Received: 8 February 2022 | Revised: 4 April 2022 | Accepted: 13 May 2022

DOI: 10.1002/mgg3.1994

Molecular Genetics & Genomic Medicine Open Access WILEY

ORIGINAL ARTICLE

The significance of the fusion partner gene genomic neighborhood analysis in translocation-defined tumors

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Abstract

Introduction: This study presents a novel molecular parameter potentially co-defining tumor biology—the total tumor suppressor gene (TSG) count at chromosomal loci harboring genes rearranged in fusion-defined tumors. It belongs to the family of molecular parameters created using a black-box approach.

Method: It is based on a public curated Texas TSG database. Its data are regrouped based on individual genes loci using another public database (Genecards). The total TSG count for *NTRK* (*NTRK1*; OMIM: 191315; *NTRK2*; OMIM: 600456; *NTRK3*; OMIM: 191316), *NRG1* (OMIM: 142445), and *RET* (OMIM: 164761) rearranged tumors in patients treated with a theranostic approach is calculated using the results of recently published studies.

Results: Altogether 138 loci containing at least three TSGs are identified. These include 21 "extremely hot" spots, with 10 to 28 TSGs mapping to a given locus. However, the study falls short of finding a correlation between tumor regression or patient survival and the TSG count owing to a low number of cases meeting the study criteria.

Conclusion: The total TSG count alone cannot predict the biology of translocation-defined tumors. The addition of other parameters, including microsatellite instability (MSI), tumor mutation burden (TMB), homologous recombination repair deficiency (HRD), and copy number heterogeneity (CNH), might be helpful. Thus a multi-modal data integration is advocated. We believe that large scale studies should evaluate the significance and value of the total TSG count.

KEYWORDS

artificial intelligence, cancer, chromosomal instability, chromothripsis, copy number heterogeneity, gene, gene rearrangement, homologous recombination repair, microsatellite instability, translocation, tumor mutation burden, tumor suppressor gene

1 | INTRODUCTION

If a tumor suppressor gene (TSG) is altered, the respective oncogenic pathway is modified, and the development of a more deregulated cell population leading to a more aggressive tumor could be possible. Many translocation-defined tumors share the same driver gene, and at the same time, they present different histomorphology

and biology (Chiang, 2021; Collins et al., 2022; Croce et al., 2021; Dermawan et al., 2021; Gatalica et al., 2019; Jonna et al., 2019; Kuroda et al., 2020; Misove et al., 2021; Sharma et al., 2018). We can appreciate that gene fusion is just one part of a tumor genomic landscape by taking a broader view (Hanahan & Weinberg, 2011; Rheinbay, 2020; Vogelstein et al., 2013). Available molecular data present a very complex picture. It needs a comprehensive interpretation. Identifying crucial biomolecular information and defining useful descriptive parameters is the urgent task that pathologists face. It is conceivable that in this regard, sometimes a black-box approach is taken given the complexity of genetic events involved in fusion genes expression (which includes alteration of gene structure, upstream and downstream elements, transcriptional controls, etc.), a phenomenon of chromatin fragility, the stochastic nature of the DNA damage, and current technological limitations. This study aims to review chromosomal loci in human chromosomes harboring multiple tumor suppressor genes (TSG)s. Also, it serves as a proof of concept study applying rudimentary genomic neighborhood analysis by using some high-quality data published on the *NTRK* (*NTRK1*; OMIM: 191315; *NTRK2*; OMIM: 600456; *NTRK3*; OMIM: 191316), *NRG1* (OMIM: 142445), and *RET* (OMIM: 164761) rearranged tumors with recorded patient clinical outcomes. The idea is potentially expandable and may improve bioinformatic tools to predict biology and targeted therapy response in translocation-defined tumors.

