

NRG1 Fusions in Solid Tumors

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Background

- *NRG1* gene fusions are rare but actionable genomic drivers that occur across a growing number of tumor types.
- *NRG1* has an EGF-like domain that serves as a ligand for ErbB (HER3) receptors, thereby inducing heterodimerization, usually with HER2, and subsequent activation of relevant downstream signaling pathways.
- Agents targeting the HER2/HER3 pathway have shown early clinical promise in *NRG1* fusion-positive cancers.
- The HER2/HER3 bispecific antibody zenocutuzumab has FDA Fast Track Designation for tumors with *NRG1* fusions

Objectives and Methods

- Samples were submitted for clinical molecular profiling at Caris Life Sciences via Caris MI Tumor Seek (Phoenix, AZ).
- Gene fusion detection was performed on mRNA isolated from a formalin-fixed paraffin-embedded tumor sample using the Illumina NovaSeq platform (Illumina, Inc., San Diego, CA) and Agilent SureSelect Human All Exon V7 bait panel (Agilent Technologies, Santa Clara, CA).
- All *NRG1* fusions with ≥ 3 junction reads were identified for manual review and for characterization of fusion class, intact functional domains, domain prediction, breakpoints, frame retention and co-occurring alterations by next-generation sequencing.

Contact Information

Abstract #3132

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In an analysis of 169,273 tumor specimens, 261 tumors with an *NRG1* fusion were identified for an overall incidence of 0.154% across tumors. NSCLC was the most common tumor type (42.4%) in this cohort.

