Detection of *NRG1* Fusion Events in Ovarian, Fallopian Tube, and Primary Peritoneal Carcinomas

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Introduction

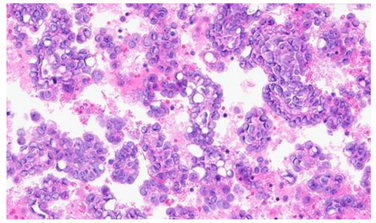
- NRG1 has been explored as the target of emerging HER2/HER3-directed anti-cancer agents, and the recent discovery of *NRG1* fusion events may have important therapeutic implications.
- While these fusions are relatively uncommon, they have been most thoroughly described in lung and pancreaticobiliary neoplasms.
- A recent study by Gupta et al. reported over 150 *NRG1* fusion partners in a wide variety of tumor types.
- This study seeks to further characterize *NRG1* fusions in ovarian, fallopian tube, and primary peritoneal carcinomas.

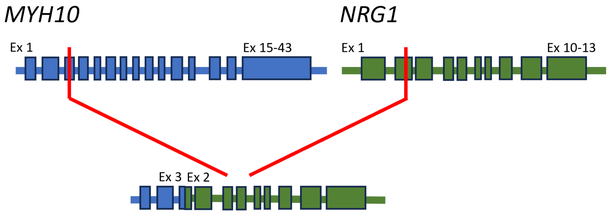
Materials and Methods

- Paraffin-embedded tumor samples submitted to Caris Life Sciences (Phoenix, AZ) underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing, utilizing the Agilent SureSelect Human All Exon V7 bait panel (Santa Clara, CA) and Illumina NovaSeq technology (San Diego, CA).
- NRG1 fusion events were included for analysis if they demonstrated ≥ 3 junction reads.

Cohort

Figure 1. Representative image of a hematoxylin and eosin-stained ovarian high-grade serous carcinoma metastatic to pleural fluid harboring a *MYH10* exon 3*::NRG1* exon 2 fusion (400x magnification, Case 22)