2 | MATERIAL AND METHODS

The curated TSG database (Zhao et al., n.d., 2013) data were regrouped based on individual genes loci by using Genecards information (Stelzer et al., 2016). The chromosomal loci harboring at least three known TSGs were listed (Table 1). The loci containing less than three TSGs were arbitrarily scored as 0. Due to the unique biology of the chromosomes X and Y, their respective loci were excluded from the analysis. The Pubmed database was searched for papers reporting targeted treatment of the *NTRK*, *NRG1*, and *RET* rearranged tumors containing tumor molecular analysis employing at least two methods, with NGS being one of them. The reported *NTRK*, *NRG1*, and *RET* translocation partners were listed. The locus information was rendered from the Genecards database for each enlisted gene. Subsequently, the number of known TSGs in a given chromosomal locus was added based on Table 1. The co-localized TSG count for both partner genes was summed up in each tumor. Individual fusion-defined tumor groups were analyzed. The patient outcome, tumor regression score, and total TSG count were correlated. The predictive and prognostic values of the total TSG count were discussed.

3 | RESULTS

The curated Texas TSG database (Zhao et al., n.d., 2013) contains 1217 TSGs at the time of writing. We were able to identify 138 loci containing at least three TSGs (Table 1). These include 21 "extremely hot" spots, with 10 to 28 TSGs identified at a given locus (Table 2). Known *NTRK1*, *NTRK2*, *NTRK3*, and *RET* translocation partners described by papers included in this study (Drilon et al., 2018, 2020, 2021; Jones et al., 2019; Wirth et al., 2020) with respective loci and the TSG count for these loci are listed in Tables 3 and 4. The *NRG1* rearranged cases are discussed separately. The individual chromosomal locus TSG count ranged from 0 to 28. It seems that most of the genes involved in gene fusions map to chromosomal loci containing more than three TSGs.

3.1 | NTRK

Favorable-targeted therapy response was noticed in the vast majority of cases. Furthermore, it was associated with a total TSG count equal to or below 6 (mostly four and lower). Moreover, in patients developing *NTRK* rearranged tumors with fusion partner genes *LMNA* (OMIM: 150330), *TPM3* (OMIM: 191030), and *ETV6* (OMIM: 600618), six cases with unfavorable-targeted therapy responses were reported. There was no correlation between the total TSG count and the clinical outcome (Table 3).

3.2 | RET

Overall, 162 selpercatinib treated patients with *RET* rearranged thyroid carcinomas were characterized by Wirth et al. (2020) Unfortunately, in Figure S9 partner gene information is not available for the reported maximum change in tumor size. Thus, the co-localized TSG count-based analysis could not be performed.

In *RET* rearranged lung NSCLCs Drilon reported on clinical outcomes following selpercatinib-targeted therapy in 105 cases (Drilon et al., 2020). Tumor regression of 80% to 100% was associated with a total TSG count of 9 to 15. Interestingly, *KIF5B-RET* (*KIF5B*; OMIM: 602809) fusion with the total TSG count of 10 was associated with cases presenting up to 90% tumor regression and the others showing up to 15% tumor progression (Table 4).

3.3 | NRG1

Drilon reported on 20 patients with *NRG1* rearranged NSCLC treated with afatinib (Drilon et al., 2021). The clinical outcome data on progression-free and overall survival are partly summarized in Figures 1 and 2. Based on these, statistically significant conclusions related to the total TSG count could not be made due to different

TABLE 1 Each chromosome (Chr. No.) contains several loci with multiple tumor suppressor genes (TSG) so-called TSG hot spot

