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SHORT REPORT

Prevalence of *BRCA1*/*BRCA2* pathogenic variation in Chinese Han population

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jmedgenet-2020-106970).

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Received 2 March 2020
Revised 18 April 2020
Accepted 20 April 2020

To cite: Dong H, Chandratre K, Qin Y, *et al*. *J Med Genet* Epub ahead of print: [please include Day Month Year]. doi:10.1136/jmedgenet-2020-106970

ABSTRACT

Background Pathogenic variation in *BRCA1* and *BRCA2* (*BRCA*) is one of the most frequent genetic predispositions for hereditary breast cancer. The identification of the variant carriers plays an important role in prevention and treatment of cancer. Despite a population size of 1.4 billion and a quarter million annual new breast cancer cases, knowledge regarding the prevalence of *BRCA* variation in the Chinese population remains elusive.

Methods In this study, we used *BRCA*-targeted sequencing and bioinformatics approaches to screen for *BRCA* variants in 11 386 Chinese Han individuals, including 9331 females and 2055 males.

Results We identified 1209 *BRCA* variants, 34 of which were pathogenic, including 11 in *BRCA1* and 23 in *BRCA2*. These variants were distributed among 43 individuals (37 females and 6 males), with 13 carrying *BRCA1* and 30 carrying *BRCA2* variants. Based on these data, we determined a prevalence of 0.38%, or 1 carrier of a *BRCA* pathogenic variant out of every 265 Chinese Han individuals, and 5.1 million carriers among the Chinese Han population of 1.3 billion.

Conclusion Our study provides basic knowledge about the prevalence of *BRCA* pathogenic variation in the Chinese Han population. This information should be valuable for *BRCA*-related cancer prevention and treatment in the population.

INTRODUCTION

Approximately 25%–30% of familial breast cancers are attributed to genetic predisposition, circumscribed to a group of high-risk genes. Highly significant genetic elements include the pathogenic mutations in *BRCA1* and *BRCA2* (*BRCA*).[1] Identifying *BRCA* variant carriers before cancer occurrence is key to prevent *BRCA* variation–caused cancer in the carriers and to treat patients with *BRCA* variant–positive cancer effectively by using PARP inhibitors. Traditionally, this task is performed by using the family cancer history–based approach. However, this approach has been deemed ineffective, as it can only identify less than a third of *BRCA* variant carriers,[2] leaving the unidentified variant carriers missing opportunities for cancer prevention and treatment. To overcome this obstacle, a population screening–based approach has been proposed to obtain comprehensive identification of *BRCA* variant carriers in the general population, regardless of family cancer history, gender or cancer status.[3] This has inspired extensive discussions regarding legal, clinical, epidemiological, psychological, ethical and public health issues. In general, population screening is considered as a favourable approach to be used in the near future, but it has not yet been put into practice, except in the Jewish population to a certain degree, for various reasons.[4–6] Among the factors required for the use of population screening for disease prevention and treatment is the knowledge of the prevalence of targeted variants in a given population. As population screening requires substantial resources, such information is essential to determine the cost-effectiveness and comprehensiveness of variant carrier identification. This is particularly important for the populations without known *BRCA* founder variation, as the entire coding region of the *BRCA* genes needs to be analysed. The prevalence of *BRCA* variations is approximately one in 189–556 individuals in different ethnic groups.[2 7–10] However, this information is largely derived from Caucasian populations, whereas the rates in non-Caucasians remain largely undetermined.

China has the largest population in the world with approximately 1.4 billion people, of which the Han ethnicity accounts for over 1.3 billion. In addition, China has the largest number of patients with breast cancer, registering a quarter million cases each year. As there is no noticeable high-frequent founder *BRCA* pathogenic variation in the Chinese population,[9] comprehensive identification of *BRCA* variant carriers could have a profound impact on preventing and treating *BRCA* variation–caused cancer in this group. Moreover, as the prevalence of *BRCA* variant carriers in the Chinese population has not been determined, the number of individuals at increased risk of cancer development due to *BRCA* variations is unknown. In this study, we aimed to fill this information gap by testing *BRCA* genes in the Chinese Han population.

