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# **Tandem duplications contribute to not one but two distinct phenotypes**

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Menghi and co-workers report a metric to classify tumours into those with and without a tandem duplicator phenotype (TDP) using the frequency of tandem duplications (TDs) in 277 whole genome sequenced samples (1). Building on a previous method (2), the authors identified TDs from SNP array data, and found that the TDP was strongly associated with response to the DNA damaging chemotherapeutic, cisplatin. These findings supplement the growing recognition that genome-wide signatures of mutator phenotypes may prove to be important additions to the companion diagnostic repertoire (3, 4). Although the findings of this report are highly stimulating, accumulating evidence suggests that an elevated abundance of TDs features in not just one but two distinct phenotypes.

Two of the original studies on the TDP reported a mutual exclusion with *BRCA1/2* inactivation (2, 5), which conflicts with the enrichment of *BRCA1* loss among TDP cancers observed by Menghi and colleagues. Using TCGA breast cancer data (6), we established allele-specific copy number profiles using ASCAT (7) before calling TDP status as described previously (2) using two different size ranges for the TD-like features: (i) between 1Kbp and 2Mbp in accordance with the study by Menghi and associates; and (ii) between 2Mbp and 10Mbp. Five samples with *BRCA1* inactivation exhibited the TDP when considering only shorter TDs (Fig. 1A); however, we found no instances of tumours with *BRCA1* inactivation among 2–10Mbp TDP cancers (Fig. 1B). Furthermore, while 56% of the Menghi *et al* study's TDP calls were shared with our 1Kbp–2Mbp TDP calls, only 10% of the Menghi *et al* study's TDP calls agreed with our 2–10Mbp TDP calls (Fig. 1C). In addition, we found that while the 1Kbp–2Mbp TDP calls and the Menghi *et al* study's TDP calls were enriched for triple-negative breast cancers ( $P < 0.001$ , Fisher's exact test), the 2Mbp–10 Mbp TDP calls were not ( $P = 0.81$ , Fisher's exact test). These findings support the notion that the study by Menghi and associates captures one particular TDP distinguishable from a second TDP by length and contrasting relationships with loss of *BRCA1* function.

Our results are reinforced by two recent analyses. The first study extracted two TD-enriched rearrangement signatures from 560 whole breast cancer

genomes (8). 'Signature-1' mostly comprised TDs between 1 and 10Mbp, whereas 'signature-3' mostly comprised TDs  $\leq 100$ Kbp. Signature-3 was associated with *BRCA1* disruption, signatures of homologous recombination deficiency (HRD), and was observed in ~15% of the cohort. By contrast, signature-1 was independent of *BRCA1/2* disruptions, exhibited links with mutational signatures of both HRD and mismatch repair deficiency, and presented in ~8.5% of the cohort. The second study identified an ovarian and prostate cancer-linked TDP featuring TDs up to 10Mbp, mutual exclusion with *BRCA1/2* inactivation and enrichment for inactivation of the *CDK12* kinase (9).

In conclusion, we propose that there are actually two TDPs, with the study by Menghi and colleagues providing a comprehensive characterisation of the *BRCA1* inactivation-linked TDP. The existence of two TDPs has important implications for the robust development of genomic instability-based biomarkers of drug response.

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## **Figure legend**

**Fig. 1. Tandem duplication phenotypes in 940 TCGA breast cancers.** (A and B) TDP status was determined using genomic segments between 1 Kbp and 2 Mbp (A), or 2 Mbp and 10 Mbp (B) followed by Gaussian mixture modelling of the ratio of TDs to non-TD segments (total number of segments minus double the number of TD segments as per (2)). Odds ratio and p-value represent Fisher's exact test of *BRCA1* mutation enrichment in the TDP subset of tumours. *BRCA1* loss was defined as germline or somatic point mutation, or deletion. TDP tumours are coloured in red and non-TDP tumours in grey. All samples are denoted by a cross with the exception of tumours with *BRCA1* loss, which are denoted by a square. (C) Bar plots illustrate the overlaps between the different TDP calling methods.

**Figure 1**