Chr. No.	Locus	Number of TSG	Chr. No.	Locus	Number of TSG	Chr. No.	Locus	Number of TSG
1	1p22	3	6	6q22	4	12	12q13	11
	1p32	5		6q23	5		12q14	3
	1p33	3		6q24	3		12q21	3
	1p35	6		6q25	6		12q23	8
	1p36	17		6q27	3		12q24	12
	1q21	3	7	7p15	3	13	13q12	12
	1q32	4		7q11	3		13q14	13
	1q41	3		7q21	4		13q21	3
	1q42	3		7q22	11		13q22	3
2	2p11	4		7q31	7		13q31	4
	2p13	4		7q32	6	14	14q11	3
	2p21	6		7q34	4		14q13	4
	2q11	4		7q35	5		14q23	6
	2q23	3		7q36	3		14q24	4
	2q24	3	8	8p11	4		14q32	16
	2q32	3		8p12	4	15	15q15	3
	2q33	6		8p21	13		15q21	5
	2q34	4		8p22	9		15q22	3
	2q35	5		8p23	9		15q26	5
3	3p21	17		8q22	4	16	16p11	7
	3p25	5		8q24	7		16p12	4
	3q13	4	9	9p13	5		16p13	13
	3q23	3		9p21	6		16q12	4
	3q26	5		9p24	4		16q13	4
4	4q12	3		9q21	4		16q21	3
	4q21	4		9q22	12		16q22	6
	4q22	3		9q31	3		16q23	4
	4q24	4		9q33	6		16q24	6
	4q25	3		9q34	8	17	17p13	18
	4q26	4	10	10p11	4		17q11	4
	4q31	3		10q11	6		17q12	4
	4q35	3		10q21	3		17q21	14
5	5p13	3		10q22	4		17q25	3
	5p15	5		10q23	4	18	18p11	4
	5q13	3		10q24	7		18q11	4
	5q21	4		10q25	7		18q21	9
	5q31	16		10q26	5	19	19p13	22
	5q32	3	11	11p11	6		19q13	28
	5q35	8		11p13	4	20	p11	3

(Continues)

TABLE 1 (Continued)

Chr. No.	Locus	Number of TSG	Chr. No.	Locus	Number of TSG	Chr. No.	Locus	Number of TSG
6	6p12	4		11p15	11		q11	7
	6p21	9		11q13	11		q13	17
	6p22	3		11q22	5	21	q21	5
	6p23	3		11q23	10		q22	5
	6p24	4		11q24	3	22	q11	6
	6q14	3	12	12p12	7		q12	7
	6q21	5		12p13	6		q13	10

Notes: In the human genome (excluding X, Y chromosomes), there are 138 TSG hot spots containing at least three TSGs identified in a curated database of 1217 TSGs. (The University of Texas, School of Biomedical Informatics TSG database, accessed December 2021).

TABLE 2 A summary of 21 "extremely hot "chromosomal loci with 10 to 28 individual tumor suppressor genes (TSG) co-localized to a given locus (Sourced from The University of Texas, School of Biomedical Informatics TSG database, accessed December 2021)

