Luminal Androgen receptor (LAR) and Androgen receptor (AR)-High triple negative breast cancers (TNBC) are genetically similar to Luminal breast cancers

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Triple negative breast cancers (TNBCs)

- **Triple negative breast cancer (TNBC)**
  - Defined by lack of ER, PR and HER2
  - Account for 12-17% of breast cancers
  - Young age, aggressive biology, BRCA 1-associated
  - **Heterogeneous disease** encompassing a wide spectrum of entities with marked *genetic, transcriptional, histological and clinical differences*

![Images of different types of cancer tissues](image1.png)

- High grade IDC NOS
- Low grade Acinic cell ca
- High grade metaplastic
- Low grade metaplastic

Somatic mutations affecting the 50 cancer genes most frequently mutated in TNBCs (TCGA data)

F Pareja et al. Nat PJ 2017
Molecular classification of TNBCs

- 7 TNBC subtypes by Lehmann and colleagues
- Cluster analysis of 21 gene expression datasets of 587 TNBC cases

- Basal-like; Basal-like 1, 2 (BL1 and BL2), Immunomodulatory (IM)
- Mesenchymal-like; Mesenchymal(M), Mesenchymal stem-like(MSL)
- Luminal androgen receptor (LAR)
- Unstable (UNS)

- Luminal Androgen receptor (LAR) subtype
  - Most differential among other TNBCs
  - Display a luminal-like GE pattern despite ER negativity, most likely due to heavily enriched in hormone regulated pathways with high AR gene expression

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Aim

✓ Investigate the genomic landscape of TNBC of LAR subtype and
✓ Compare with Non-LAR TNBCs and each intrinsic subtypes of non-TNBCs
✓ Illustrate the overall genomic instability across the TNBC subtypes
Methods

• Gene expression, targeted sequencing and copy number data from the METABRIC study (n=1972) retrieved

• TNBCs identified (n=313) and classified into the 1) TNBC molecular subtypes (Lehmann et al) and according to 2)AR mRNA expression levels

• Mutation, copy number and large-scale state transition (LST) profiles of LAR-TNBCs were compared to those of non-LAR TNBCs,
• and to each intrinsic subtypes non-TNBCs classified as luminal A, luminal B, and HER2-enriched by PAM50
LAR TNBC and AR-High/low TNBC

• 12% of TNBCs (26/215) were classified as LAR-TNBC subtype

• High levels of AR mRNA expression were associated with only one case of LAR subtype

• High AR was not restricted to LAR-TNBC that 18 of Non-LAR showed high AR expression

313 TNBCs
(excluding unstable subtype)

<table>
<thead>
<tr>
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<th>LAR</th>
<th>Non-LAR</th>
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<tbody>
<tr>
<td>LAR</td>
<td>26 (8%)</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>Non-LAR</td>
<td>287 (92%)</td>
<td>189 (88%)</td>
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Top 20% High-AR TNBCs (N=43/313)

LAR (25/26)
Non-LAR (18/287)
Mutation profile of LAR TNBC

- LAR TNBCs displayed a high frequency of mutations affecting genes commonly mutated in luminal breast cancers, such as **PIK3CA, AKT1, GATA3** and **CDH1**

- Most frequently mutated gene was **TP53** consistent as re-known in TNBCs (upto 85%), though relatively displaying lower frequency of 61.5% (16/26)
Mutation comparisons among TNBCs

LAR TNBC vs Non-LAR TNBC

- LAR TNBCs displayed a higher frequency of mutations affecting genes commonly mutated in luminal breast cancers, such as **PIK3CA, AKT1, GATA3** and **CDH1** (marked in red, \( p<0.05 \))
- **AKT1** and **GATA3** were mutated exclusively in LAR TNBCs, while none in Non-LAR TNBCs
- Notably, the single difference between LAR vs AR-high non-LAR TNBCs, was a higher frequency of **AKT1** mutations in the former imposing genetic similarity
• LAR TNBCs displayed comparable rate of **PIK3CA** mutations to luminal A/B BCs
• **AKT1** was more frequently mutated in LAR TNBCs than luminal A/B non-TNBCs
• Despite similarities between LAR TNBCs and luminal cancers, **TP53** was more frequently mutated in the former.
• Similar results were obtained when comparisons were performed with luminal A or B separately
Level genomic instability and response to treatment exploiting HR deficiency vary widely among TNBCs.

Large scale state transition (LST) score were calculated to address the genomic instability of TNBCs in each subtypes.

LAR and AR-high TNBCs displayed LST scores significantly lower than non-LAR and non-AR-high TNBCs implying that these tumors harbor more stable genome.

*LST calculation; Popova et al. Cancer Research 2012
Summary

• The transcriptomic similarities between LAR and luminal breast cancers are mirrored by similarities at the genetic level, in particular by a high rate of mutations affecting PIK3CA and AKT1 gene.

• Supporting evidence for clinical trials evaluating effectiveness of PI3K pathway inhibitors for this LAR/AR-High TNBCs along with AR inhibitor.

• LAR and AR-high TNBCs displayed markedly lower rate of homologous recombination deficiency than non-LAR/ non-AR-high TNBCs (eg. Basal like), respectively, implying less likelihood of having benefit to PARP inhibitor/platinum agents.
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