Differences in BRCAness/PARP Inhibitor Response Signatures and Homologous Recombination Gene Expression Across Lung Adenocarcinoma and Squamous Cell Carcinoma Gene Expression Subtypes.

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BACKGROUND

Gene expression based subtyping has consistently identified 3 distinct biologic subtypes in Lung Adenocarcinoma (AD), Terminal Respiratory Unit (TRU) formerly Bronchioid, Proximal Proliferative (PP) formerly Magnoid, and Proximal Inflammatory (PI) formerly Squamoid[1,2] and 4 subtypes within lung SQ, Primitive, Classical, Basal and Secretory[3,4] (See Figure 1). AD and SQ subtypes demonstrate key differences in genomic alterations, tumor drivers, prognosis, and likely response to various therapies.[1-4]

Figure 1.

Lung Cancer Subtyping
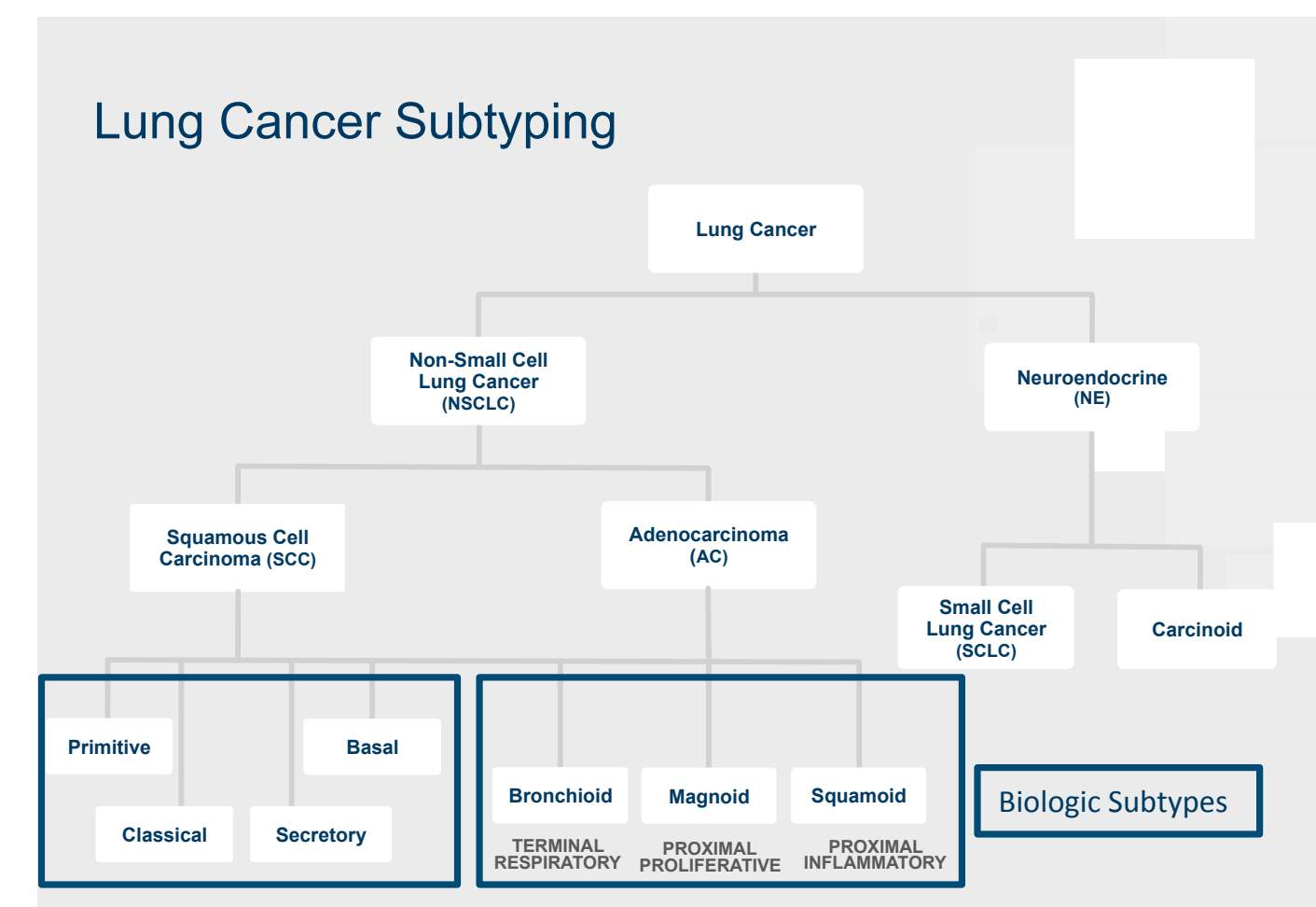
METHODS

Using the TCGA lung cancer gene expression datasets (AD n = 515, and SQ n = 501),[2,4] differential drug target gene expression was evaluated in AD and SQ subtypes. Previously published AD subtypes (TRU, PP, and PI) and SQ subtypes (Primitive, Classical, Secretory, Basal) were defined using gene expression profiles. Association between subtype and BRCAness/PARP inhibitor response signatures was evaluated separately in AD and SQ using linear regression. Correlations between proliferation,[5] BRCA1, BRCA2, and research versions of 3 published BRCAness/PARP inhibitor response signatures developed in ovarian and/or breast cancer (Konstantinopoulos et al.