Locus	No of TSGs	Co-localized TSGs
1p36	17	*RUNX3, E2F2, EPHA2, EXTL1, TCEB3, NR0B2, SFN, ALPL, EPHB2, RAP1GAP, RPL11, SDHB, PRDM2, ZBTB48, TP73, TNFRSF18, DFFA*
3p21	17	*GNAT1, MST1, ACY1, BAP1, RHOA, MLH1, MST1R, SEMA3F, SEMA3B, LIMD1, DLEC1, LTF, PRKCD, SMARCC1, TDGF1, WNT5A, PLCD1*
5q31	16	*PCDHGC3, TGFBI, HDAC3, CXCL14, KDM3B, CSF2, EGR1, IRF1, PPP2CA, PDLIM4, HINT1, MZB1, PAIP2, CXXC5, SPRY4, SPARC*
7q22	11	*CDK6, ACHE, EPHB4, TFPI2, AZGP1, CUX1, ARMC10, FBXL13, NAPEPLD, HBP1, RINT1*
8p21	13	*BNIP3L, EXTL3, TNFRSF10A, NKX3-1, TRIM35, PPP3CC, DOK2, RHOBTB2, PIWIL2, MIR320A, CLU, TNFRSF10B, PDGFRL*
9q22	12	*GAS1, NINJ1, ROR2, SYK, NR4A3, GADD45G, FBP1, PTCH1, WNK2, MIRLET7A1, MIRLET7D, MIRLET7F1*
11p15	11	*ARNTL, ST5, TSG101, SAA1, ILK, PHLDA2, EIF3F, CDKN1C, NUP98, RNH1, TSPAN32*
11q13	11	*CST6, GSTP1, MEN1, PLCB3, PPP1CA, RBM4, PHOX2A, FADD, AIP, UVRAG, WNT11*
11q23	10	*ATM, PGR, RARRES3, SDHD, ZBTB16, PPP2R1B, TAGLN, CBL, H2AFX, THY1*
12q13	11	*ITGA5, CDK2, NR4A1, ITGA7, LIMA1, VDR, CBX5, ZC3H10, GLI1, GLS2, MYO1A*
12q24	12	*RASAL1, PRDM4, PTPN11, SH2B3, TBX5, TCHP, RITA1, PEBP1, HSP90B1, CDK2AP1, DIABLO, CHFR*
13q12	12	*GJB2, FLT3, KL, PDX1, IFT88, LATS2, TPTE2, USP12, RASL11A, BRCA2, CDX2, PDS5B*
13q14	13	*TSC22D1, TRIM13, FOXO1, RB1, ARL11, KCNRG, MIR15A, MIR16-1, DLEU2, DLEU1, OLFM4, INTS6, THSD1*
14q32	16	*DLK1, MEG3, DICER1, MIR127, MIR136, MIR370, MIR493, PPP2R5C, MIR134, MIR329-1, MIR409, MIR410, MIR494, MIR495, MIR487B, MIR203A*
16p13	13	*SOCS1, LITAF, EMP2, GRIN2A, CREBBP, IGFALS, PKD1, TSC2, AXIN1, DNAJA3, STUB1, TNFRSF12A, SLX4*
17p13	18	*TNFSF12, ALOX15B, SOX15, TP53, TNK1, GABARAP, XAF1, ZBTB4, ALOX15, DPH1, HIC1,MNT, PAFAH1B1, PFN1, RPA1, MYBBP1A, VPS53, SMYD4*
17q21	14	*BRCA1, JUP, PHB, BECN1, IKZF3, EZH1, IGFBP4, KRT19, HOXB13, NME1, STAT3, ITGB3, SPOP, NGFR*
19p13	22	*PIN1, MIR181C, DNMT1, DNAJB1, SMARCA4, GADD45GIP1, MIR199A1, CNN1, NOTCH3, AMH, DAPK3, GADD45B, STK11, TCF3, TNFSF9, SAFB2, ANGPTL4, FZR1, SIRT6, PLK5, DIRAS1, SAFB*
19q13	28	*ERF, KLK10, SIRT2, CEBPA, TGFB1, ZFP36, SPINT2, PDCD5, ZNF382, ZFP82, MAP4K1, CEACAM1, LGALS7, MIA, CIC, KLK6, GLTSCR2, GLTSCR1, CADM4, MIR150, BAX, IRF3, BBC3, CNOT3, PEG3, BRSK1, MIRLET7E, MIR125A*
20q13	17	*PTPRT, HNF4A, NCOA5, ZFAS1, PTPN1, NFATC2, SALL4, CDH4, RBM38, CTCFL, MIR296, DIDO1, GATA5, MIR1-1, MIR124-3, MIR133A2, MIR941-1*
22q13	10	*PRR5, MYH9, ST13, MIR33A, BIK, FBLN1, PPARA, MIRLET7A3, MIRLET7B, PANX2*

TABLE 3 The total tumor suppressor gene (TSG) count of the partner gene loci in *NTRK* rearranged lung carcinomas correlated with reported tumor size change in larotrectinib-treated patients

