Germline mutations and the presence of clonal hematopoiesis of indeterminate potential (CHIP) in 20,963 patients with BRCA-associated cancers

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INTRODUCTION

- The contribution of germline (g) genetics on the emergence of CHIP in patients with solid tumors is not well understood.
- We hypothesized that those with germline alterations in homologous recombination repair genes (gHRR) and BRCA-associated cancers would have different rates of CHIP than those with sporadic BRCA-associated cancers.

METHODS

20,963 patients profiled with tumor/normal matched Tempus xT testing*

Selection criteria:
- Presence or Absence of pathogenic/likely pathogenic alteration in select CHIP-associated genes inferred from tumor
- VAF minimum of 2%

List of CHIP-Associated Genes			
ASXL1	*BCOR*	*BCORL1*	*CBL*
CREBBP	*CUX1*	*DNMT3A*	*GNB1*
JAK2	*PPM1D*	*PRPF8*	*SETDB1*
SF3B1	*SRSF2*	*TET2*	*U2AF1*

Retrospective Analysis

Patients with g alterations in *BRCA1, BRCA2, ATM, CHEK2*, and *PALB2* were compared to those without gHRR alterations (sporadic).

*Tempus xT assay - a targeted panel that detects single nucleotide variants, insertions and/or deletions, and copy number variants in 598-648 genes, as well as chromosomal rearrangements in 22 genes with high sensitivity and specificity.

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SUMMARY

- Women with **g*PALB2* alterations and breast cancer**, as well as **men with g*CHEK2* mutations and prostate cancer**, had higher rates of CHIP.
- These data suggest that gHRR mutations may **influence the prevalence of CHIP** among patients with BRCA-associated cancers.
- The clinical implications of these data, especially in terms of complications from therapies like PARP inhibitors and platinum chemotherapy, deserves further study.

RESULTS

Breast Cancer

Table 1. Breast cancer cohort demographics

	Sporadic N = 6,546	g*BRCA1* N = 104	g*BRCA2* N = 148	g*ATM* N = 57	g*PALB2* N = 42	g*CHEK2* N = 57
Age at Diagnosis	56 (46, 65)	43 (35, 52)	52 (40, 60)	52 (42, 62)	55 (47, 69)	53 (42, 59)
Gender, n (%) Female	6,470 (99%)	104 (100%)	138 (93%)	56 (98%)	42 (100%)	56 (98%)
Race & Ethnicity, n(%)						
White	3,274 (75%)	42 (68%)	65 (71%)	27 (82%)	19 (68%)	33 (89%)
Black or African American	635 (15%)	10 (16%)	13 (14%)	4 (12%)	3 (11%)	1 (2.7%)
Asian	193 (4.4%)	5 (8.1%)	4 (4.3%)	2 (6.1%)	3 (11%)	0 (0%)
Other race	267 (6.1%)	5 (8.1%)	10 (11%)	0 (0%)	3 (11%)	3 (8.1%)
Hispanic or Latino	399 (16%)	8 (24%)	11 (17%)	2 (10%)	2 (17%)	5 (23%)
Stage of Disease, n(%)						
Stage 1	109 (2.7%)	0 (0%)	3 (3.4%)	0 (0%)	1 (3.6%)	1 (2.4%)
Stage 2	263 (6.5%)	5 (9.1%)	7 (7.9%)	3 (7.5%)	3 (11%)	1 (2.4%)
Stage 3	280 (6.9%)	3 (5.5%)	5 (5.6%)	5 (12%)	0 (0%)	1 (2.4%)
Stage 4	3,392 (84%)	47 (85%)	74 (83%)	32 (80%)	24 (86%)	39 (93%)
Any CHIP mutation	**338 (5.2%)**	**3 (2.9%)**	**5 (3.4%)**	**2 (3.5%)**	**6 (14%)**	**4 (7.0%)**

Fig 1. CHIP altered patients

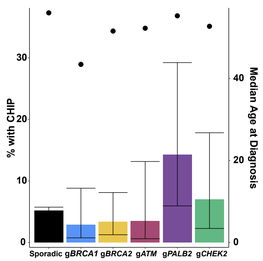

Fig 2. Age-adjusted CHIP risk

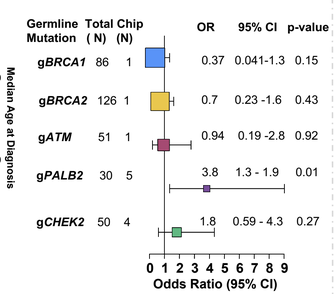

Table 2. Age-adjusted germline effect on CHIP status

	Total (N=6,954)	CHIP (N=358)	OR	95% CI	p-value
Age Diagnosis	**5,987**	**315**	**1.01**	**1.01, 1.02**	**0.002**
Sporadic	5,644	299	Ref	Ref	Ref
g*BRCA1*	86	1	0.37	0.04, 1.34	0.15
g*BRCA2*	126	4	0.70	0.23, 1.61	0.4
g*ATM*	51	2	0.94	0.19, 2.77	>0.9
g*PALB2*	**30**	**5**	**3.82**	**1.35, 9.02**	**0.014**
g*CHEK2*	50	4	1.82	0.59, 4.34	0.3

