Identification of Novel CDH1-NRG2α and F11R-NRG2α Fusions in NSCLC Plus Additional Novel NRG2α Fusions in Other Solid Tumors by Whole Transcriptome Sequencing

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BRIEF REPORT

ABSTRACT

Introduction: A novel CD74-NRG2α fusion has recently been identified in NSCLC. We surveyed a large tumor database comprehensively profiled by whole transcriptome sequencing to investigate the incidence and distribution of NRG2 fusions among various solid tumors.

Methods: Tumor samples submitted for clinical molecular profiling at Caris Life Sciences (Phoenix, AZ) that underwent whole transcriptome sequencing (NovaSeq [llumina, San Diego, CA]) were retrospectively analyzed for NRG2 fusion events. All NRG2 fusions with sufficient reads (≥ three junctional reads spanning ≥ seven nucleotides) were identified for manual review, characterization of fusion class, intact functional domains, EGF-like domain isoforms, breakpoints, frame retention, and co-occurring alterations by next-generation sequencing (NextSeq [llumina, San Diego, CA], 592 genes).

Results: Seven inframe functional (containing the intact EGF-like domain) NRG2α fusions were identified, namely, the following: (1) NSCLC (two of 9600, 0.02%: CDH1-NRG2α [C11, N2], F11R-NRG2α [F1, N4]); (2) endometrial (two of 3060, 0.065%: CPM-NRG2α [C2, N2], OPA3-NRG2α [O1, N2]); (3) ovarian (one of 5030, 0.02%: SPON1-NRG2α [S6, N2]); (4) prostate (one of 1600, 0.063%: PLLP1-NRG2α [P1, N2]); and (5) carcinoma of unknown origin (one of 1400, 0.07%: CYSTM1-NRG2α [C2, N2]). No NRG2β fusions were identified. Both NSCLC samples contained the reciprocal NRG2 fusions (NRG2-CDH1, NRG2-F11R). Almost all inframe

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NRG2α fusions have no (N = 6, 85.7%) or low (N = 1, 14.3%) programmed death-ligand 1 expression. No additional known driver mutations were identified in these seven NRG2α fusion-positive tumor samples.

Conclusions: Similar to NRG1 fusions, NRG2α fusions are recurrent and rare ligand-fusions in NSCLC and other multiple tumor types, especially gynecologic malignancies.

Keywords: NRG2 fusion; CDH1-NRG2α; F11R-NRG2α; Whole transcriptome sequencing; ligand-fusion positive malignancies

Introduction

Recently, a novel CD74-NRG2α fusion was identified in a Japanese NSCLC patient by whole transcriptome sequencing (WTS). Neuregulin-2 (NRG2) belongs to a family of six closely related members (NRG1-6) of signaling ligands to the HER receptor tyrosine kinase family members through the frequently shared EGF-like domain. The EGF-like domain is encoded by a core EGF-like domain exon and either an α- or β-specific EGF domain exon among each NRG gene. NRG1 fusions have been identified in multiple tumor types, albeit at a very low frequency, with anecdotal evidence of NRG1 fusions responding to HER2/HER3 or pan-HER blockade approach. We undertook this study to assess the incidence of NRG2 fusions in solid tumors that had undergone profiling by WTS.

Materials and Methods

This study was conducted in accordance with guidelines of the Declaration of Helsinki, Belmont report, and U.S. Common rule. In keeping with 45 CFR 46.101(b)(4), this study was performed utilizing retrospective, deidentified clinical data. Therefore this study is considered IRB exempt and no patient consent was necessary from the subject. All unique cases submitted to a Clinical Laboratory Improvement Amendments–certified laboratory (Caris Life Sciences, Phoenix, AZ) for comprehensive genomic profiling, that underwent successful fusion testing by WTS were identified. All histologic characteristics were reviewed by board-certified pathologists. An American Board of Medical Genetics and Genomics–certified geneticist (Dr. Swensen) determined whether the NRG2 fusions were inframe or out-of-frame, including occasionally midexonic breakpoints, which can sometimes be indicators of artificial fusion events (that arise through misalignment, mispriming, etc.).