[6], Daemen et al.[7], and McGrail et al.[8]) were analyzed using scatterplots. Expression patterns of 15 recognized homologous recombination (HR) related genes (ATM, ATR, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCI, FANCD2, MRE11A, RAD51L1, RAD51C, PTEN) among AD and SQ subtypes were examined using heatmaps. Association between subtype and HR gene expression was evaluated using linear regression, with and without adjustment for proliferation and BRCAness/PARP inhibitor response signatures.

RESULTS

Table 1. TCGA lung AD and SQ datasets

TCGA AD	
Total # of samples	515
GeneCentric Subtype	
TRU (Bronchioid)	196
PP (Magnoid)	134
PI (Squamoid)	185
Stage	
Stage I	276
Stage II	123
Stage III	84
Stage IV	27
Stage NA	5

TCGA SQ	
Total # of samples	501
GeneCentric Subtype	
Basal	149
Classical	178
Primitive	70
Secretory	104
Stage	
Stage I	241
Stage II	152
Stage III	85
Stage IV	7
Stage NA	16

Table 2.
Association test p values of BRCAness/PARP inhibitor signatures and proliferation in AD and SQ gene expression subtypes.

	AD n=515	SQ n=501
Daemen et al.	1.06E-13	8.17E-11
Konstantin et al.	0.022172835	5.23E-06
McGrail et al.	9.60E-31	5.40E-14
Prolif Score	8.47E-89	4.93E-06

Figure 2.
Scatterplots of proliferation (pscore), BRCAness/PARP inhibitor signatures, BRCA1, and BRCA2.