Prostate Cancer

Table 5. Prostrate cancer cohort demographics

	Sporadic N = 4,183	g*BRCA1* N = 16	g*BRCA2* N = 109	g*ATM* N = 44	g*PALB2* N = 12	g*CHEK2* N = 12
Age at Diagnosis	66 (60, 72)	64 (56, 74)	63 (56, 67)	66 (62, 72)	69 (59, 72)	66 (62, 74)
Race & Ethnicity, n(%)						
White	1,944 (75%)	7 (78%)	54 (77%)	21 (78%)	9 (90%)	7 (100%)
Black or African American	456 (18%)	0 (0%)	12 (17%)	4 (15%)	0 (0%)	0 (0%)
Asian	80 (3.1%)	2 (22%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)
Other race	113 (4.4%)	0 (0%)	4 (5.7%)	1 (3.7%)	1 (10%)	0 (0%)
Hispanic or Latino	187 (13%)	1 (20%)	6 (15%)	3 (17%)	0 (0%)	0 (0%)
Stage of disease, n(%)						
Stage 1	8 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage 2	54 (2.4%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage 3	165 (7.3%)	1 (25%)	3 (5.0%)	1 (4.0%)	0 (0%)	0 (0%)
Stage 4	2,048 (90%)	2 (50%)	57 (95%)	24 (96%)	8 (100%)	8 (100%)
Any CHIP mutation	**174 (4.2%)**	**0 (0%)**	**4 (3.7%)**	**2 (4.5%)**	**1 (8.3%)**	**2 (17%)**

Fig 5. CHIP altered patients

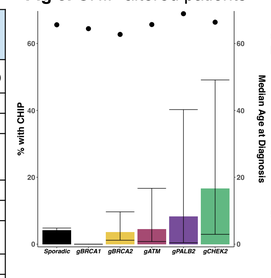

Fig 6. Age-adjusted CHIP risk

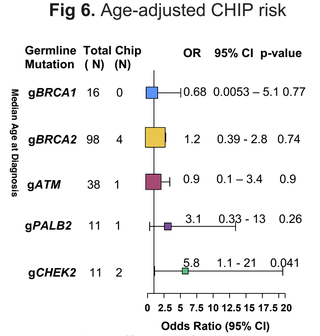

Table 6. Age-adjusted germline effect on CHIP status

	Total (N=3,773)	CHIP (N=158)	OR	95% CI	p-value
Age at Diagnosis	**3,773**	**158**	**1.02**	**1.01, 1.04**	**0.011**
Sporadic	3,599	150	Ref	Ref	Ref
g*BRCA1*	16	0	0.68	0.01, 5.07	0.8
g*BRCA2*	98	4	1.18	0.39, 2.78	0.7
g*ATM*	38	1	0.90	0.10, 3.40	0.9
g*PALB2*	11	1	3.11	0.33, 13.4	0.3
g*CHEK2*	**11**	**2**	**5.75**	**1.09, 20.6**	**0.041**

Ovarian Cancer

Table 3. Ovarian cancer cohort demographics

	Sporadic N = 3,979	g*BRCA1* N = 137	g*BRCA2* N = 83	g*ATM* N = 23	g*PALB2* N = 11	g*CHEK2* N = 9
Age at Diagnosis	63 (54, 71)	53 (48, 60)	61 (55, 68)	61 (54, 71)	68 (61, 72)	59 (42, 71)
Race & Ethnicity, n (%)						
White	2,186 (82%)	76 (78%)	39 (78%)	12 (71%)	9 (100%)	4 (100%)
Black or African American	225 (8.4%)	9 (9.3%)	6 (12%)	2 (12%)	0 (0%)	0 (0%)
Asian	106 (4.0%)	7 (7.2%)	3 (6.0%)	2 (12%)	0 (0%)	0 (0%)
Other race	151 (5.7%)	5 (5.2%)	2 (4.0%)	1 (5.9%)	0 (0%)	0 (0%)
Hispanic or Latino	220 (14%)	10 (19%)	2 (7.7%)	0 (0%)	0 (0%)	1 (20%)
Stage of disease, n (%)						
Stage 1	72 (5.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stage 2	85 (6.0%)	3 (7.3%)	1 (4.8%)	0 (0%)	1 (25%)	0 (0%)
Stage 3	547 (39%)	14 (34%)	9 (43%)	0 (0%)	1 (25%)	1 (33%)
Stage 4	716 (50%)	24 (59%)	11 (52%)	3 (100%)	2 (50%)	2 (67%)
Any CHIP mutation	**99 (2.5%)**	**5 (3.6%)**	**3 (3.6%)**	**0 (0%)**	**1 (9.1%)**	**0 (0%)**

