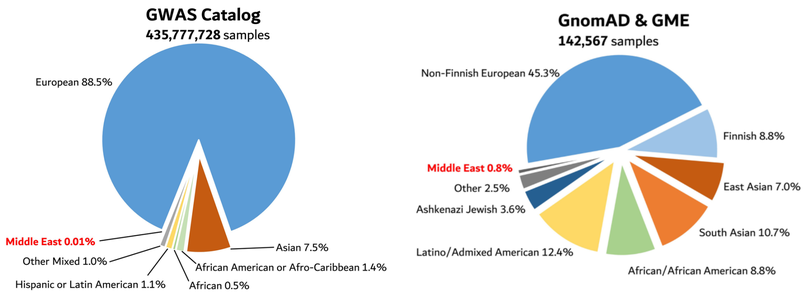
Germline *BRCA2* Founder Mutation and MYC Partial Duplication Modify Breast Cancer Risk and Presentation in the Indigenous Arab Population

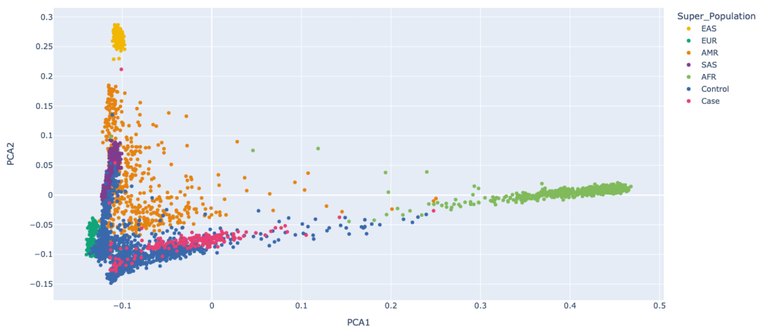
Intro: Arab populations are severely underrepresented in genomic studies and the breast cancer risk landscape is unclear



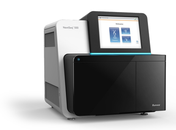
Abou Tayoun, A.N., Rehm, H.L. Genetic variation in the Middle East—an opportunity to advance the human genetics field. *Genome Med* **12**, 116 (2020)

Methods:

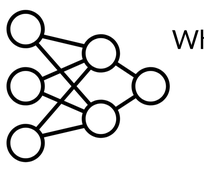
- Whole Exome Sequencing (WES) of Arab breast cancer patients and ancestry-matched controls
- Short variant calling and copy number variant calling in cancer-related genes
- Variant Pathogenicity classified based on ACMG guidelines
- Gene burden analysis and clinical associations



Arab Female Breast Cancer Patients (n=215 after QC)

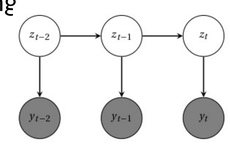


Cancer-free Middle Eastern Female Individuals (n=1290 after QC)



Whole-Exome Sequencing

DeepVariant



gCNV

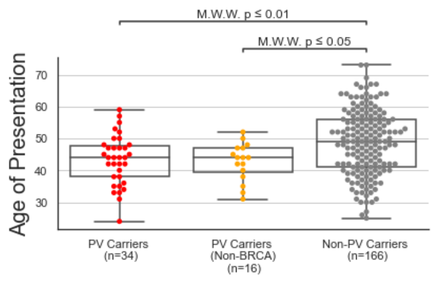
Tier 1 Germline Cancer-predisposition Genes only (n=143)

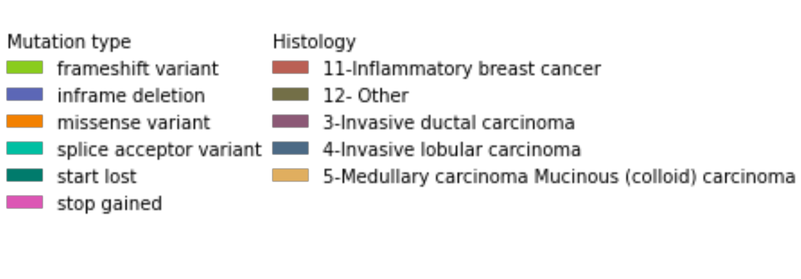
All cancer-related genes (n=824)

Results:

