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 (TSGs). 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

| 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        |        |              |
|          | 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            | 9q21     | 6     | 16q12        | 4        |        |              |
|          | 3q26  | 5            | 9q24     | 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            | 10p11    | 4     | 17q11        | 4        |        |              |
|          | 4q31  | 3            | 10p11    | 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            | 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 |
|----------|-------|---------------|----------|-------|---------------|----------|-------|---------------|
| 6p12     |       | 4             | 11p15    |       | 11            | q11       | 7     |
| 6p21     |       | 9             | 11q13    |       | 11            | q13       | 17    |
| 6p22     |       | 3             | 11q22    |       | 5             | 21        | 5     |
| 6p23     |       | 3             | 11q23    |       | 10            | q22       | 5     |
| 6p24     |       | 4             | 11q24    |       | 3             | 22        | 6     |
| 6q14     |       | 3             | 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, EXT1L, TCEB3, NR0B2, SFN, ALPL, EPHB2, RAP1GAP, RPL11, SDHB, PRDM2, ZBTB48, TP73, TNFRSF18, DFRA |
| 3p21  | 17         | GNAT1, MST1, ACY1, BAPI, HOA, MLH1, MST1R, SEMA3F, SEMA3B, LIMD1, DLEC1, LTF, PRKCD, SMARCC1, TDGF1, WNT5A, PLCd1 |
| 5q31  | 16         | PCDHG3C, TGFBI, HDAC3, CXCL14, KDM3B, CSF2, EGR1, IRF1, PPP2CA, PDLM4, HINT1, MZB1, PAIP2, CXXC5, SPRY4, SPARC |
| 7q22  | 11         | CDK6, ACHE, EPHB4, TPFP2, AGZP1, CUX1, ARMC10, FBX13, NAPAFLD, HBP1, RINT1 |
| 8p21  | 13         | BNP3L, EXT3L, TNFRSF10A, NKKX3-1, TRIM35, PPP3CC, DOK2, RHOBTB2, PIWIL2, MIR320A, CLU, TNFRSF10B, PDSFPL |
| 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 | 10         | CSTM6, GSTP1, MEN1, PLCB3, PPP1CA, RBM4, PHOX2A, FADD, AIP, UVRAG, WNT11 |
| 11q23 | 10         | ATM, PGR, RARRE53, 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, RIT1A, PEBP1, HS990B1, CDK2AP1, DIABLO, CHFR |
| 13q12 | 12         | GJB2, FLT3, KL, PDX1, IFT88, LATS2, TPT2, USP12, RASL11A, BRCA2, CDX2, PDSSB |
| 13q14 | 13         | TSC22D1, TRIM13, FOXO1, RB1, ARL1, KCNQG, MIR15A, MIR16-1, DLEU2, DLEU1, OLFM4, INT5S6, THSD1 |
| 14q32 | 16         | DLK1, MEG3, Dicer1, MIR127, MIR136, MIR370, MIR493, PPP2R5C, MIR134, MIR329-1, MIR409, MIR410, MIR494, 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, PNN1, RPA1, MYBPP1A, VPS33, SMYD4 |
| 17q21 | 14         | BRCA1, JUP, PHB, BECN1, IKZF3, EZH1, IGFBP4, KRT19, HOXB13, NME1, STAT3, IGBP3, SPOP, NGFR |
| 19p13 | 22         | PIN1, MIR181C, DNMT1, DJNA1B1, SMARCA4, GADD45GIP1, MIR199A1, CN1, NOTCH3, AMH, DAPK3, GADD45B, STK11, TCF3, TNFSF9, SAFB2, ANGPT14, FZRI, SIRT6, PLK5, DnRAS1, SAFB |
| 19q13 | 28         | ERF, KLK10, SIRT2, CEBPA, TGFBI, ZFP36, SPINT2, PDCD5, ZNF382, ZFP82, MAP4K1, CEACAM1, LGALS7, MIA, CIC, KL6, GLTSCR2, GLTSCR1, CADM4, MIR150, BAX, IRF3, BBC3, CNOT3, PEG3, BRK1, 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 |
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 pancreaticobiliary 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.

### Table 3

| 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

| Partner gene | Locus  | TSG count | Driver gene | Total TSG | Tumor size change |
|--------------|--------|-----------|-------------|-----------|------------------|
| PRKAR1A      | 17q24.2| 0         | RET 1q11.21 (TSG 6) | 6         | −50%             |
| CCDC6        | 10q21.2| 3         | RET 1q11.21 (TSG 6) | 9         | (−30% to −100%)  |
| KIF5B        | 10p11.22| 4        | RET 1q11.21 (TSG 6) | 10        | (+15% to −90%)   |
| RBPM4        | 8q12   | 4         | RET 1q11.21 (TSG 6) | 10        | −90%             |
| TRIM24       | 7q33-q34| 4        | RET 1q11.21 (TSG 6) | 10        | −45%             |
| DOCK1        | 10q26.2| 5         | RET 1q11.21 (TSG 6) | 11        | −90%             |
| NCOA4        | 10q11.22| 6       | RET 1q11.21 (TSG 6) | 12        | −80%             |
| ARHGAPI2     | 10p11.22| 6       | RET 1q11.21 (TSG 6) | 12        | −60%             |
| ERC1         | 12p13.33| 6        | RET 1q11.21 (TSG 6) | 12        | NA               |
| RELCH        | 18q21.33| 9        | RET 1q11.21 (TSG 6) | 15        | −80%             |
| CCDC88       | 11q13.1| 11        | RET 1q11.21 (TSG 6) | 17        | −35%             |
| CLIP         | 12q24.31| 12       | RET 1q11.21 (TSG 6) | 18        | −70%             |

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
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

**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.
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. Large 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...
Martinek 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.

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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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