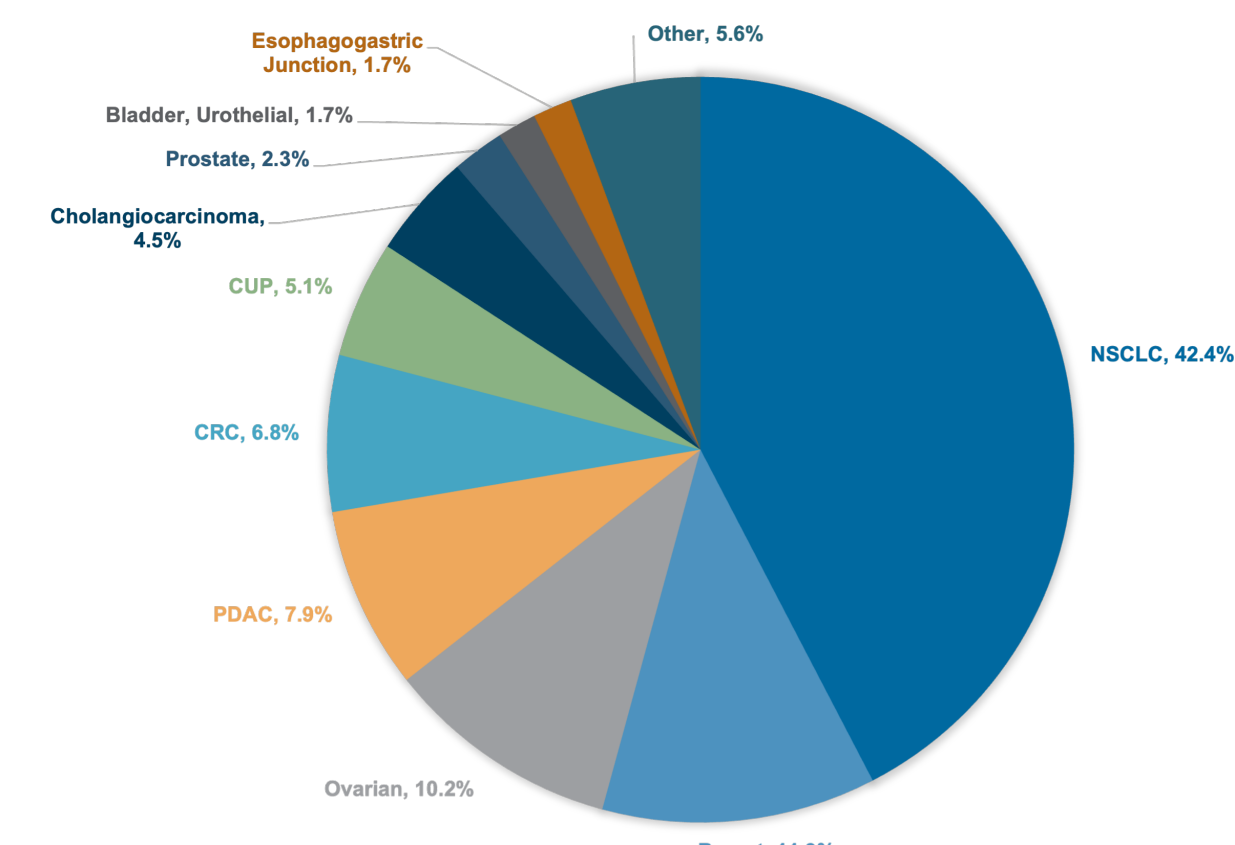


Figure 1. Detected *NRG1* fusion positive tumors by type

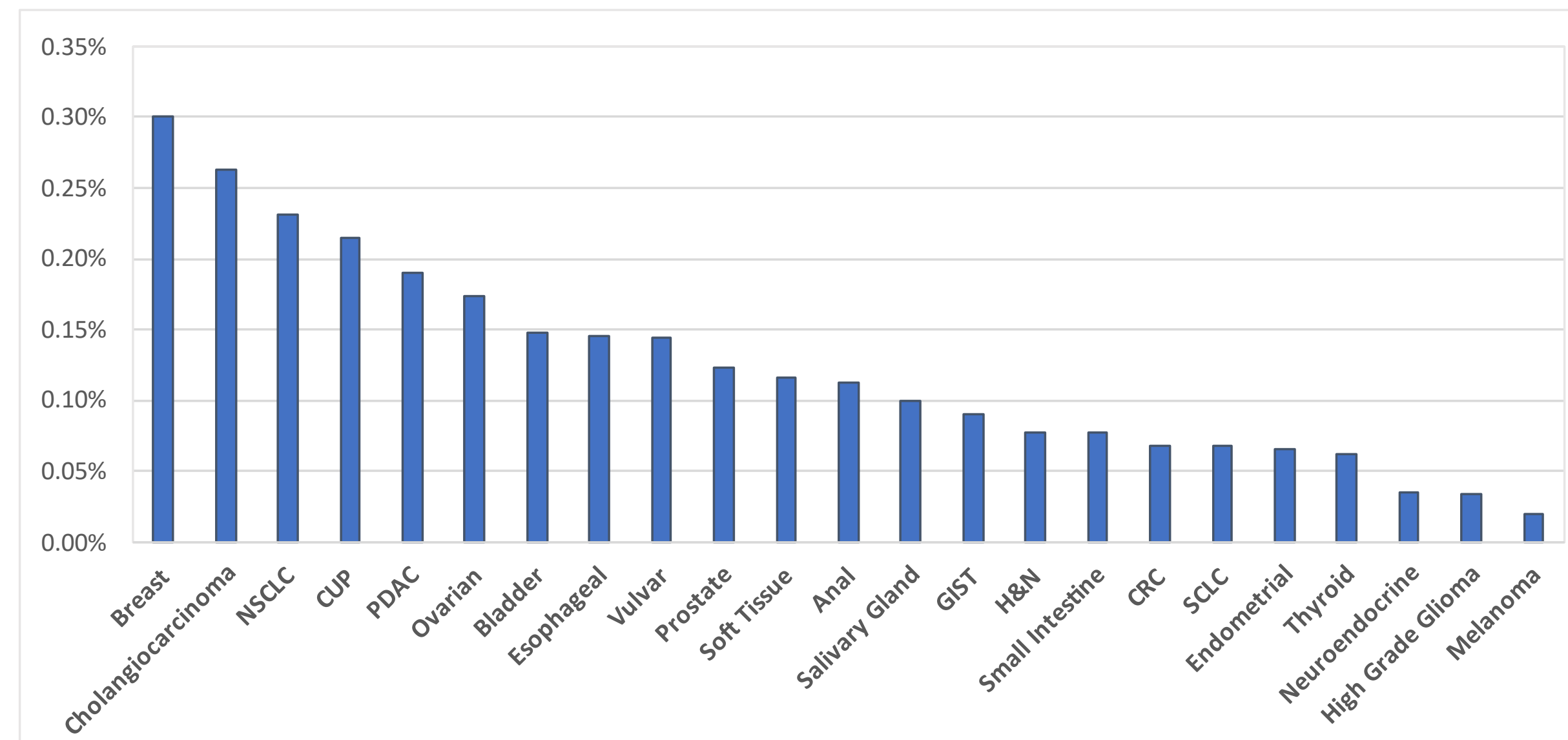


Figure 3. *NRG1* fusion prevalence by tumor type

Results

Upstream										Downstream														
Partner	Frame	Result	N	%	Partner	Frame	Result	N	%	Partner	Frame	Result	N	%	Partner	Frame	Result	N	%					
CD74	IF	P/LP	35	12.37%	TNFSF15	IF	P/LP	2	0.71%	HEATR5A	NIF	VUS	1	0.35%	SEC23B	NIF	VUS	1	0.35%	ASH2L	NIF	VUS	2	0.71%
SLC3A2	IF	P/LP	23	8.13%	TUSC3	NIF	VUS	2	0.71%	HGSNAT	IF	P/LP	1	0.35%	SEL1L	IF	P/LP	1	0.35%	C3orf67	NIF	VUS	2	0.71%
ATP1B1	IF	P/LP	13	4.59%	VTGN1	IF	P/LP	2	0.71%	HMBOX1	IF	P/LP	1	0.35%	SH1I	NIF	VUS	1	0.35%	CPQ	NIF	VUS	2	0.71%
RBPMS	IF	P/LP	12	4.24%	AGPAT5	IF	P/LP	1	0.35%	INSR	IF	P/LP	1	0.35%	SKIV2L2	IF	P/LP	1	0.35%	WASIR1	NIF	VUS	2	0.71%
WRN	NIF	P/LP	5	1.77%	AP2A1	IF	P/LP	1	0.35%	LOC100130964	NIF	VUS	1	0.35%	SHANK2	IF	P/LP	1	0.35%	ADAM2	NIF	VUS	1	0.35%
PPP2R2A	IF	P/LP	4	1.41%	ASH2L	NIF	VUS	1	0.35%	SLC16A1	NIF	VUS	1	0.35%	SKIV2L2	IF	P/LP	1	0.35%	ADAM5	NIF	VUS	1	0.35%
SDCA	IF	P/LP	4	1.41%	AUTS2	NIF	VUS	1	0.35%	SLC38A9	NIF	P/LP	1	0.35%	ADAM7	NIF	VUS	1	0.35%	ATP5B	NIF	VUS	1	0.35%
