Editorial Commentary

High-resolution genomic configuration of *FGFR* rearrangements dictates the therapeutic vulnerability of squamous cell lung cancers

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Comment on: Malchers F, Nogova L, van Attekum MH, *et al.* Somatic rearrangements causing oncogenic ectodomain deletions of FGFR1 in squamous cell lung cancer. J Clin Invest 2023;133:e170217.

Keywords: Sequencing; squamous cell lung cancer (SQCLC); FGFR1 amplification; FGFR1 dependency

Submitted Oct 30, 2023. Accepted for publication Jan 10, 2024. Published online Feb 20, 2024.
doi: 10.21037/tlcr-23-705
View this article at: https://dx.doi.org/10.21037/tlcr-23-705

Squamous cell lung cancers (SQCLC) have significant cellular heterogeneity and few therapeutic targets. In the paper by Malchers *et al.*, 8p11-p12 amplifications involving *FGFR1*, frequently altered in SQCLC, have been examined by high-resolution deep-sequencing (1). The amplification of 8p11-p12 arises from breakage-fusion-bridges (BFB) and its genomic impact can vary with respect to genomic architecture of *FGFR1*. Of note, the tail-to-tail rearrangements in or close to *FGFR1* lead to *FGFR1*-centered, focal high-level amplifications, which showed responsiveness to FGFR inhibitors *in vitro* and *in vivo*, indicative of FGFR dependency. This correlation between the genetic dependency and genomic configurations suggests that the traditional arm- or cytoband-level genomic markers can be elaborated using high-resolution genomic tools to ensure their clinical relevance.

There has been a recent improvement in the survival of patients with SQCLC due to the advent of anti-PD1-based immune checkpoint inhibitors. However, only a limited number of patients benefit from these treatments. Along with few molecular targets approved for the disease, this makes the treatment of SQCLC particularly challenging (2,3). The Cancer Genome Atlas group has provided a comprehensive molecular profiling of 178 early-stage SQCLC tumors in 2012 (4). This study revealed frequently altered somatic changes encompassing multiple biological pathways, e.g., genes with significant amplifications or deletions such as *SOX2*, *FGFR1*, *WHSC1L1*, *PGFRA*, *KIT*, *CCND1*, *CDNK2A*, *NFE2L2*, *MYC*, *CDK6*, and *PTEN* along with recurrent mutations in *TP53*, *CDKN2A*, *PTEN*, *PIK3CA*, *KEAP1*, *HLA-A*, *MLL2*, *NFE2L2*, *NOTCH1*, and *RB1*. Compared to lung adenocarcinomas with well-recognized alterations such as *EGFR* exon19 del or exon 21-L858R, oncogenic driver mutations are relatively deficit in SQCLC. However, some recurrent alterations such as the amplification of *FGFR1* observed in approximately 20% of SQCLC, may be eligible candidates for targeted treatments (5). A variable correlation between gene

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amplification, mRNA expression, and protein expression of *FGFR1* have been reported in cell lines and tumors indicative of heterogeneity in the mechanisms of *FGFR* amplification and their transcriptional-translation regulation (6). This heterogeneity may contribute to variable response rates to FGFR inhibitors, e.g., not all cells or animal models with *FGFR1* amplification respond to FGFR1 inhibitors (5). Of note, a number of FGFR inhibitors, especially small molecule inhibitors such as infigratinib (BGJ398), AZD4547, erdafitinib (JNJ-42756493), have been tested in phase I and II trials, but the overall response rates were 8–15%, and *FGFR1* amplification was not particularly meaningful as a predictive biomarker (7-9).

To dissect the heterogeneity in terms of molecular mechanisms of *FGFR1* amplification and their impact on the efficacy to FGFR inhibitors, Malchers *et al.* performed deep sequencing (hybrid capture-based sequencing) on 8p11-p12 amplifications across primary SQCLCs, cancer cell lines and patient-derived xenografts (1). Out of ten primary cases with *FGFR1* amplification detected by traditional methods such as fluorescence in situ hybridization (FISH), only four responded to FGFR inhibitors confirming that *FGFR1* amplification alone does not serve as predictive markers for FGFR inhibitors. Of note, two patients who showed the sensitivity to FGFR inhibitors, demonstrated unique genomic configurations near the *FGFR1* locus. The configurations consisted of the deletion of *FGFR1* ectodomain (up to exon 8) and the 'stair-like' amplification centered at *FGFR1*. While the ectodomain deletion indicates the loss of self-inhibitory, immunoglobulin-like domains, the resulting N-terminally truncated *FGFR1* still have intact transmembrane and kinase domains with active transcription. These patient-derived N-terminally truncated *FGFR1* version were tested *in vitro* for the FGFR dependency. Moreover, the examination of 8p-amplified cell lines and patient-derived xenografts confirmed that those with FGFR dependency typically display *FGFR1*-centered amplicons, that pattern of which can be detected by relatively low-resolution copy number profiles encompassing *FGFR1* locus. The second notable feature associated with FGFR1 dependency is the 'stair-like' amplification at *FGFR1* locus, which is a typical feature of BFB recursive cycles. Moreover, tail-to-tail rearrangements at or close in the *FGFR1* were associated with the *FGFR1*-centered amplifications and potentially with FGFR dependency. Overall, tail-to-tail rearrangements in or close to *FGFR1* were observed in 78% of the observed responders (7 out of 9) while only 25% of non-responders (3 out of 12) showed the tail-to-tail rearrangements suggesting the tail-to-tail rearrangements as the distinguishing features of FGFR1 dependency.