Case Number	Diagnosis	*NRG1* Fusion/Isoform	Splice Site	Co-ocurring Pathogenic Genetic Alterations	Tumor Mutational Burden (Muts/Mb)
1	high-grade serous carcinoma	*SCAF4::NRG1*	exon 18::exon 2 (NM_001256095.1/NM_001159999.2)	*TP53* p.R175H	7
2	high-grade serous carcinoma	*WFDC2::NRG1*	exon 2::exon 2 (NM_006103.3/NM_001159999.2)	*TP53* p.P47fs	8
3	high-grade serous carcinoma	*NOTCH2::NRG1*	exon 12::exon 6 (NM_024408.3/NM_001159999.2)	*TP53* c.376-7_386delinsGT; *CDK12* p.E182fs	5
4	high-grade serous carcinoma	*MUC16::NRG1*	exon 1::exon 2 (NM_024690.2/NM_001159999.2)	*TP53* p.M237I	4
5	low-grade serous carcinoma	*CLU::NRG1*	exon 2::exon 6 (NM_001831.3/NM_001159999.2)	None	1
6	high-grade serous carcinoma	*APP::NRG1*	exon 6::exon 6 (NM_001136130.2/NM_001159999.2)	*TP53* p.K132T; *RET* p.P1067L	3
7	borderline serous carcinoma	*CLU::NRG1*	exon 2::exon 6 (NM_001831.3/NM_001159999.2)	*RET* p.K1060R	3
8	low-grade serous carcinoma	*SPIDR::NRG1*	exon 16::exon 2 (NM_001080394.3/NM_001159999.2)	*ESR1* p.L536R	3
9	high-grade serous carcinoma	*HGSNAT::NRG1*	exon 1::exon 6 (NM_152419.2/NM_001159999.2)	*TP53* p.N131_C141del; *NTRK1* p.F327S	1
10	high-grade serous carcinoma	*SPINT2::NRG1*	exon 5::exon 2 (NM_001166103.1/NM_001159999.2)	*TP53* p.R282G	2
11	high-grade serous carcinoma	*SARAF::NRG1*	exon 1::exon 2 (NM_001284239.1/NM_001159999.2)	*TP53* p.K139fs; *PTEN* p.C136R	5
12	clear cell carcinoma	*RBPMS::NRG1*	exon 5::exon 2 (NM_001008712.2/NM_001159999.2)	*TERT* c.-124C>T; *FGFR3* p.G380R; *ARID1A* p.R1461*	4
13	high-grade serous carcinoma	*JAG1::NRG1*	exon 13::exon 6 (NM_000214.2/NM_001159999.2)	*TP53* p.G245S; *BRCA1* p.S1253fs	11
14	high-grade serous carcinoma	*NRP2::NRG1*	exon 15::exon 6 (NM_201267.1/NM_001159999.2)	*TP53* p.C275F; *FANCE* p.V311fs	3
15	high-grade serous carcinoma	*CHMP4C::NRG1*	exon 1::exon 6 (NM_152284.3/NM_001159999.2)	*TP53* p.Q317*; *PIK3CA* p.S72C	5
16	high-grade serous carcinoma	*CXADR::NRG1*	exon 1::exon 2 (NM_001207063.1/NM_001159999.2)	*TP53* p.N239fs	1
17	high-garde serous carcinoma	*TMEM65::NRG1*	exon 1::exon 2 (NM_194291.2/NM_001159999.2)	*TP53* p.N345fs; *NTHL1* p.Q90*; *KMT2D* p.E3244fs	6
18	low-grade serous carcinoma	*CLU::NRG1*	exon 2::exon 2 (NM_001831.3/NM_001159999.2)	*WRN* p.R369*; *FANCC* p.R548*	1
19	high-grade serous carcinoma	*INSR::NRG1*	exon 14::exon 6 (NM_000208.3/NM_001159999.2)	*TP53* p.C141Y	3
20	high-grade serous carcinoma	*ADAM9::NRG1*	exon 1::exon 6 (NM_003816.2/NM_001159999.2)	*TP53* p.S215I; *EP300* c.3671+1G>A	1
21	high-grade serous carcinoma	*SPON1::NRG1*	exon 12::exon 6 (NM_006108.3/NM_001159999.2)	*TP53* p.C176W; *BRCA1* p.Q1756fs	1
22	high-grade serous carcinoma	*MYH10::NRG1*	exon 3::exon 2 (NM_001256095.1/NM_001159999.2)	*TP53* p.K132R; *RET* p.C618Y	3
23	high-grade serous carcinoma	*SARAF::NRG1*	exon 1::exon 2 (NM_001284239.1/NM_001159999.2)	*TP53* p.L265del	1
24	high-grade serous carcinoma	*LDLR::NRG1*	exon 2::exon 6 (NM_001195800.1/NM_001159999.2)	*TP53* p.P27fs	1
25	high-grade serous carcinoma	*TNFRSF12A::NRG1*	exon 1::exon 2 (NM_016639.2/NM_001159999.2)	*TP53* p.Q331=	4
26	low-grade serous carcinoma	*CLU::NRG1*	exon 2::exon 6 (NM_001831.3/NM_001159999.2)	*CHEK2* p.T367fs	3

Table 1. Cohort of 26 women (median age 65.5 years, range 48-83 years) diagnosed with ovarian, fallopian tube, or primary peritoneal carcinomas harboring *NRG1* fusions

Results

- Ovarian, fallopian tube, and primary peritoneal carcinomas demonstrated an incidence of 0.174% for *NRG1* fusions, which were detected in 26 samples.
- Breakpoints occurred exclusively within either exon 2 (46%, n=12) or exon 6 (54%, n=14) of *NRG1*, in which the immunoglobulin and EGF-like domains are both retained with exon 2 splicing, but not when it occurs within exon 6.
- Of note, the *CLU::NRG1* fusion event was exclusive to those cases diagnosed as borderline/low-grade serous carcinoma.

Conclusions

- *NRG1* fusion events are infrequently observed in ovarian, fallopian tube, and primary peritoneal carcinomas and include a diversity of previously unknown partner genes.
- They may carry diagnostic significance in the context of borderline/low-grade serous tumors and have important therapeutic implications with the emergence of new targeted treatments.

References

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