Gene Fusions Detection by WTS

Gene fusion detection was performed on mRNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor samples using the Illumina NovaSeq platform (Illumina, Inc., San Diego, CA) and Agilent SureSelect Human All Exon V7 bait panel (Agilent Technologies, Santa Clara, CA). FFPE specimens underwent pathology review to diagnose percent tumor content and tumor size; a minimum of 10% tumor content in the area for microdissection was required to enable enrichment and extraction of tumor-specific RNA. Qiagen RNA FFPE tissue extraction kit (Qiagen, Hilden, Germany) was used for extraction, and RNA quality and quantity were determined using the Agilent TapeStation (Agilent Technologies). Biotinylated RNA baits were hybridized to the synthesized and purified complementary DNA targets, and the bait-target complexes were amplified by postcapture polymerase chain reaction. The resultant libraries were quantified and normalized. The pooled libraries were denatured, diluted, and sequenced; the reference genome used was GRCh37/hg19, and analytical validation of this test revealed greater than or equal to 97% positive percent agreement, greater than or equal to 99% negative percent agreement, and greater than or equal to 99% overall percent agreement with a validated comparator method.

Immunohistochemistry was performed on full FFPE sections of glass slides. Slides were stained using automated staining techniques per manufacturer’s instructions and were optimized and validated per Clinical Laboratory Improvement Amendments and College of American Pathologists and International Organization for Standardization requirements. For NSCLC, the primary programmed death-ligand 1 (PD-L1) antibody clone was 22c3 (Dako, Agilent Technologies). The tumor proportion score, or the percentage of viable tumor cells exhibiting partial or complete membrane staining at any intensity, was measured. For non-NSCLC tumors, the primary PD-L1 antibody used was SP142 (Spring Biosciences, Pleasanton, CA). The staining was regarded as positive if the intensity on the membrane of the tumor cells was greater than or equal to plus 2 (on a semiquantitative scale of 0–3: 0 for no staining, 1+ for weak staining, 2+ for moderate staining, or 3+ for strong staining) and the percentage of positively stained cells was greater than 5%. The determination of tumor mutational burden (TMB) microsatellite status has also been described. The α-isoforms and β-isoforms of NRG2 fusions are determined by manually reviewing the junction reads of exon 4 and 5 of the EGF domains.
| Fusion Partner | Chromosomal Location | Exons Breakpoints | Junctional Read | TMB (muts/MB) | PD-L1 (TPS, %) | MSI/ MMR | Associated Genetic Alterations | Chromosomal Breakpoints | RNA TPM | RNA TPM | RNA TPM | RNA TPM |
|----------------|----------------------|-------------------|----------------|----------------|----------------|--------|-------------------------------|-------------------------|---------|---------|---------|---------|
| **NSCLC**      |                      |                   |                 |                |                |        |                               |                         |         |         |         |         |
| 1              | 81, M, primary lung  | CDH1 \[\text{\textsuperscript{b}}\] | 16q22.1         | (C11, N2)      | 88             | 7      | 0                | Stable ARID1A,                | chr16:68853328:--;       | 34.3865 | 35.4288 | 150.347 | NA      |
|                | (adenocarcinoma)      |                   |                 |                |                |        |                  | CTNNB1, EAS, SMAD4            | chr5:139267096:--;       |         |         |         |         |
| 2              | 63, M, primary lung  | F11R \[\text{\textsuperscript{b}}\] | 1q23.3          | (F1, N4)       | 87             | 7      | 10             | Stable FH, HOXB13, TP53,     | chr1:160990800:--;        | 13.0594 | 25.289  | 52.5874 | 2.0615  |
|                | (adenocarcinoma)      |                   |                 |                |                |        |                  | CNA: NOTCH2, CDK6            | chr5:139251426:--;       |         |         |         |         |
| **Endometrial carcinoma** |               |                   |                 |                |                |        |                               |                         |         |         |         |         |
| 3              | 65, F, lung metastasis | CPM                | 12q15           | (C2, N2)       | 43             | 9      | 0                | Stable ARIAD1A; PIK3CA;     | chr12:69326458:--;        | 20.3438 | 179.383 | 155.371 | 82.8706 |
|                | (adenocarcinoma)      |                   |                 |                |                |        |                  | SPOP; TP53                   | chr5:139267096:--;       |         |         |         |         |
| 4              | 64, F, lymph node    | OPA3               | 19q13.32        | (O1, N2)       | 11             | 10     | 0                | Stable TP53, CNA: RARA,     | chr19:46087881:--;        | 30.7567 | 92.4570 | 419.4975 | 75.2951 |
|                | metastasis (carcinosarcoma) |                   |                 |                |                |        |                  | NSD2, ERBB3, FGFR3          | chr5:139267096:--;       |         |         |         |         |
| **Ovarian adenocarcinoma** |               |                   |                 |                |                |        |                               |                         |         |         |         |         |
| 5              | 61, F, liver metastasis | SPON1              | 11p15.2         | (S6, N2)       | 14             | 5      | 0                | Stable TP53, MAP3K1, CNA: MCL1, | chr11:14101567:++;        | 2.9828  | 35.3005 | 24.6104 | 26.926  |
|                | (serous adenocarcinoma) |                   |                 |                |                |        |                  | CCNE1, ATP1A1, TRIM33       | chr5:139267096:--;       |         |         |         |         |
| **Prostate adenocarcinoma** |               |                   |                 |                |                |        |                               |                         |         |         |         |         |
| 6              | 81, M, supra-clavicular lymph node metastasis | PLPP1 | 5q11.2 | (P1, N2) | 4 | 9 | 0 | Stable TMPRSS2-ERG ARv7 variant | chr5:54830400:--; | 34.1716 | 39.888  | 59.7252 | 12.5726 |
|                | (adenocarcinoma)      |                   |                 |                |                |        |                  | chr5:139267096:--;          |                       |         |         |         |         |
| **Carcinoma of unknown primary** |               |                   |                 |                |                |        |                               |                         |         |         |         |         |
| 7              | 71, M, liver metastasis | CYSTM1            | 5q31.3          | (C2, N2)       | 9              | 3      | 0                | Stable CHEK2, TP53          | chr5:139574237:++;       | 26.7383 | 26.2464 | 62.0065 | 0.58000 |
|                | (adenocarcinoma)      |                   |                 |                |                |        |                  | chr5:139267096:--;          |                       |         |         |         |         |