TACC1	IF	P/LP	4	1.41%	CADM1	IF	P/LP	1	0.35%	SLC38A14	NIF	P/LP	1	0.35%	CYTOR	NIF	VUS	1	0.35%	ATP5B	NIF	VUS	1	0.35%
VAMP2	IF	P/LP	4	1.41%	CCAT1	NIF	VUS	1	0.35%	SLC44A	IF	P/LP	1	0.35%	DDX11L2	NIF	VUS	1	0.35%	EMSY	IF	VUS	1	0.35%
AGRN	IF	P/LP	3	1.06%	CD44	IF	P/LP	1	0.35%	SPECC1	IF	P/LP	1	0.35%	ERBB4	NIF	VUS	1	0.35%	GINS4	NIF	VUS	1	0.35%
APP	IF	P/LP	3	1.06%	CD9	IF	P/LP	1	0.35%	SPINT2	IF	P/LP	1	0.35%	PPP3CC	NIF	VUS	1	0.35%	PPP3CC	NIF	VUS	1	0.35%
EFNA5	IF	P/LP	3	1.06%	CDH1	IF	P/LP	1	0.35%	SPON1	IF	P/LP	1	0.35%	RAB11FIP1	NIF	VUS	1	0.35%	RAP1A	NIF	VUS	1	0.35%
L2HGHD	NIF	VUS	3	1.06%	CHCHD3	NIF	VUS	1	0.35%	SPTY2D1	NIF	VUS	1	0.35%	SLC20A2	NIF	VUS	1	0.35%	SYNE2	IF	VUS	1	0.35%
ADAM9	IF	P/LP	2	0.71%	CHMP4C	IF	P/LP	1	0.35%	ST14	IF	P/LP	1	0.35%	TANC1	IF	VUS	1	0.35%	TUSC3	NIF	VUS	1	0.35%
APLP2	IF	P/LP	2	0.71%	CLNS1A	NIF	VUS	1	0.35%	TEX15	IF	P/LP	1	0.35%	ZAK	IF	VUS	1	0.35%	ZMAT4	NIF	VUS	1	0.35%
ATP13A5	NIF	VUS	2	0.71%	CRKL	IF	P/LP	1	0.35%	THBS1	IF	P/LP	1	0.35%										
CDK13	IF	P/LP	2	0.71%	CSMD1	IF	P/LP	1	0.35%	TMEM127	IF	P/LP	1	0.35%										
CHKA	NIF	VUS	2	0.71%	CXADR	IF	P/LP	1	0.35%	TNFRSF10B	IF	P/LP	1	0.35%										
CLU	IF	P/LP	2	0.71%	DECR1	NIF	VUS	1	0.35%	TNFRSF10D	IF	P/LP	1	0.35%										