Partner gene	Locus	TSG count	Driver gene	Total TSG	Tumor size change
LMNA	1q22	0	*NTRK1* 1q23.1 (TSG 0)	0	(+50% to −100%)
GON4L	1q22	0	*NTRK1* 1q23.1 (TSG 0)	0	NA
TPR	1q31	0	*NTRK1* 1q23.1 (TSG 0)	0	−20%
TPM3	1q21.3	3	*NTRK1* 1q23.1 (TSG 0)	3	(+45% to −100%)
IRF2BP2	1q42.3	3	*NTRK1* 1q23.1 (TSG 0)	3	−60%
PDE4DIP	1q21.2	3	*NTRK1* 1q23.1 (TSG 0)	3	−60%
PLEKHA6	1q32.1	4	*NTRK1* 1q23.1 (TSG 0)	0	NA
STRN	2p22.2	0	*NTRK2* 9q21.33 (TSG 4)	4	−55%
ETV6	12p13.2	6	*NTRK3* 15q25.3 (TSG 0)	6	(+30% to −100%)
SQSTM1	5q35.3	8	*NTRK1* 1q23.1 (TSG 0)	8	−90%
PPL	16p13.3	13	*NTRK1* 1q23.1 (TSG 0)	13	−65%
CTRC	1p36.21	17	*NTRK1* 1q23.1 (TSG 0)	17	−32%
TRIM63	1p36.11	17	*NTRK1* 1q23.1 (TSG 0)	17	−100%
TPM4	19p13.12–13.11	22	*NTRK3* 15q25.3 (TSG 0)	22	−75%

Abbreviation: NA, non analyzable.

TABLE 4 The total tumor suppressor gene (TSG) count of the partner gene loci in *RET* rearranged lung carcinomas correlated with reported tumor size change in larotrectinib-treated patients

Partner gene	Locus	TSG count	Driver gene	Total TSG	Tumor size change
PRKAR1A	17q24.2	0	*RET* 10q11.21 (TSG 6)	6	−50%
CCDC6	10q21.2	3	*RET* 10q11.21 (TSG 6)	9	(−30% to −100%)
KIF5B	10p11.22	4	*RET* 10q11.21 (TSG 6)	10	(+15% to −90%)
RBPM4	8p12	4	*RET* 10q11.21 (TSG 6)	10	−90%
TRIM24	7q33-q34	4	*RET* 10q11.21 (TSG 6)	10	−45%
DOCK1	10q26.2	5	*RET* 10q11.21 (TSG 6)	11	−90%
NCOA4	10q11.22	6	*RET* 10q11.21 (TSG 6)	12	−80%
ARHGAP12	10p11.22	6	*RET* 10q11.21 (TSG 6)	12	−60%
ERC1	12p13.33	6	*RET* 10q11.21 (TSG 6)	12	NA
RELCH	18q21.33	9	*RET* 10q11.21 (TSG 6)	15	−80%
CCDC88	11q13.1	11	*RET* 10q11.21 (TSG 6)	17	−35%
CLIP	12q24.31	12	*RET* 10q11.21 (TSG 6)	18	−70%

therapeutic regimes administered to a relatively low number of patients. The analyzed gene loci: *CD74* (OMIM: 142790), *SDC4* (OMIM: 600017), *SLC3A2* (OMIM: 158070) contain 0, 17, and 0 TSGs, with a total TSG count of 4, 21, and 4, respectively.

Jones reported on two patients with *NRG1* rearranged pancreatobiliary carcinoma with follow-up data (Jones et al., 2019) showing significant tumor regression associated with the fusion partner genes *ATP1B1* (OMIM: 182330) (patient 45) and *APP* (OMIM: 104760) (patient 46). Those gene loci contain 0 and 5 TSGs, with a total TSG count of 4 and 9, respectively.

4 | DISCUSSION

Assuming that the occurrence of gene fusion itself could be the "marker" of the chromothripsis-type event taking place precisely at a given gene locus, it is conceivable that chromosomal instability could lead to the alteration and dysfunction of other genes, including TSGs sharing the same chromosomal locus. Chromothripsis is a poorly understood complex genetic mechanism characterized by multiple DNA breaks leading to severe chromatin damage, including gene breaks and amplifications. It was initially reported in hematologic malignancies by Rausch