\[\text{\textsuperscript{a}}\]The nomenclature of fusion breakpoint is first alphabet of the fusion partner, followed by the exon number in which the fusion occurs. Similarly, the same nomenclature for NRG2 fusion in which the exon number in which the fusion occurred is listed after N.
\[\text{\textsuperscript{b}}\]Reciprocal fusions were identified.
CNA, copy number alterations; F, female; M, male; MMR, mismatch repair; MSI, microsatellite instability; Muts/MB, mutations per megabase; NA, not applicable; NFR2, neuregulin-2; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden; TPM, transcript per millions; TPS, tumor proportion score.
The following number of samples by selected tumor types underwent WTS at Caris Life Sciences: (1) 9600 cases of NSCLC; (2) 6400 cases of colon cancer; (3) 5400 cases of breast cancer; (4) 5030 cases of ovarian cancer; (5) 3060 cases of endometrial cancer; and (6) 1600 cases of prostate cancer. Seven inframe predicted functional (containing the EGF domain) \( \text{NRG2} \) fusions (all \( \text{NRG2}\alpha \)) were identified. Six of the seven \( \text{NRG2}\alpha \) fusions had breakpoints at exon 2, whereas the other one had its breakpoint at exon 4 (Table 1, Fig. 1A). The distribution of junction reads of \( \text{NRG2} \) reported here were not different from other actionable fusions like \( \text{ALK} \) in NSCLC. The average \( \text{NRG2} \) junctional reads were 36.5 copies (SD = 36.9), with average junctional reads from 100 randomly selected \( \text{ALK} \)-positive NSCLC tumors was 16.9 (SD = 25.3, \( p \) by \( t \) test is 0.2).

