A RET::GRB2 fusion in pheochromocytoma defies the classic paradigm of RET oncogenic fusions

Cynthia M. Estrada-Zuniga, 1,8 Zi-Ming Cheng,1,8 Purushoth Ethiraj, 1,8 Qianjin Guo,1 **Hector Gonzalez-Cantú ,1** Elaina Adderley, 2 Hector Lopez, 1 Bethany N. Landry, 1 Abir Zainal,2 Neil Aronin, 2 Yanli Ding, 3 Xiaojing Wang, 4,5 Ricardo C.T. Aguiar, 1,6,7 and Patricia L.M. Dahia 1,6,9,*

1Division of Hematology and Medical Oncology, Department of Medicine, University of Texas Health San Antonio (UTHSA), San Antonio, TX, USA 2Division of Endocrinology, University of Massachusetts Worcester, Worcester, MA, USA 3Department of Pathology, UTHSA, San Antonio, TX, USA4Department of Population Health Sciences, UTHSA, San Antonio, TX, USA 5Greehey Children's Cancer Research, UTHSA, San Antonio, TX, USA 6Mays Cancer Center, UTHSA, San Antonio, TX, USA7South Texas Veterans Health Care System, Audie Murphy VA Hospital, San Antonio, TX 78229, USA 8These authors contributed equally 9Lead contact

Pheochromocytomas and paragangliomas are highly heritable neural-crest derived tumors that are components of VHL disease and other hereditary syndromes. About 2/3 of the tumors are sporadic, and their main drivers remain poorly known. Disruptions of the tyrosine kinase receptor RET are known driver events in neural crest tumors and epithelial cancers, including mutations in pheochromocytomas, where sustained cell proliferation is maintained by constitutive RET signaling. Here we report the characterization and experimental validation of a novel driver oncogenic *RET* fusion with *GRB2*, a physiological RET-signaling partner protein, in a sporadic pheochromocytoma. The *RET::GRB2* fusion architecture positions RET as the 5' partner, retaining its kinase domain, while losing critical C-terminus motifs, a configuration not seen in *RET* fusions detected in epithelial cancers. RET::GRB2 endows oncogenic competence via constitutive, ligand-independent signaling that is both kinase and GRB2 dependent. Translationally, RET::GRB2-transformed cells are sensitive to clinical grade selective RET inhibitors, thereby broadening the therapeutic scope of these agents towards another type of RET oncogenic fusion. The characterization of the role RET::GRB2 in pheochromocytoma presents a novel oncogenic driver event in these tumors with potential therapeutic implications, and an additional target for genetic screening.