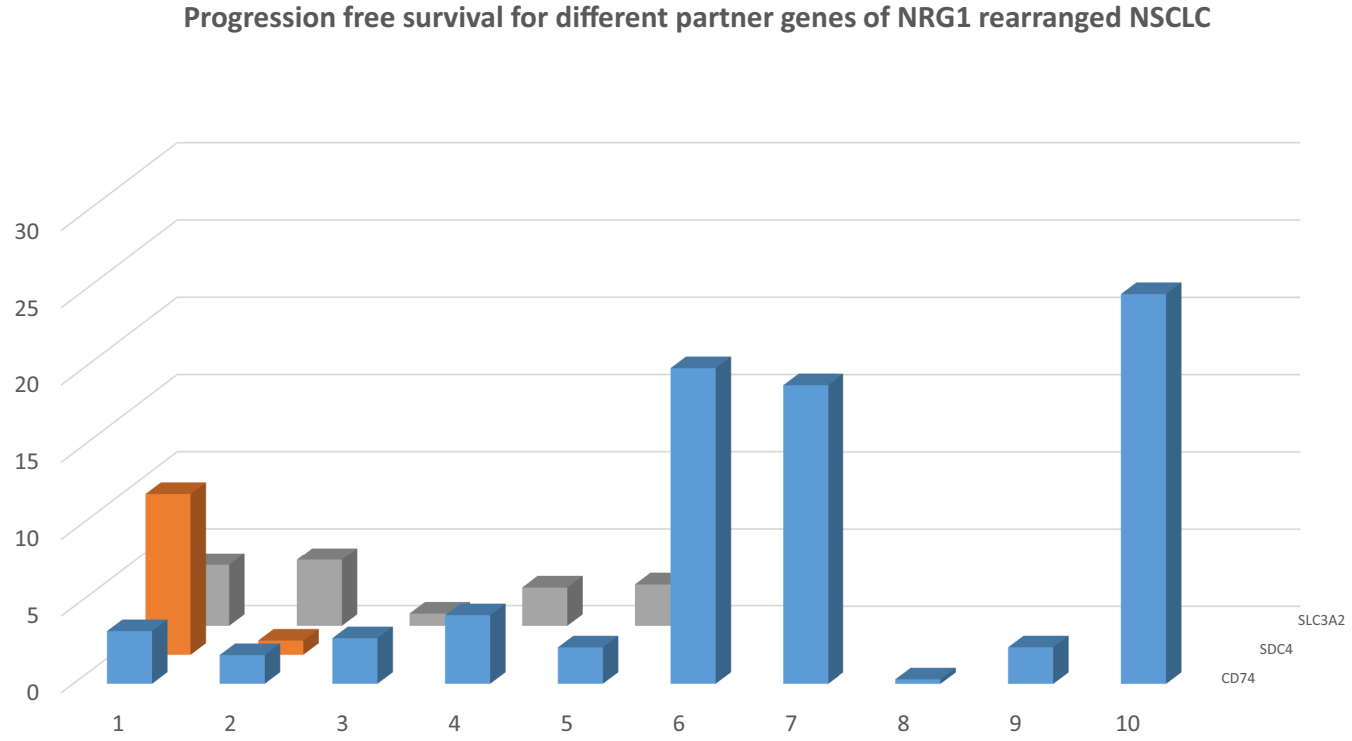

FIGURE 1 The progression-free survival (months) of individual cases for partner genes (*CD74, SDC4*, and *SLC3A2*) of the neuregulin 1 (*NRG1*) rearranged non-small cell lung carcinomas (NSCLC) in larotrectinib-treated patients.