CTNNB1	IF	VUS	2	0.71%	DTNA	NIF	VUS	1	0.35%	TRPV1	NIF	VUS	1	0.35%										
FN1	IF	P/LP	2	0.71%	EFR3A	IF	P/LP	1	0.35%	TTC31	NIF	VUS	1	0.35%										
FUT10	IF	VUS	2	0.71%	EIF3H	IF	P/LP	1	0.35%	TT12	NIF	VUS	1	0.35%										
H00K3	IF	P/LP	2	0.71%	ENPP3	IF	P/LP	1	0.35%	UBE2K	NIF	VUS	1	0.35%										
INTS9	NIF	VUS	2	0.71%	ERP44	NIF	VUS	1	0.35%	UBR5	NIF	VUS	1	0.35%										
KAT6A	IF	P/LP	2	0.71%	EXTL3	NIF	VUS	1	0.35%	VPS13B	NIF	VUS	1	0.35%										
KIF13B	IF	P/LP	2	0.71%	F11R	IF	P/LP	1	0.35%	WASL	NIF	VUS	1	0.35%										
LSM1	IF	VUS	2	0.71%	FBXL20	NIF	VUS	1	0.35%	WDR43	NIF	VUS	1	0.35%										
NSD3	IF	P/LP	2	0.71%	FDFT1	NIF	VUS	1	0.35%	YTHDF3	NIF	VUS	1	0.35%										
PLPP1	IF	P/LP	2	0.71%	GPHN	IF	P/LP	1	0.35%	ZDHHC2	IF	P/LP	1	0.35%										
PPP3CC	IF	VUS	2	0.71%	GPR137C	NIF	VUS	1	0.35%															
RGPD5	IF	VUS	2	0.71%	GTFE2E	IF	P/LP	1	0.35%															
SARAF	IF	P/LP	2	0.71%	GTF3C1	IF	P/LP	1	0.35%															
SPDR	IF	P/LP	2	0.71%	H2AFY	IF	P/LP	1	0.35%															

Table 1. *NRG1* fusion partners

IF: In-frame
NIF: Not in-frame
P/LP: Pathogenic/Likely Pathogenic
VUS: Variant of uncertain Significance/Unclassified

