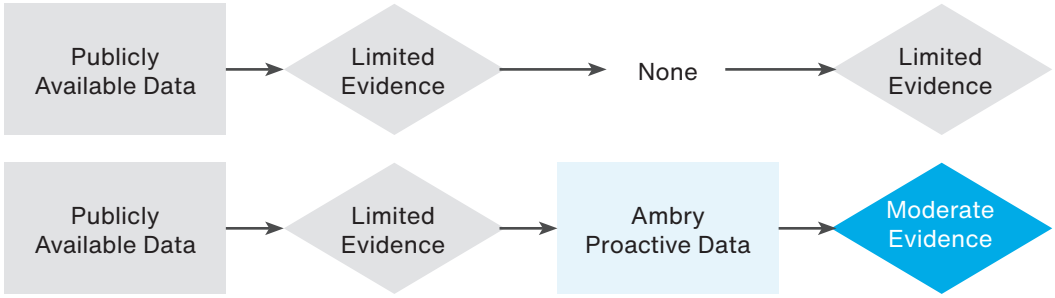
Figure 1. Scoring of gene-disease validity evidence for common cancers

Criteria	Points
Clinical/Population Evidence	
Number of unrelated patients with variants reported	0 - 18
Number of publications reporting independent probands	0 - 3
Case-control study data	-18 - 18
Statistical evidence	0 - 1
Experimental Evidence	
Gene function	0 - 2
Gene disruption experiments	0 - 2
Model organism	0 - 2
Gene-Disease Validity Category	
Definitive	17+
Strong	13+
Moderate	8 - 12
Limited	1 - 7
None	0
Disputed	<0

EVIDENCE SCORING IN ACTION

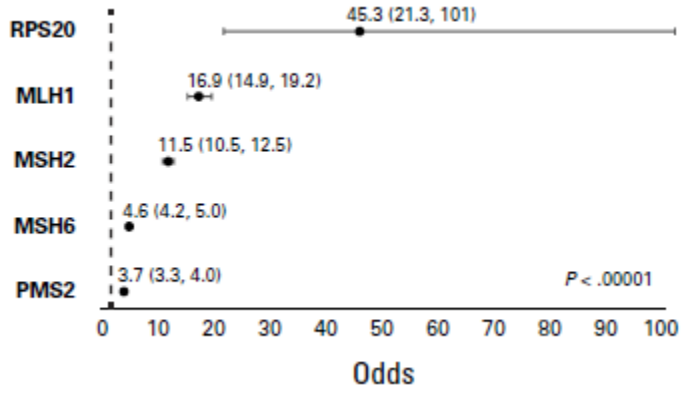
Building on these established GDV criteria, the characterization of *RPS20* illustrates the stepwise process by which evidence accumulates for an emerging gene–disease association. Although early studies identified this gene as a candidate for colorectal cancer (CRC) predisposition, the rarity of pathogenic variants made it difficult for independent groups to generate sufficient data, and without **Ambry's proactive evidence generation**, *RPS20* remained a limited-evidence gene (Figure 2). By leveraging a large clinical cohort, researchers were able to track segregation across numerous families and perform both case–control and case-case analyses.[2]

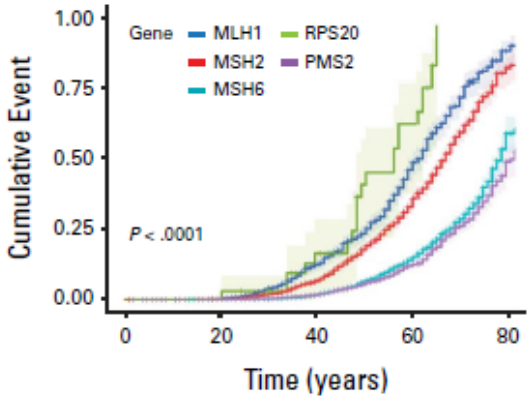
Figure 2. Impact of proactive data generation on GDV



Results indicate that CRC risk associated with *RPS20* may even exceed that of well-established Lynch syndrome genes such as *MLH1* (Figure 3). Functional studies further supported a role in tumorigenesis, providing the critical evidence to elevate *RPS20* GDV score to moderate, **allowing actionable results to be reported**. These findings not only strengthened gene–disease validity but also have the potential to inform future clinical management recommendations for patients with *RPS20* variants.

Figure 3. CRC risk in individuals with pathogenic variants in *RPS20* and Lynch syndrome genes





SUMMARY

Together, these studies illustrate how systematic evaluation and real-world case discovery work in tandem: broad frameworks help laboratories prioritize genes for inclusion, while detailed family-based investigations, such as *RPS20*, show how new genes are validated. This dual approach ensures that cancer genetic testing remains both clinically meaningful and scientifically rigorous.

1. Herrera-Mullar J, et al. Understanding how gene-disease relationships can impact clinical utility: adaptations and challenges in hereditary cancer testing. Genome Med. 2025 Jul 1;17(1):73. doi: 10.1186/s13073-025-01499-5.
2. Herrera-Mullar J, et al. Association of RPS20 Loss-of-Function Variants With Colorectal Cancer Risk in a Cohort of Over 950,000 Individuals. JCO Precis Oncol. 2025 Aug;9:e2500214. doi: 10.1200/PO-25-00214.

1 Enterprise, Aliso Viejo, CA 92656 USA Toll Free +1.866.262.7943 Fax +1.949.900.5501 **ambrygen.com**

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