BRCA2 Exon 3 Deletion in Assyrian Families

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Background

BRCA1/2-associated hereditary breast and ovarian cancer is the most common hereditary breast and ovarian cancer syndrome and occurs in all ethnicities and racial populations.[1]
In certain ethnicities or in geographically or culturally isolated groups, there is a higher rate of recurrent pathogenic variants, called founder mutations.[2]

This case series describes a recurrent *BRCA2* pathogenic variant in seemingly unrelated Assyrian families. The variant resulted in deletion of exon 3 in the *BRCA2* gene.

Fig.1: The Assyrian empire arose from northern Mesopotamia (now parts of Iraq, Syria and Turkey) at least 4000 years ago.[3]

The Assyrian population is spread worldwide, especially in United States/Canada, Iran, Europe (predominately Sweden) and Australia.[4]

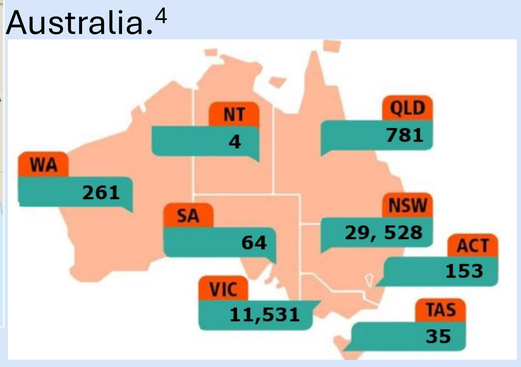

Fig: 2: 2021 Australia Census reported 42,346 individuals who identified Ancestry as Assyrian, living in Australia. Broken down by state.[5]

Methods

Individuals had been referred to a NSW cancer genetics services due to their personal or family history of cancer and assessed due to standard guidelines. The families that had a BRCA2 exon 3 deletion were identified using the Trakgene database. Details of tumour pathology, germline testing, and family history were extracted from electronic and paper medical records. Results are presented as probands (subject of initial genetic testing) and predictive cases (variant specific testing of family members) and are descriptive.

Results

11 Probands identified with BRCA2 exon 3 del
*9 of the 11 families identified as Assyrian, for two the country of origin (Iraq) was recorded rather than ethnic background

45 Family members assessed. For nine families, predictive testing was performed.

22 Carriers identified and received cancer risk management advice

***BRCA2* NM_000059.3:c.(67+1_68-1)_(316+1_317-1)del:p.?**

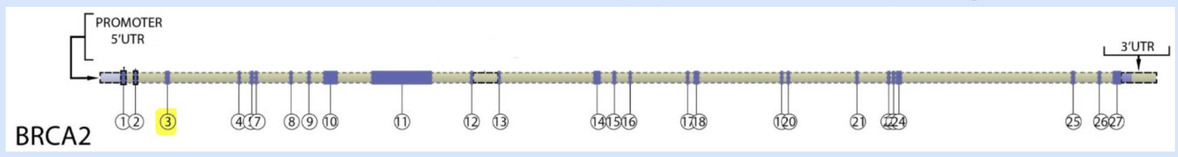

Fig. 3: BRCA2 gene in-frame deletion of exon 3

- Predicted to result in loss of 83 amino acids.
- RNA analysis indicated a loss of exon 3 which contains the PALB2-binding domain required for gene function.[6,7]

Table 1: The personal history and family history for probands identified with the *BRCA2* pathogenic variant

Personal cancer history	**No. (%)**
Any cancer	10 (91%)
Unilateral breast cancer	5 (45%)
Bilateral breast cancer	2 (18%)
Ovarian cancer	2 (18%)
Pancreatic cancer	1 (9%)
Age at first diagnosis (years)	
Breast cancer	46
Ovarian cancer	54
Pancreatic cancer	56
Family history of cancer	**No (%)**
Family history of cancer	11 (100%)
Family history of; (more than one)	
Breast cancer	9 (82%)
Ovarian cancer	2 (18%)
Pancreatic cancer	1 (9%)
Prostate cancer	2 (18%)
Other cancer	7 (64%)

Table 2: The family assessment of relatives of probands identified with the *BRCA2* pathogenic variant

Family assessment	**No.**
Relatives tested by a clinic	43
Obligate carriers	2
Carriers identified	22

Insights and Implications

This multi centre study identified 33 individuals from 11 unrelated families with the same *BRCA2* exon 3 deletion suggesting a shared underlying genetic susceptibility.
The spectrum of cancers identified in the family are consistent with BRCA2-related hereditary cancer predisposition syndrome.

One other report has described this same *BRCA2* exon 3 deletion in Assyrian population. This series reported 6 carriers from 5 families in a single centre in California, USA.[8] Our report supports a potential role of the *BRCA2* exon 3 deletion as a potential Founder variant in Assyrian families describing many more individuals and families.

The variant frequency and the extent to which it accounts for hereditary breast/ovarian cancer in the Assyrian population, is not known. Further studies are required to clarify these questions.

Understanding genetic risk factors within populations can allow more accurate assessment of cancer risk, inform targeted and cost-effective screening programs when a founder variant is confirmed to be sufficiently common, and result in initiation of appropriate surveillance strategies. Asking for ethnicity beyond country of origin is important in identifying Assyrian individuals.

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