Disease Group	N	Total	%
Breast	47	15625	0.301%
Cholangiocarcinoma	11	4182	0.263%
CUP	13	6053	0.215%
PDAC	17	8939	0.190%
Ovarian	25	14394	0.174%
Bladder	9	6071	0.148%
Esophageal	8	5513	0.145%
Vulvar	1	692	0.145%
Prostate	9	7286	0.124%
Soft Tissue	4	3432	0.117%
Anal	1	887	0.113%
Salivary Gland	1	1007	0.099%
GIST	1	1112	0.090%
H&N	3	3890	0.077%
Small Intestine	1	1297	0.077%
CRC	17	24865	0.068%
SLCL	1	1464	0.068%
Endometrial	9	13616	0.066%
Thyroid	1	1592	0.063%
Neuroendocrine	1	2802	0.036%
High Grade Glioma	2	5815	0.034%
Melanoma	1	5091	0.020%
Total	261	169273	0.154%

Table 2. *NRG1* fusion prevalence by tumor type

Features	Pos/Total	NRG1 %
IHC-Androgen Receptor	41/56	73.21
IHC-ER	45/76	59.21
NGS-TP53	126/237	53.16
IHC-PR	28/70	40.00
IHC-PD-L1 (22c3)	52/141	36.88
IHC-PD-L1 FDA (28-8)	15/57	26.32
CISH-Her2 CISH	6/26	23.08
NGS-LOH	42/194	21.65
IHC-PD-L1 FDA(SP142)	10/83	12.05
NGS-PIK3CA	26/236	11.02
CNA-FGFR1	24/233	10.30
NGS-ARID1A	22/237	9.283
NGS-RAS1	1/11	9.091
NGS-CDKN2A	19/234	8.120
CNA-ADGHA2	3/37	8.108
CNA-ZNF103	3/37	8.108
TMB High	18/232	7.759
CNA-CCND1	17/234	7.265
CNA-FGF19	16/232	6.897
CNA-ZMYM2	2/26	6.522
CNA-FGF4	15/230	6.522
NGS-APC	15/237	6.329
NGS-HR23	12/187	5.882
IHC-Her2/Neu	5/87	5.747
CNA-FGF14	2/36	5.556
CNA-ICP1	2/37	5.405
CNA-FGF3	19/226	5.310
NGS-KRAS	12/237	5.063
NGS-PTEN	11/231	4.762
NGS-KMT2D	11/233	4.721
NGS-ATM	11/236	4.661
NGS-TERT*	9/198	4.545
IHC-PD-L1 (SP142)	4/91	4.396
CNA-CCNE1	9/228	3.947
NGS-CDH1	9/237	3.797
NGS-EPHA2	7/197	3.553
CNA-ZNF217	8/234	3.419
CNA-ERBB2	7/232	3.017
NGS-ARID2	7/233	3.004
NGS-MUTYH	7/236	2.966
CNA-EMSY	3/104	2.884
NGS-NF1	6/208	2.885
CNA-RARA	1/36	2.778
CNA-SS18L1	1/36	2.778
CNA-ERCC5	1/37	2.703
NGS-ESR1	6/236	2.542
CNA-HOOK3	5/197	2.538
NGS-BRAF	6/237	2.532
NGS-ERBB3	6/237	2.532
NGS-NFE2L2	4/174	2.299

Table 3. Co-altered genes

Among the 261 unique tumors with an *NRG1* fusion, there were 153 unique fusion partners.