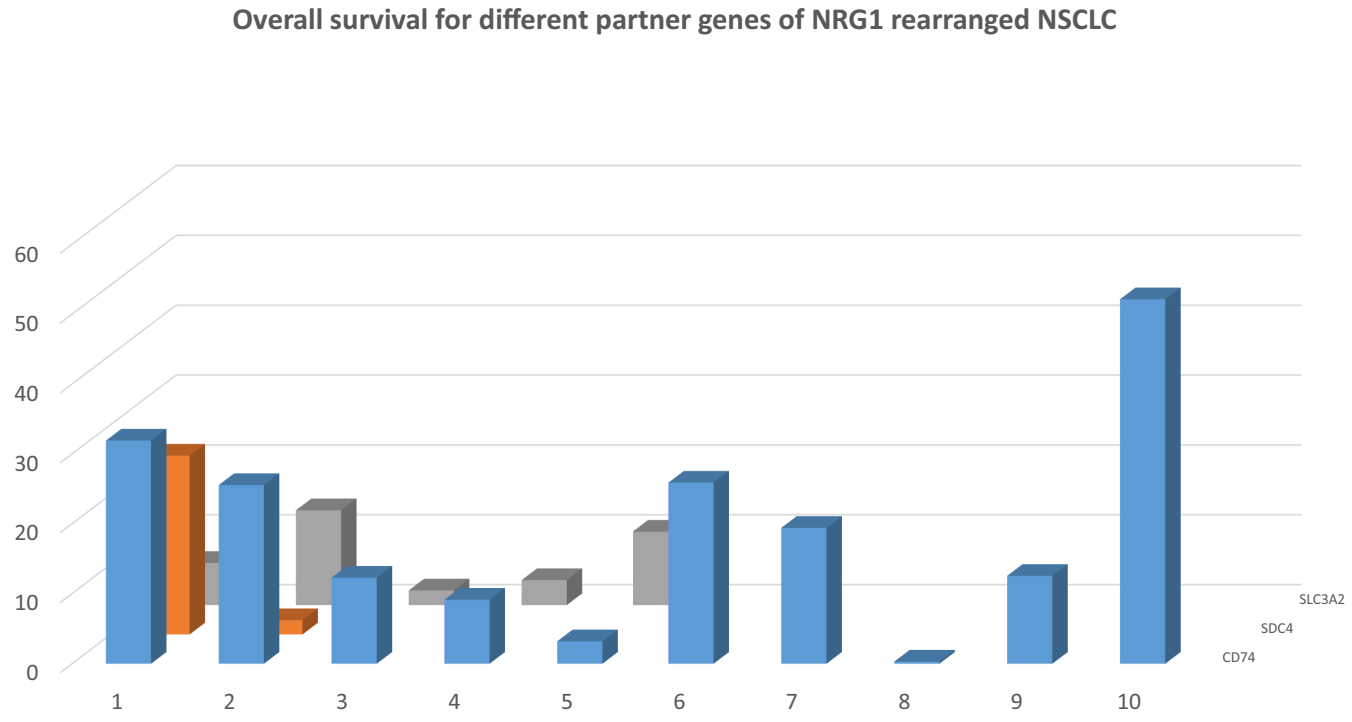

FIGURE 2 The overall survival (months) of individual cases for partner genes (*CD74, SDC4*, and *SLC3A2*) of the neuregulin 1 (*NRG1*) rearranged non-small cell lung carcinomas (NSCLC) in larotrectinib-treated patients.

et al. (2012), Stephens et al. (2011) and recently thoroughly reviewed by Voronina et al. (2020). Presumably, it consists of different types of chromosomal events co-occurring in different genomic regions, and including extrachromosomal circular DNA recombination of an oncogene followed by the amplicon reinsertion into the human

genome (Rosswog et al., 2021). In parallel, the chromosomal instability (possibly represented by a newly defined parameter of the copy number heterogeneity (CNH)) (van Dijk et al., 2021) characterizes the phenomenon of DNA fragility (Davoli et al., 2013; Watkins et al., 2020). If a TSG is altered, the respective oncogenic pathway is modified, and the development of a more deregulated cell population leading to a more aggressive tumor could be possible. Thus, the knowledge of the genomic neighborhood of the translocation partner genes may become important. Any tumor with known translocation could be analyzed by identifying and counting the known co-localized TSGs in the fusion involved genes' genomic neighborhood defined by both partner genes' loci.