The RNA reads from the transcriptome analysis were investigated for unique EGF domain splice junctions (139246294:139251305 for \( \alpha \), and 139244757:139251305 for \( \beta \)) and alternative splicing of exon 5 that forms part of the EGF domain (Fig. 1B). The

Figure 1. (A) A schematic of the seven inframe \( \text{NRG2}\alpha \) fusions. (B) A schematic of the generation of the full EGF-like domain from the differential splicing of the EGF-like core domain and the \( \alpha \) or \( \beta \) isoform. The alignment of amino acid sequences of EGF-like domain between \( \text{NRG2}\alpha \) and \( \text{NRG2}\beta \) with reference to the EGF domain of EGFR are shown with the aqua color highlighted region representing the \( \alpha \)-isoform and the green color highlighted representing the \( \beta \)-isoform. Modified from Jones et al.15 Ig-like, immunoglobulin-like; \( \text{NFR2} \), neuregulin-2.

Results

The following number of samples by selected tumor types underwent WTS at Caris Life Sciences: (1) 9600 cases of NSCLC; (2) 6400 cases of colon cancer; (3) 5400 cases of breast cancer; (4) 5030 cases of ovarian cancer; (5) 3060 cases of endometrial cancer; and (6) 1600 cases of prostate cancer. Seven inframe predicted functional (containing the EGF domain) \( \text{NRG2} \) fusions (all \( \text{NRG2}\alpha \)) were identified. Six of the seven \( \text{NRG2}\alpha \) fusions had breakpoints at exon 2, whereas the other one had its breakpoint at exon 4 (Table 1, Fig. 1A). The distribution of junction reads of \( \text{NRG2} \) reported here were not different from other actionable fusions like \( \text{ALK} \) in NSCLC. The average \( \text{NRG2} \) junctional reads were 36.5 copies (SD = 36.9), with average junctional reads from 100 randomly selected \( \text{ALK} \)-positive NSCLC tumors was 16.9 (SD = 25.3, \( p \) by \( t \) test is 0.2).

The RNA reads from the transcriptome analysis were investigated for unique EGF domain splice junctions (139245209:139251305 for \( \alpha \), and 139244757:139251305 for \( \beta \)) and alternative splicing of exon 5 that forms part of the EGF domain (Fig. 1B).
splice junction reads for the α isoform revealed an average of 64 (range: 9–267), whereas no β isoform-specific splice junction was detected similar to the observations by Kohsaka et al. All NRG2 fusions were detected by WTS as we did not bait for NRG2 gene in DNA next-generation sequencing.

**Tumor With Inframe NRG2 Fusions**

The full list of inframe NRG2α fusions with molecular characteristics is listed in Table 1. None of the seven NRG2α fusions was mucinous adenocarcinoma. The four quartiles of TMB are 0 to 7, greater than 7 to 10, greater than 10 to 14, greater than 14 mutations per megabase. Hence the TMB of NRG2α falls within the two lower quartiles. All seven NRG2α fusions were microsatellite stable.

**NSCLC (CDH1-NRG2α, F11R-NRG2α)**

The first 585 amino acids of CDH1, which contains five cadherin repeats, were fused to NRG2. Of note, an inframe reciprocal fusion of NRG2-CDH1 (N5, C12; chr5:139245134:−/chr16:68855904:+) with 205 junction reads were also identified in the same tumor sample. F11R is junctional adhesin molecule A. The first 22 amino acids of F11R were fused to NRG2 (Fig. 1). Again, an inframe complete reciprocal fusion of NRG2-F11R (N5, F11; chr5:139245134:−/chr1:160971143:−) with 37 junctional reads was also identified in the same tumor sample. The PD-L1 expression in the F11R-NRG2α tumor is 10% (tumor proportion score), and it was the only NRG2α fusion with a positive PD-L1 expression. No other known driver mutations were identified in these two samples.