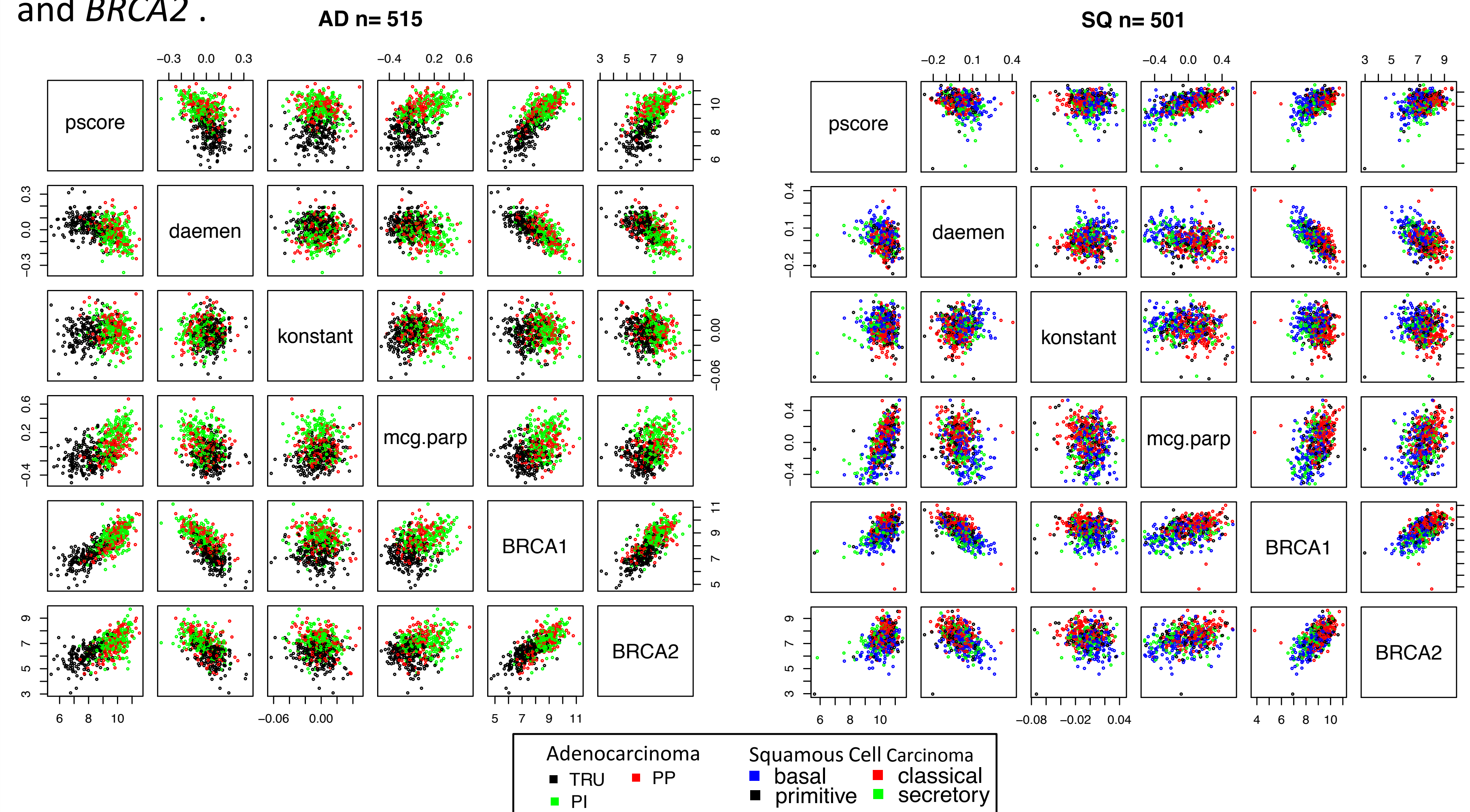
Adenocarcinoma AD n = 515
Squamous Cell Carcinoma SQ n = 501

Figure 3.
AD and SQ subtypes show marked differences in gene expression patterns of 15 recognized homologous recombination related genes.