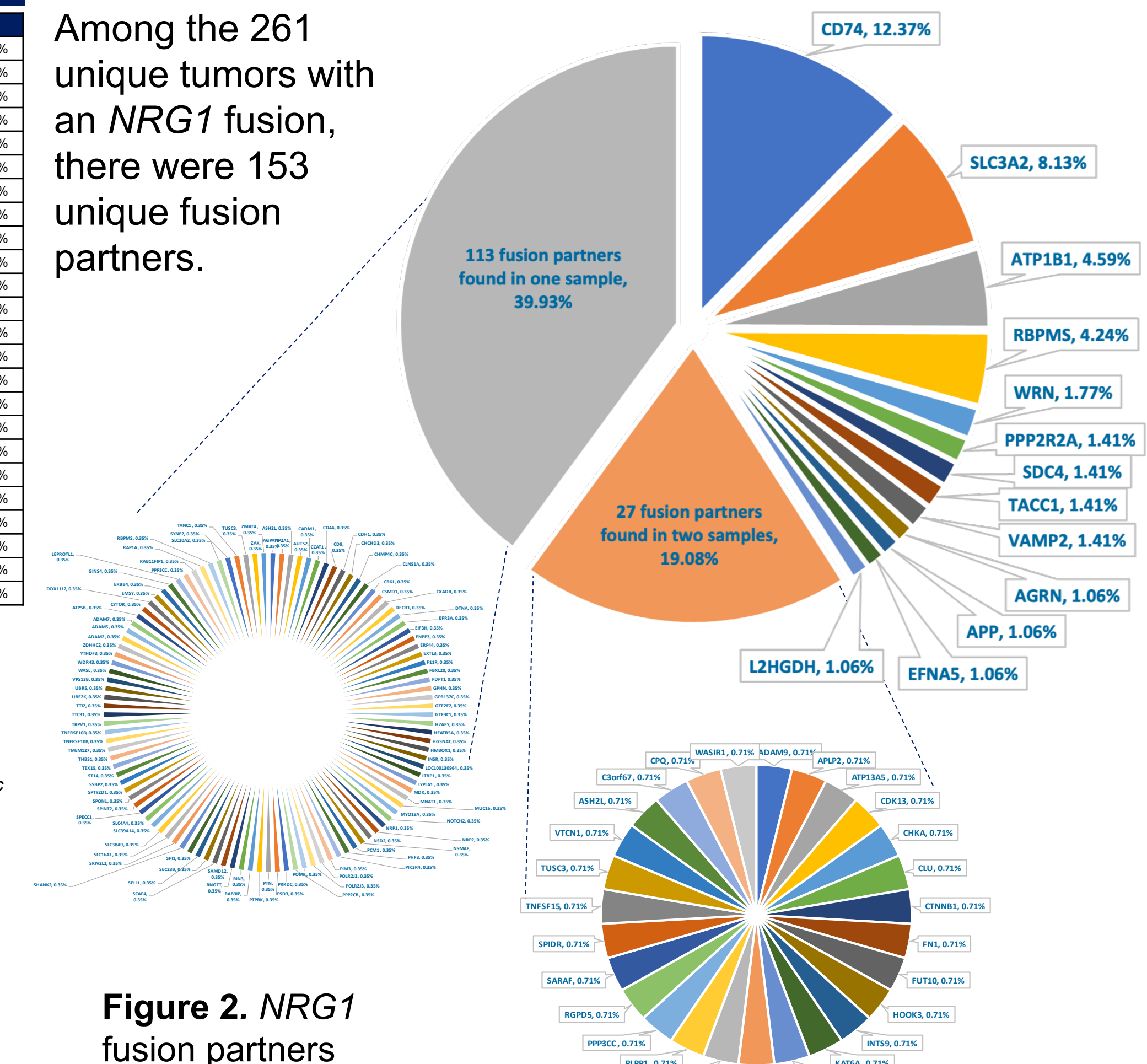


Figure 2. *NRG1* fusion partners

Conclusions

- *NRG1* fusions are rare but actionable genomic events that occur across many tumor types.
- There are a wide variety of fusion partners within and across tumor types.
- The clinical implications of the heterogeneity among fusion partners warrants further investigation.

Reference

- Jonna, Sushma, et al. "Detection of NRG1 Gene Fusions in Solid Tumors." *Clinical Cancer Research* 25.16 (2019): 4966-4972.
- Schram, Alison M., et al. "Efficacy and safety of zenocutuzumab, a HER2 x HER3 bispecific antibody, across advanced NRG1 fusion (NRG1+) cancers." (2022): 105-105.