METHODS

Study samples

Individuals undergoing routine health examinations were recruited across mainland China between January and June 2019 (figure 1). Both males and females over 19 years of age without history of cancer were recruited. Each participant provided written informed consent to join the study. Saliva DNA was collected from each participant and anonymised.

BRCA-targeted sequencing

The Fluidigm D3 Assay Design program was used to design PCR primers for 349 amplicons

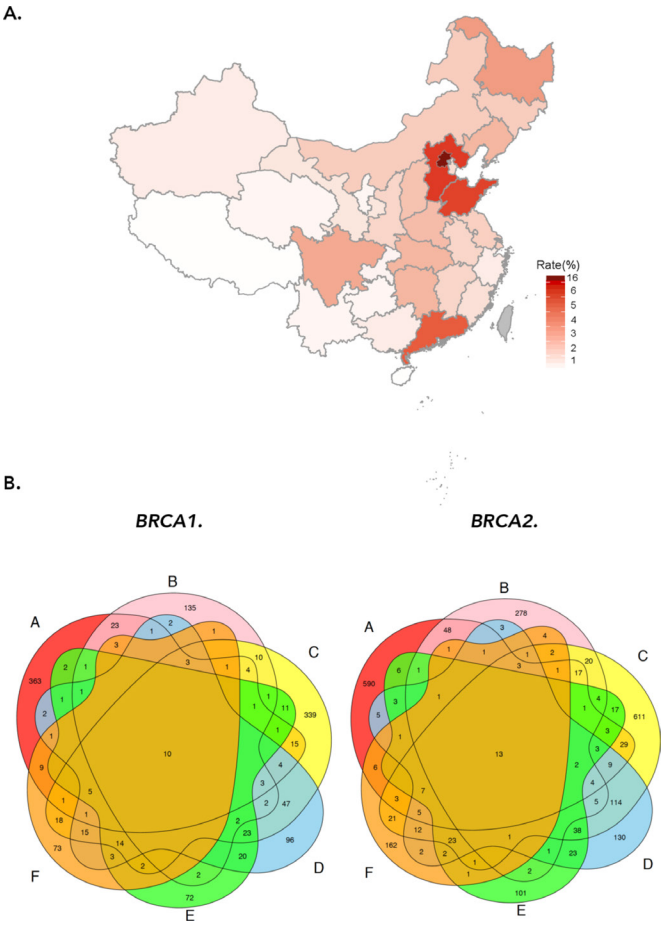

Figure 1 Sample sources from mainland China and comparison of *BRCA* variants between Chinese and non-Chinese individuals. (A) Number of participants from different regions of mainland China. The colour gradients represent the percentage of participants from each region. (B) Total number of *BRCA1* variants: 452 Chinese, 283 Japanese, 533 American, 256 European, 172 African and 160 Mexican; and total number of *BRCA2* variants: 757 Chinese, 549 Japanese, 970 American, 412 European, 255 African and 274 Mexican. A, Chinese; B, Japanese; C, American; D, European; E, African; F, Mexican.

covering the coding sequences and intron/exon boundaries of *BRCA1* and *BRCA2* (Fluidigm, San Francisco, CA, USA). These primers were for *BRCA* template amplification. Next-generation sequencing libraries were constructed by using the targeted DNA Sequencing Library Preparation kit on Fluidigm LP 192.24 IFC (Fluidigm) and sequenced on a HiSeq X Ten instrument (Illumina, San Diego, CA, USA) with a mean sequencing depth of 6267X.