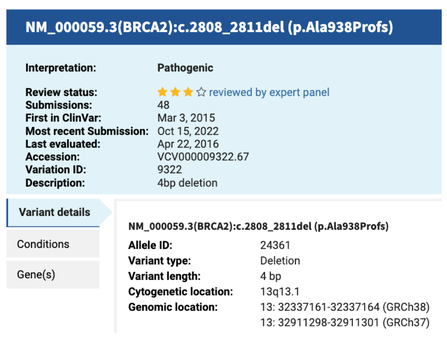
15.8% (n=34/215) of Arab breast cancer patients were pathogenic variant (PV) carriers

Pathogenic variants carriers on average present 5.2 years earlier

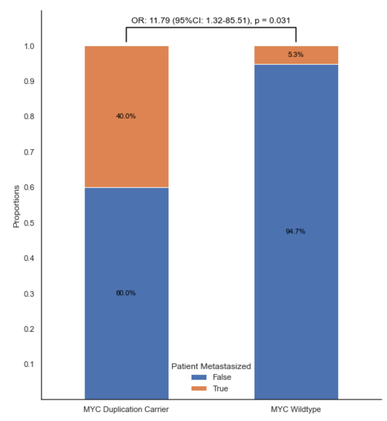




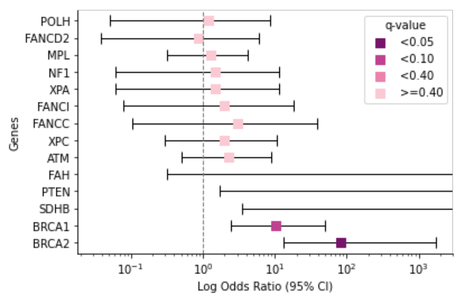
The *BRCA2* frameshift founder mutation (rs80359351) was found in 5.1% (n=11/215) of the patients



2.3% (n=5/215) carried germline partial duplications in *MYC* (2nd-3rd exon) which is associated with increased risk of metastasis



BRCA2, *BRCA1*, *SDHB* and *PTEN* pathogenic variants were enriched in cases



14.9% (n=32/215) patients carried germline variants with evidence for alternate clinical management

Gene	PV Carriers	Frequency (%)	Theraputic Actionability
BRCA1	5	2.325581395	Tier 1
BRCA2	13	6.046511628	Tier 1
ATM	3	1.395348837	Tier 2
FANCC	1	0.465116279	Tier 2
FANCI	1	0.465116279	Tier 2
FANCD2	1	0.465116279	Tier 2
NF1	1	0.465116279	Tier 3
PTEN	2	0.930232558	Tier 3
SDHB	3	1.395348837	Tier 3
XPA	1	0.465116279	Tier 3
MYC (Duplication)	5	0.023255814	Tier 3

Theraputic Actionability

Tier 1: sufficient evidence of clinical benefit to gain regulatory approval
Tier 2: similar quality and level of evidence to tier 1 but without regulatory approval to date; currently undergoing clinical trial for an already FDA-approved drug targeting similar gene
Tier 3: any evidence of clinical benefit for selecting a treatment on the basis of the presence of the specified germline variant; has any clinical trial targeting the specific gene

Subotheni Thavaneswara et al, Therapeutic implications of germline genetic findings in cancer, 2019, Nature Reviews Clinical Oncology

Conclusion:

- Testing for the novel founder variant alone can lead to change in clinical management for 5.1% of the cohort. This is a rate comparable to the BRCA2 6174del variant among Ashkenazi Jewish Women, for whom ancestry is a qualifying factor for genetic screening.
- MYC amplification is frequently observed in breast tumor prior to metastasis. A previous study has found Saudi breast cancer patients had a markedly higher frequency of MYC amplification in tumors than Swiss cancers, Germline *MYC* duplication may be an potential explanation
- Larger studies are needed to confirm well-established moderately penetrant breast cancer genes such as ATM, PALB2 and CHEK2

Multi-modal characterization of ultra-rare germline genetic variants driving breast cancer risk in the indigenous Arab population

Hoyin Chu, Abdullah Al-Sulaiman, Mohammed Al-Jumaan, Seunghun Han, Sabrina Y. Camp, Riaz Gillani, Yousef Al Marzooq, Fatmah Almulhim, Chitti Babu Vatte, Arij Alnimer, Afnan Almuhanna, Eliezer Van Allen, Amein Al-Ali, Saud H AlDubayan
Email: hoyin_chu@dfci.harvard.edu

Dana-Farber Cancer Institute
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL
BROAD INSTITUTE