AD n=515 — TRU, PP, PI
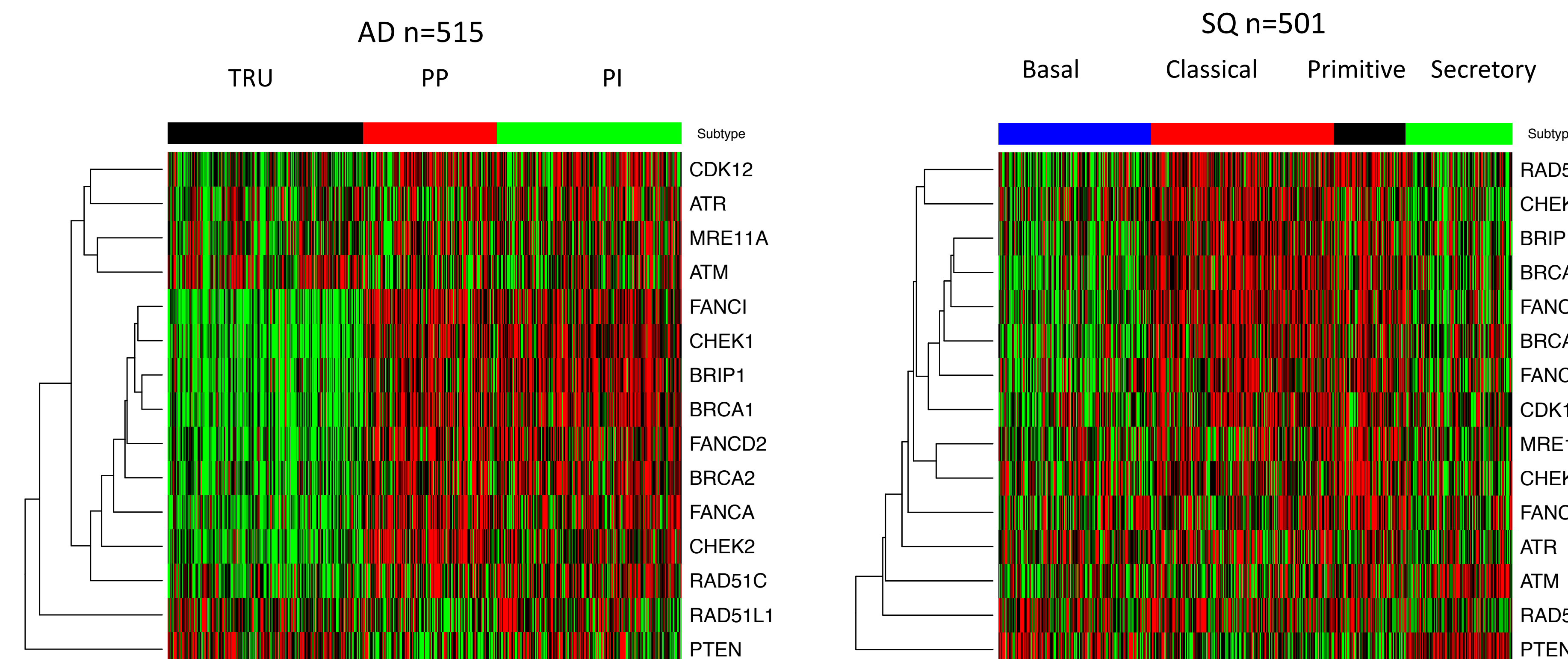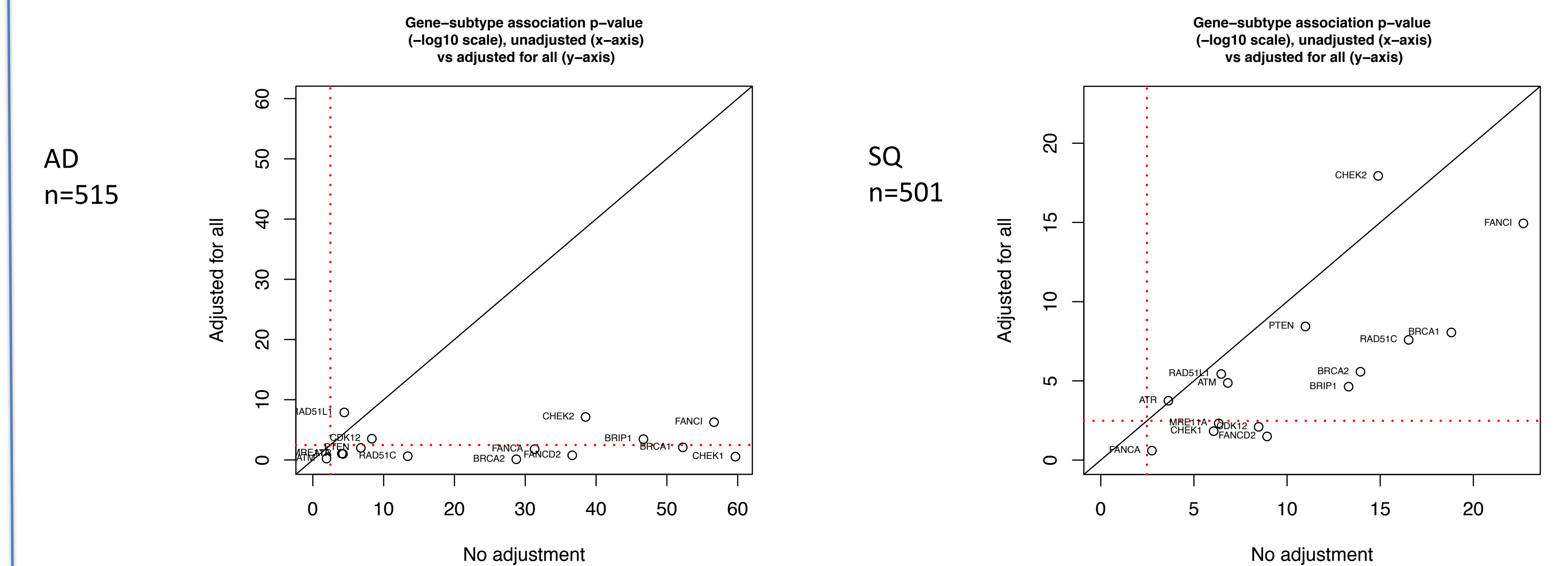SQ n=501 — Basal, Classical, Primitive, Secretory

Table 3.
Association test p-values between homologous recombination (HR) genes and subtype, BRCAness/PARP inhibitor signatures, and proliferation score, in AD and SQ.

