Comparative Analysis of *GATA3* Mutation Profiles Between Asian and Western Patients With Breast Cancer

Is There Really a Difference?

Jiang et al[1] provided an interesting overview of the prevalence of *GATA3* (GATA-binding protein 3) mutations in a cohort of Chinese patients with breast cancer and a comparison of their clinical features with *GATA3*-mutant tumors collected by The Cancer Genome Atlas (TCGA).[2] Given the prevalence of *GATA3* mutations among patients with estrogen receptor (ER)-positive breast cancer (approximately 15% in prior studies), retrospective studies such as this will be very important in informing our understanding of the contribution of these mutations to breast cancer pathobiology and patient outcomes.

We have identified 2 significant areas of concern in the article by Jiang et al[1] that would benefit from further clarification from these authors. First, the mutation profile identified in their cohort is strikingly, perhaps even implausibly, different from that observed in larger well-controlled studies. Second, their claims regarding the relationship between *GATA3* mutation status and patient survival in the TCGA study are simply not correct.

Prior analyses of *GATA3* mutations in >1000 cases from several large cohorts[2-5] have indicated that the vast majority of mutations ($>98\%$) affect exons 5 and 6, which encode a region including the second of 2 zinc fingers. Given the overwhelming bias toward mutations in this region as observed in previous studies, we were astonished to note that only one-half of the mutations observed by Jiang et al[1] affected this region of the protein. In addition, these prior studies have identified hotspot mutations resulting in disruption of a splice site at codon 308 and causing a frameshift at codon 409fs. In the latest data from TCGA, 28 of 85 *GATA3* mutations (32.9%) affect 1 of these 2 hotspot loci. It is striking that not a single patient in the Fudan University Shanghai Cancer Center cohort had a mutation at these loci. The lack of information in the report concerning the sequencing primers used makes it impossible to determine whether the sequencing strategy was sufficient to detect these mutations, if indeed they existed in the studied Chinese population.

Another interesting disparity between the study by Jiang et al[1] and prior investigations is the high prevalence of point mutations in the *GATA3* coding sequence in the Fudan University Shanghai Cancer Center cohort, including a recurrent L190M mutation in 10 of the 46 *GATA3*-mutant cases, an unprecedented frequency of 21.7%. Prior studies have generally found frameshift mutations to be predominant and, when they occur, point mutations tend not to accumulate at hotspots (with the possible exception of mutations at M294 that have now been noted in 3 cases). It is remarkable that from such a relatively small number of cases, these investigators managed to identify an apparently new hotspot at L190M.

The authors correctly note that prior sequencing studies were performed primarily in Western populations.[1] Although this is true, 57 Asian females were included in the most recent breast cancer data from TCGA. Of these, 36 had ER-positive breast cancer, including 8 patients with *GATA3* mutations. It is important to note that these 8 *GATA3*-mutant tumors included 2 cases with the 308 splice site and 2 with 407fs hotspot mutations, whereas the remaining 4 *GATA3* mutations affected codons 327 to 433 (encoded by exons 5 and 6), a pattern that is not dissimilar to that found in other ethnic groups. These data suggest that that invoking putative fundamental biological differences between breast tumors of Asian and Western women is not a plausible explanation for the *GATA3* mutation profiles reported by Jiang et al.[1]

The authors claim, without providing data, that *GATA3* mutations were associated with significantly better outcomes among the patients in the TCGA study with ER-positive disease ($P = .041$; data not shown). We have tried and failed to replicate this using data from the cBioPortal, and downloaded directly from TCGA. In both cases, we found no statistically significant difference in overall survival between patients with *GATA3*-mutant and *GATA3* wild-type ER-positive tumors with the available length of follow-up. Thus, contrary to the claim in the article by Jiang et al,[1] we do not believe that, as of this date, there is any evidence from TCGA data to suggest that *GATA3*-mutant tumors are associated with a better outcome among patients with ER-positive breast cancer.

In conclusion, given the significant disparity between the mutational spectra reported by these investigators and the strong consensus in mutations from TCGA[2] and other studies,[3-5] we believe that the study by Jiang et al[1] should be interpreted with caution until such time as more detailed information is provided by the authors and/or confirmatory data are available from other independent cohorts. In particular, the claim by the authors that *GATA3* mutations may identify a subgroup

of patients for whom limited therapy may be appropriate should be viewed with great caution.

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CONFLICT OF INTEREST DISCLOSURES

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Reply to Comparative Analysis of *GATA3* Mutation Profiles Between Asian and Western Patients With Breast Cancer

Is There Really a Difference?

We appreciate the letter by Chandiramani and Kenny bringing our attention to 2 areas of concern in our recent article that would benefit from our clarification.[1]

Regarding the first point, we would like to reassure our readers that our sequencing strategy, using both polymerase chain reaction and Sanger sequencing, was sufficient to detect any existing mutations in the exome domains, and if mutations at codon 308 or 409fs loci existed in our cohort of Chinese patients, we should have been able to detect them. There is another line of evidence from a study by Gonzalez-Bosquet et al[2] in which 2 cases of a *GATA3* (GATA-binding protein 3) point mutation were observed in the 60 breast cancer samples that underwent bidirectional sequence analysis; no cases of gene insertion or deletion were found in the *GATA3* exome domain. Furthermore, we have conducted *GATA3* mutation analysis in an additional validation cohort of 153 patient samples, and observed a similar mutation profile. In this validation cohort, somatic mutations in *GATA3* were detected in 11.8% of tumors (18 of 153 tumors), 77.8% of which (14 tumors) were missense point mutations whereas 11.1% (2 tumors) were frameshift insertions and 11.1% (2 tumors) were frameshift deletions. We believe that the fundamental biological differences between breast cancers occurring in Chinese compared with Western populations best explain the difference in *GATA3* mutation profiles. We would like to emphasize that the "Asian" category in The Cancer Genome Atlas (TCGA) database includes a wide range of ethnic groups, and the percentage of "Chinese" patients included is unknown.[3] This may account for the difference between TCGA and the findings of our study.[1]

Although we stated in our original article[1] that the follow-up period of patients in the TCGA cohort ranged from 1 month to 226.5 months, a clarification we did not make clearly was that in our survival analysis of the TCGA cohort, we included only those patients whose follow-up data exceeded 1 month, excluding all patients who lacked follow-up data. It is interesting to note that our conclusion regarding improved survival in patients with luminal A breast cancer with a *GATA3* mutation was mainly drawn from data of the Fudan University Shanghai Cancer Center cohort, because the TCGA database lacked comprehensive follow-up data and only provided statistics regarding overall survival. In addition, the TCGA database is continuously being updated, and newly included data may cause current analysis results to differ from previously conducted analysis.

We therefore maintain our main conclusion that *GATA3* mutations in patients with luminal-like breast cancer may define a subgroup, and fully acknowledge that further studies are needed to validate these findings.

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CONFLICT OF INTEREST DISCLOSURES

The authors have declared no conflicts of interest.

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