Currently, the black-box approach to tumor molecular data are employed when interrogating DNA damage repair mechanisms by calculating tumor mutation burden (TMB), microsatellite instability (MSI), homologous recombination repair deficiency (HRD) (Gonzalez & Stenzinger, 2021), and also CNH. The proposed total TSG count-based genomic neighborhood analysis also takes this approach by using readily available means and free molecular data. In some tumors, the biology is probably defined to a significant extent by the TSG malfunction (primarily due to homozygous or even heterozygous TSG loss or chimeric protein formation). The chromosomal loci of translocation involved partner genes may contain multiple TSGs. In the case of chromosomal instability, those TSGs may be randomly altered as well. A higher total TGS count at a given locus might increase the probability of some TSGs being indeed altered with the respective oncogenic pathway being modified due to a gene break or deletion. These events may significantly define tumor biology regarding its aggressiveness and/or targeted therapy response. Most of the gene fusion partner genes described so far map to chromosomal loci containing more than three TSGs. This is a significant finding given the size of the human genome, and it possibly adds evidence to the notion that the human genome naturally contains areas of increased fragility. Moreover, these loci contain a high number of TSGs. We can appreciate that the phenomenon of chromosomal instability, the concept of TSG, and oncogenic canonical pathways deregulation are interconnected.

The chromosomal TSG hot spots were first summarized by Santarius et al. (2010). The extreme hot spots identified by our study concur with and enrich the original findings. Altogether, 138 loci are enumerated by regrouping the curated TSG database (Zhao et al., n.d., 2013). The proposed total TSG count-based genomic neighborhood analysis could not be adequately tested on the data published so far. Despite tremendous scientific efforts, the pool of targeted therapy treated patients with fusion-defined cancers is still not large enough to draw any significant conclusion. Using a more diverse set of parameters might improve bioinformatic analysis's prognostic/predictive power. Adding computational prediction of protein–protein interaction analysis (Skrabanek et al., 2008) might also provide insight into a possible association between altered genes and some essential biological pathways in tumor cells. Other parameters like TMB and MSI are already used. Calculating the CNH^{25} might also be considered. Also, molecular genetic investigation of translocation-defined tumors could probably further focus on co-localized oncogene amplification as already suggested by Davoli et al. (2013) and reinforced by van Dijk et al. (2021). Perhaps, in any given case, the individual locus-specific TSGs (and oncogenes) could be interrogated by using produced raw NGS data. Alternatively, the whole locus deletion/amplification could be assessed by FISH, CGH, or low depth copy number variation analysis using NGS. We fully agree with Horak et al. (2022) that combining multiple bioinformatic parameters might prove more useful in tumor biology evaluation. Also, these data might better inform the final decision on the usefulness of the genomic neighborhood analysis in translocation-defined tumors. Finally, applying a multi-modal data integration, the approach described above is compatible with future artificial intelligence (AI) development envisioned by Stenzinger et al. (2021) as the final step in the evolution of AI suitable for clinical applications.

5 | CONCLUSIONS

The human genome contains at least 138 TSG enriched loci. Of those, 21 contain more than 10 TSGs. By counting and investigating co-localized TSGs at respective loci, the genomic neighborhood of partner genes in the translocation-defined tumors can be assessed. This small pilot study failed to show that the total TSG count alone can predict tumor biology and targeted therapy response. Larger scale studies and probably as well more detailed multifaceted genomic neighborhood analysis might further improve the predictive value of the fusion partner gene genomic neighborhood analysis. This approach of multi-modal data integration concurs with the aims of multidisciplinary molecular tumor boards and possible future AI development.

AUTHOR CONTRIBUTIONS

Elaheh Mosaieby performed data analysis, drafted the manuscript, and contributed to its final version. Petr

Martínek consulted the study design and contributed to the final version of the manuscript. Ondrej Ondič conceived the study, performed data collection and analysis, drafted the manuscript, and contributed to its final version. All authors read and approved the final manuscript.

ACKNOWLEDGMENT

The authors are grateful for unlimited support and the inspiring working environment at Bioptická laboratory, Pilsen.

CONFLICT OF INTEREST

All authors have no duality of interest to declare.

ETHICAL COMPLIANCE

The ethics committee approval was not necessary for this study.

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How to cite this article: Mosaieby, E., Martínek, P., & Ondič, O. (2022). The significance of the fusion partner gene genomic neighborhood analysis in translocation-defined tumors. *Molecular Genetics & Genomic Medicine*, *10*, e1994. https://doi.org/10.1002/mgg3.1994