AD n=515

	Subtype	Daemen et al.	Konstant et al.	McGrail et al.	Prolif Score
ATM	0.01152349	0.000119324	2.59E-08	1.20E-06	0.028359508
ATR	5.44E-05	2.71E-20	2.59E-08	0.358886537	0.035398714
BRCA1	5.62E-53	1.77E-79	0.789881619	2.70E-17	5.87E-111
BRCA2	1.84E-29	1.56E-41	0.00623859	8.90E-13	8.47E-62
BRIP1	2.05E-47	6.81E-50	0.465150242	1.13E-22	1.61E-98
CDK12	4.61E-09	5.17E-40	0.438534102	0.018827483	2.19E-08
CHEK1	2.09E-60	6.63E-36	0.361758242	2.47E-32	4.37E-55
CHEK2	3.01E-39	0.000845004	0.743289683	5.33E-08	4.87E-55
FANCA	4.76E-32	1.82E-15	0.456770937	1.24E-08	1.04E-59
FANCD2	2.32E-37	1.17E-28	0.020952713	1.30E-22	4.59E-62
FANCI	2.20E-57	1.86E-37	0.916121327	1.67E-24	1.04E-135
MRE11A	7.97747E-05	6.97E-23	0.640583098	3.88E-07	1.66E-59
PTEN	1.64E-07	0.222656415	0.643158767	0.017817327	1.19E-05
RAD51C	3.91E-14	9.38E-09	0.680183998	2.70E-27	2.72E-27
RAD51L1	3.57E-05	0.250867139	0.599982125	0.854928024	0.232206655

SQ n=501

	Subtype	Daemen et al.	Konstant et al.	McGrail et al.	Prolif Score
ATM	1.52E-07	8.77E-07	0.023359508	0.000560081	3.02E-08
ATR	5.62E-53	6.45E-11	0.834504844	0.146097927	0.000167912
BRCA1	1.52E-19	5.16E-74	0.0245646?	3.59E-24	1.19E-33
BRCA2	1.15E-14	1.83E-24	0.004889389	5.70E-17	3.55E-24
BRIP1	4.97E-14	1.05E-27	0.244904199	1.35E-20	1.11E-45
CDK12	3.37E-09	4.02E-32	0.590864218	1.33E-06	0.000575991
CHEK1	8.73E-07	3.26E-10	0.235831128	2.85E-20	4.32E-54
CHEK2	1.29E-15	1.31E-09	0.239551869	5.94E-15	6.19E-34
FANCA	6.71E-06	0.1141838	0.000510715	1.15E-09	5.38E-54
FANCD2	1.14E-16	1.65e08755	0.198082751	8.94E-17	7.57E-59
FANCI	2.06E-23	1.02E-15	0.167983257	9.56E-24	7.57E-59
MRE11A	4.66E-07	1.65E-17	0.318888817	0.003421322	0.000187893
PTEN	1.04E-11	0.016552739	0.215475917	0.098586599	1.10E-05
RAD51C	2.97E-17	4.25E-09	0.008038394	5.74E-15	2.94E-24
RAD51L1	3.42E-07	0.633764978	0.349594411	0.000701233	0.002547001

Figure 4.
Subtype-HR gene association test p-values (-log10 scale) without adjustment (x-axis) and with adjustment for 3 BRCAness/PARP inhibitor signatures and proliferation (y-axis). Dotted red lines shows bonferroni threshold for 15 tests and alpha = 0.05.

AD n=515
SQ n=501
Gene–subtype association p-value (−log10 scale), unadjusted (x–axis) vs adjusted for all (y–axis)

CONCLUSIONS

- Molecular subtypes of lung AD and SQ vary in expression of several BRCAness/PARP inhibitor response signatures.
- Subtypes reveal differential expression of HR-related genes.
- Adjustment for proliferation and 3 BRCAness/PARP inhibitor signatures reduced association strength in AD to 5 significant HR genes, whereas in SQ 10/15 HR genes remained significant.
- Evaluation of subtypes as potential biomarkers for PARP inhibitor drug response, particularly in SQ is warranted.

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ABBREVIATIONS

AD = Adenocarcinoma
SQ = Squamous cell carcinoma
TRU = Terminal Respiratory Unit
PP = Proximal Proliferative
PI = Proximal Inflammatory
HR = Homologous Recombination