BFB has been first proposed by Barbara McClintock in maize as a mechanism of chromosomal instability (10). BFB cycles begin with telomere loss (breakage) followed by the formation of a dicentric chromosome (fusion) and subsequent breakage at bridge-like structure. These steps can iterate repeatedly as BFB cycle. BFB cycles can generate complex chromosomal rearrangements and amplifications often responsible for copy number gains of oncogenes in cancer genomes (11). BFB cycles are often associated with chromothripsis, a catastrophic genomic event where multiple chromosomal breakages occur simultaneously and reassemble randomly, creating a complex mixture of chromosomal segments (12). The association of BFB cycles and chromothripsis suggests a mechanistic connection thereby contributing to pronounced genomic instability of cancer genomes (13). Moreover, the extensive BFB cycles often generate the extrachromosomal DNAs instead of creating homogeneously staining regions in *cis* (14). While reports have highlighted oncogene amplifications through BFB cycles, the impact of their resulting genomic configurations, especially in clinical contexts, remains largely unexplored.

In summary, the tail-to-tail rearrangement at or close to *FGFR1* leading to the *FGFR1*-centered amplifications, indicate the FGFR1 dependency with the sensitivity to FGFR inhibitors. The unique genomic characteristics, marked by copy number profiles with peaks at or near the *FGFR1* locus, are identifiable across a range of DNA sequencing platforms, including panel sequencing (those covering *FGFR1* locus) and whole genome sequencing. This adaptability makes this biomarker a viable option for incorporation into current clinical practices. The challenge remains due to the limited performance in predicting the FGFR1 dependency (sensitivity =77.8% and specificity =75%, respectively, on pooled data including cell lines, xenograft models and patients of the report) (1). One possible explanation for this genotype-phenotype discordance may be the genomic heterogeneity, where the BFB cycles frequently gives multiple subclones with different copy number states (11). Another challenge is to discover the roles *FGFR1* amplification accompanying features, such as the deletion of *NSD3* adjacent to *FGFR1*, which co-occurs with *FGFR1* amplifications, or exclusive

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genomic alterations such as *PIK3CA* mutations enriched in genomes non-responsive to FGFR inhibitors. While Malchers *et al.* primarily examined the genetic structure of coding sequences related to *FGFR1*, there is a possibility that epigenetic abnormalities linked to chromosomal rearrangements affect the drug response. For instance, in cancer genomes, structural variations often result in enhancers being placed next to key driver genes (a process known as 'enhancer hijacking'), which leads to transcriptional upregulation of cancer driver genes (15). One interesting phenomenon is that FGFR1 expression is more concordant with protein levels than *FGFR1* copy numbers suggesting that roles of epigenetics need to be further investigated (16). Moreover, the amplification of 8p11.12, which involves *FGFR1* and additional genes such as *ZNF703*, *ERLIN2*, *PLPBP*, *ADGRA2*, *BRF2*, *RAB11FIP1*, *GOT1L1*, *ADRB3*, *EIF4EBP1*, *ASH2L*, *STAT*, *LSM1*, *BAG4*, *DDHD2*, *PLPP5*, *NSD3*, *LETM2*, and *TACC1*, is commonly observed in various tumor types, including breast, esophageal, and bladder cancers (17,18). Although FGFR1 inhibitors have shown promising responses in some tumor types (19), further research is needed to understand the detailed genomic structure of 8q11.12 and the potential influence of other neighboring genes in different types of tumors. The accompanying commentary on the article by Mäkinen and Meyerson are also available for further insights (20).

It is also of note that the Malchers *et al.* highlighted high-resolution genome features that can significantly benefit from whole genome sequencing (1). Despite the cost of whole genome sequencing remaining stable since 2015, recent advancements in sequencing technology and artificial intelligence-driven data processing have reduced it to around 200 USD recently (21). The price is anticipated to drop further as patents on key sequencing technologies expire. The reduction in sequencing costs may benefit cancer genome sequencing by expanding eligibility for whole-genome sequencing, which provides detailed insights into characteristics associated with structural variations and chromosomal rearrangements. With the anticipated drop in the cost of whole genome sequencing to around 100 USD, we expect resurgence in investigating traditional genetic markers, paving the way for next-level precision medicine.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Lung Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-705/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-705/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Hong SH, Kim TM. High-resolution genomic configuration of *FGFR* rearrangements dictates the therapeutic vulnerability of squamous cell lung cancers. Transl Lung Cancer Res 2024;13(2):236-239. doi: 10.21037/tlcr-23-705

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