Bioinformatics data analysis

Sequences were mapped to the human reference genome (hg19) using Burrows-Wheeler Aligner. NM_007294.3 (*BRCA1*) and NM_000059.3 (*BRCA2*) were used as reference sequences for variant calling using GATK best practices. Variants were annotated, classified using ANNOVAR, and used for searching genome databases, including RefGene (http://varianttools.sourceforge.net/Annotation/RefGene), dbSNP150 (https://www.ncbi.nlm.nih.gov/snp/), 1000 Genomes Project (https://www.internationalgenome.org), ESP6500 (https://evs.gs.washington.edu/EVS/) and ExAC (http://exac.broadinstitute.org), as well as in *BRCA* variant databases, including BIC (https://research.nhgri.nih.gov/bic/), ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), *BRCA* Exchange (http://brcaexchange.org), *BRCA* Mutation (http://www.arup.utah.edu/database/BRCA/), LOVD (http://www.lovd.nl/2.0/), dbBRCA-Chinese (https://dbbrca-chinese.fhs.umac.mo/) and SGE (https://sge.gs.washington.edu/BRCA1/). The variants classified as pathogenic and likely pathogenic were validated using Sanger sequencing. Those that did not match any data from existing *BRCA* reference databases had their classifications predicted using InterVar. Finally, those that were not present in any of the databases were classified as novel *BRCA* variants and deposited in dbSNP. A power calculation was performed following a previously reported procedure.[11]

RESULTS

A total of 11 386 individuals across mainland China were enrolled in this study (figure 1), including 9331 females, 34.8±8.8 years old, and 2055 males, 43.0±10.3 years old. From the collected sequences, we identified 1209 distinct *BRCA* variants, including 452 in *BRCA1* and 757 in *BRCA2*; 97% of the variants had low frequencies, with a minor allele frequency <0.01. Among the variants, 570 were previously known and had an assigned dbSNP rs number (online supplementary table 1).

The main purpose of population screening is to identify pathogenic variant carriers for cancer prevention and treatment. We performed a clinical classification of our 1209 *BRCA* variants as pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign and benign following the American College of Medical Genetics and Genomics guidelines (table 1A). We identified 34 pathogenic variants (11 in *BRCA1* and 23 in *BRCA2*) in 43 individuals (37 females and 6 males); 13 of them carried *BRCA1* variants and 30 harboured *BRCA2* variants. All 34 pathogenic variants from the 43 carriers were validated by Sanger sequencing. Based on these data, we determined that the prevalence rate was 0.38%, while individual rates were 0.11% for *BRCA1* and 0.26% for *BRCA2*. This was equal to one pathogenic variant carrier per 265 individuals within the tested population and equal to 1/876 in *BRCA1* and 1/380 in *BRCA2* (table 1B, online supplementary table 2). Statistical power calculations indicated that screening 11 386 individuals at a prevalence of 0.38% would provide 97.2% probability of detecting all variants in the studied population. Based on the prevalence of one out of every 265 individuals, we estimated that there are 5.1 million *BRCA* pathogenic variant carriers among the 1.3 billion people that constitute the Chinese Han population.

The 43 pathogenic variant carriers were all heterozygotes. Among these 34 pathogenic variants, 20 corresponded to frameshift indels, 12 to stop-gain mutations, and 2 to splicing or intron variants. All 34 variants were reported as pathogenic in ClinVar, 11 of which were also classified as pathogenic by InterVar; 30 of the 34 variants had been previously reported in dbSNP with assigned rs numbers. Notably, 26 of these 34 variants were previously detected in Chinese patients with cancer.[9] There was no frequency information for any of the 34 variants in the 1000 Genome database, whereas only a few were found in the ExAC/gnomAD database, with the highest frequency value at 0.0006. Notably, five *BRCA2* pathogenic variants are clustered within 109 bases in exon 11 of *BRCA2*, at BRC6 and BRC7 repeats (c.5574_5577delAATT—BRC6 (Ile1859); c.5599_5602delACAG—BRC6 (Asp1868); c.5645C>A—BRC7

Table 1 Clinical classification of *BRCA* variants identified in the 11 386 Chinese Han individuals