Fig 3. CHIP altered patients

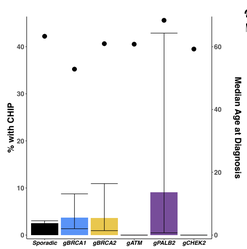

Fig 4. Age-adjusted CHIP risk

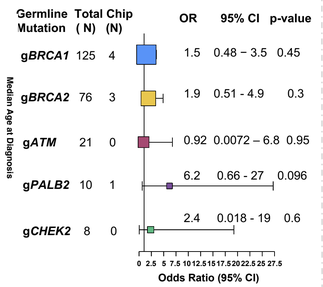

Table 4. Age-adjusted germline effect on CHIP status

Germline Group	Total (N=3,870)	CHIP (N=97)	OR	95% CI	p-value
Age at Diagnosis	3,870	97	1.00	0.99, 1.02	0.8
Sporadic	3,630	89	Ref	Ref	Ref
g*BRCA1*	125	4	1.49	0.48, 3.53	0.4
g*BRCA2*	76	3	1.88	0.51, 4.89	0.3
g*ATM*	21	0	0.92	0.01, 6.75	>0.9
g*PALB2*	10	1	6.18	0.66, 27.3	0.10
g*CHEK2*	8	0	2.37	0.02, 19.3	0.6

Pancreatic Cancer

Table 7. Pancreatic cancer cohort demographics

	Sporadic N = 5,176	g*BRCA1* N = 20	g*BRCA2* N = 89	g*ATM* N = 60	g*PALB2* N = 20	g*CHEK2* N = 16
Age at Diagnosis	67 (59, 73)	63 (56, 68)	64 (57, 71)	66 (61, 71)	62 (56, 67)	68 (64, 73)
Gender, n(%) Female	2,419 (47%)	8 (40%)	39 (44%)	29 (48%)	11 (55%)	8 (50%)
Race & Ethnicity, n (%)						
White	2,546 (82%)	9 (69%)	40 (77%)	26 (79%)	18 (100%)	12 (100%)
Black or African American	319 (10%)	2 (15%)	3 (5.8%)	5 (15%)	0 (0%)	0 (0%)
Asian	113 (3.6%)	0 (0%)	5 (9.6%)	1 (3.0%)	0 (0%)	0 (0%)
Other race	129 (4.2%)	2 (15%)	4 (7.7%)	1 (3.0%)	0 (0%)	0 (0%)
Hispanic or Latino	205 (14%)	1 (11%)	6 (17%)	5 (23%)	0 (0%)	0 (0%)
Stage of disease, n (%)						
Stage 1	174 (4.8%)	1 (6.7%)	3 (4.3%)	1 (2.6%)	0 (0%)	1 (6.2%)
Stage 2	367 (10%)	2 (13%)	5 (7.1%)	7 (18%)	1 (6.7%)	1 (6.2%)
Stage 3	272 (7.5%)	0 (0%)	3 (4.3%)	6 (16%)	1 (6.7%)	2 (12%)
Stage 4	2,807 (78%)	12 (80%)	59 (84%)	24 (63%)	13 (87%)	12 (75%)
Any CHIP mutation	**241 (4.7%)**	**2 (10%)**	**1 (1.1%)**	**3 (5.0%)**	**0 (0%)**	**1 (6.2%)**

Fig 6. CHIP altered patients

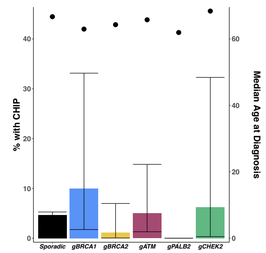

Fig 7. Age and sex-adjusted CHIP risk

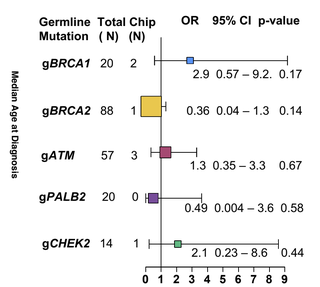

Table 8. Age and sex-adjusted germline effect on CHIP Status

Germline Group	Total (N=5,024)	CHIP (N=238)	OR	95% CI	p-value
Age at Diagnosis	**5,024**	**238**	**1.01**	**1.00, 1.02**	**0.073**
Female	**2,349**	**130**	**1.39**	**1.07, 1.80**	**0.014**
Sporadic	4,825	231	Ref	Ref	Ref
g*BRCA1*	20	2	2.87	0.57, 9.17	0.2
g*BRCA2*	88	1	0.36	0.04, 1.30	0.14
g*ATM*	57	3	1.27	0.35, 3.30	0.7
g*PALB2*	20	0	0.49	0.00, 3.62	0.6
g*CHEK2*	14	1	2.08	0.23, 8.58	0.4