**Endometrial Adenocarcinoma (CPM-NRG2α, OPA3-NRG2α)**

CPM is a membrane-bound arginine/lysine carboxypeptidase M. The first 86 amino acids of CPM were fused to exon 2 of NRG2, which retains the two zinc metal-binding sites at amino acids 83 and 86. OPA3 is an outer mitochondrial membrane lipid metabolism regulator. The first 47 amino acids of OPA3 were fused to exon 2 of NRG2. The coiled-coil domain of OPA3 is located between 103 and 163 amino acids of OPA3, thus, not contained in the fusion partner.

**Ovarian Adenocarcinoma (SPON1-NRG2α)**

SPON1 is a cell adhesion molecule likely involved in maintaining cell adhesion in both neural and nonneural tissues. The first 275 amino acids of SPON1 containing a reelin domain (heparin-binding domains that can aggregate together to bind calcium) and part of the six type I TSR repeats were fused to NRG2.

**Prostate Adenocarcinoma (PLPP1-NRG2α)**

PLPP1 contains six transmembrane regions with the first transmembrane region between seven and 27 amino acids of PLPP1. The first 19 amino acids of PLPP1 were fused to exon 2 of NRG2. The tumor also harbored an out-of-frame PLPP1-NRG2α fusion (P3, N2; chr5:54763697:−/chr5:139267096:−) with junctional reads of 57. The junctional reads were only four for the in-frame PLPP1-NRG2α fusion.

**Carcinoma of Unknown Origin**

CYSTM1 has a transmembrane region from amino acids 74 to 91. The full length of the 97 amino acids was fused to exon 2 of NRG2. CYSTM1 has a cysteine-rich region from amino acids 88 to 91 and a proline-rich region from 6 to 59.

**Discussion**

This report confirms the observation of Kohsaka et al. that NRG2α fusions are recurrent, albeit rare, ligand fusions present in NSCLC. We further extend that NRG2α fusions were identified in other solid malignancies, especially gynecologic malignancies, similarly to NRG1 fusions. Importantly, no other known actionable driver mutations were identified in these seven tumor samples. The incidence and distribution of NRG2α fusions (0.02%–0.07%) are similar to the rare incidence and broad distribution of NRG1 fusions. NRG2 is located on chromosome 5q31.2. Only one of seven fusion partners (CYSTM1 on 5q31.3) is located close to the NRG2 chromosomal locus. Of note, there were several out-of-frame NRG2 fusions and one 5′-NRG2 fusion that did not contain the EGF domain detected by WTS (data not shown); expert bioinformatics and molecular analysis of sequencing data before reporting are of critical importance. Current commercially targeted RNA next-generation sequencing does not bait for NRG2 fusions.

The limitations of this study include the lack of treatment outcome, the unknown phosphorylation status of the ERBB family members, and the lack of smoking status of the two patients with NRG2α-positive NSCLC.

The difference in biology and actionability between NRG1 and NRG2 ligand-fusions has been recently discussed (reference 2 and references therein). All NRG2 fusions identified to date have the α-isof orm of the EGF domain, which tends to bind less avidly than the β-isof orm of EGF to the HER family members of receptor tyrosine kinase. In addition, NRG2α preferentially binds to HER4, whereas NRG1α/β binds to HER3. Kohsaka et al. reported that all four HER family members were phosphorylated in NRG1 fusion-positive NSCLC samples, but only HER4 was phosphorylated in one CD74-NRG2α/β fusion–positive NSCLC tumor.
Hence, to inhibit NRG2α fusions, rather than targeting HER3, anti-HER4 (blocking NRG2α binding to HER4 together with disruption of HER4 homodimerization and heterodimerization) is likely needed. Alternatively, a pan-HER approach with a pan-HER tyrosine kinase inhibitor may be able to target both ligand fusions.\textsuperscript{2,4,5} Given the novelty and rarity of NRG2α fusions, it is hoped that tumor-agnostic clinical trials against NRG2 fusion-positive solid tumors will answer the many questions regarding the exact role that these NRG2α fusions play in the pathogenesis of these tumors and their actionability, as well as the relative contribution of α-isoform to β-isoform of NRG2 fusions.

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