A. Clinical classification of the variants

Classification	*BRCA1* (%)	*BRCA2* (%)	Total (%)
Pathogenic	11 (2.4)	23 (3.0)	34 (2.8)
Likely pathogenic	0	0	0
VUS	104 (23.0)	195 (25.8)	299 (24.7)
Likely benign	113 (25.0)	191 (25.2)	304 (25.2)
Benign	39 (8.6)	55 (7.3)	94 (7.8)
Conflicted classification	27 (6.0)	73 (9.6)	100 (8.3)
Unclassified	158 (35.0)	220 (29.1)	378 (31.3)
Total no of variants	452	757	1209

B. Pathogenic variants identified

cDNA change	Amino acid change	Carrier number	Type of variation
BRCA1			
c.961_962insAGAT	p.Trp321_Ala322delinsX	2	Stopgain
c.962G>A	p.Trp321Ter	1	Stopgain
c.1016delA	p.Lys339fs	1	Frameshift deletion
c.1504_1508delTTAAA	p.Leu502fs	1	Frameshift deletion
c.2293G>T	p.Glu765Ter	1	Stopgain
c.2302delA	p.Ser768fs	1	Frameshift deletion
c.2572C>T	p.Gln858Ter	1	Stopgain
c.3294delT	p.Leu1098fs	1	Frameshift deletion
c.4327C>T	p.Arg1443Ter	1	Stopgain
c.5406+1G>A	–	1	–
c.5521delA	p.Ser1841fs	2	Frameshift deletion
BRCA2			
c.476–3C>A	–	2	–
c.657_658delTG	p.Thr219fs	2	Frameshift deletion
c.2276_2277delTT	p.Leu759fs	1	Frameshift deletion
c.3163_3166delAATC	p.Asn1055fs	2	Frameshift deletion
c.3217C>T	p.Gln1073Ter	1	Stopgain
c.4467_4474delAATACTGAinsTGTTTTT	p.Lys1489Asnfs	1	Frameshift deletion
c.4674delT	p.Ser1558fs	1	Frameshift deletion
c.5067dupA	p.Ala1689fs	1	Frameshift insertion
c.5164_5165delAG	p.Ser1722fs	2	Frameshift deletion
c.5574_5577delAATT	p.Thr1858fs	2	Frameshift deletion
c.5599_5602delACAG	p.Thr1867fs	1	Frameshift deletion
c.5645C>A	p.Ser1882Ter	2	Stopgain
c.5681dupA	p.Tyr1894_Glu1895delinsX	1	Stopgain
c.5682C>G	p.Tyr1894Ter	1	Stopgain
c.6482_6485delACAA	p.Asp2161fs	1	Frameshift deletion
c.6597_6598delTT	p.Thr2199fs	1	Frameshift deletion
c.7377_7380delAAAC	p.Lys2459fs	1	Frameshift deletion
c.7407dupT	p.Thr2469fs	2	Frameshift insertion
c.7738C>T	p.Gln2580Ter	1	Stopgain
c.7878G>A	p.Trp2626Ter	1	Stopgain
c.8533_8534delAG	p.Arg2845fs	1	Frameshift deletion
c.9070_9073delAACA	p.Asn3024fs	1	Frameshift deletion
c.9382C>T	p.Arg3128Ter	1	Stopgain

(Ser1882); c.5681dupA—BRC7 (Tyr1894); c.5682C>G—BRC7 (Tyr1894)).

Similar to the ethnic differences seen in *BRCA* variation between Chinese and non-Chinese cancer populations,[9] ethnic differences in *BRCA* variation were also found to exist between Chinese and non-Chinese general populations. This is well reflected by the low percentage of overlapping data when different groups were compared with Chinese Han people. Among the 452 total Chinese *BRCA1* variants, only 22 (4.9%) were found in 2559 Africans, 32 (7.1%) in 7325 Europeans, 34 (7.5%) in 3985 Mexicans, 49 (10.8%) in 50 726 Americans and 51 (11.3%) in 23 731 Japanese individuals[7–10] (https://whi.color.com/about) (figure 1B). Moreover, among the 757 total Chinese *BRCA2* variants, only 41 (5.4%) were shared with Africans, 57 (7.5%) with Europeans, 42 (5.5%) with Mexicans, 100 (13.2%) with Americans and 93 (12.3%) with Japanese individuals (figure 1B).

DISCUSSION

It is widely considered that one in every 300–500 individuals carries *BRCA* variants in the general human population.[11] However, we were unable to find any supporting information for these numbers in the literature. We analysed major reports from Ashkenazim and non-Ashkenazim populations (online supplementary table 3). All seven studies on Ashkenazim populations targeted the three founder mutations in *BRCA* (ie, 185delAG and 5382insC in *BRCA1*, and 6174delT in *BRCA2*). In addition, four of the studies tested Ashkenazim individuals not selected for either cancer status or family history of cancer. These studies accurately determined the prevalence of *BRCA* variations in both the general Ashkenazim population and among those with cancer (online supplementary table 4A). In contrast, in the studies performed on non-Ashkenazim populations, individuals with either breast or ovarian cancer, or high-risk individuals were the only ones tested (online supplementary table 4B). For example, a US study tested breast and ovarian cancers in non-Hispanic white individuals,[12] then by referencing the variant data to US population census data, they reached the conclusion that there were 506 206 *BRCA* variant carriers in the US population. This is also the case of a German study in which 617 578 individuals from 21 401 families were tested, including 57 387 people with breast cancer, 7250 with ovarian cancer, 1917 with both types of cancer and 551 024 high-risk individuals.[13] Therefore, all the studies on non-Ashkenazim populations addressed the prevalence of *BRCA* variation in cancer or high-risk populations. As the prevalence information from these groups is not equivalent to the prevalence in the general population, to date, it remains largely unclear, except for some existing data of one in 189–556 individuals in a few tested populations.[7–10]

Before the development of this study, the prevalence of *BRCA* variation in the general Chinese population was poorly characterised. The 1000 Genomes Project tested only 388 Chinese individuals (CHB, CHS, CDX) (https://www.internationalgenome.org/data); the *BRCA*-targeted exome sequencing project included only 739 individuals of unspecified East/Southeast Asian origin[14]; the Asian whole-genome sequencing study tested 2780 Chinese individuals,[15] and the gnomAD contained 9435 individuals of unspecified East Asian origin (https://macarthurlab.org/2017/02/27/the-genome-aggregation-database-gnomad/). By testing 11 386 Chinese Han individuals using the *BRCA*-targeted approach, our study obtained first-hand data about the prevalence of *BRCA* variation in the Chinese Han population.

Except for the high prevalence of *BRCA* pathogenic variation in the Ashkenazi Jewish population (2.17%),[3] the 0.38% prevalence observed for the Chinese Han population may be considered intermediate compared with that in other general ethnic populations, for example, in comparison with the 0.18% prevalence determined in a Malaysian population of 2809 individuals (one in 556),[7] 0.26% in a Japanese group of 22 731 individuals (one in 384),[8] 0.38% among 3985 Mexicans (one in 265)[9] and 0.53% in 50 726 US people (one in 189).[10] Our study also showed ethnic-specific features of *BRCA* variation in general populations, indicating that ethnicity is an important factor to be considered when planning population screening. The finding that one in every 265 individuals carries a *BRCA* pathogenic variant in the Chinese Han population highlights that *BRCA* pathogenic variation is a real threat to public health, and that the identification of the variant carriers could have a profound impact on cancer prevention and treatment in the Chinese population. It is necessary to indicate that the actual prevalence in the Chinese Han population could be higher than the estimated 0.38% because the presence of large number of unclassified novel variants (online supplementary table 5), and the technique used in our study mainly targets single-base changes and indels. Many large structural changes and copy number variations, which often account for 15%–20% of the variation spectrum, could not be detected by our study.

Acknowledgements We would like to thank the Information and Communication Technology Office (ICTO), University of Macau for providing the High-Performance Computing Cluster (HPCC) resource and facilities for the study.

Contributors HD: experimental design, data collection, annotation, analysis; KC, YQ: annotation, analysis; JZ, XT, CR, NW: sample collection; MG: statistics data analysis; GZ: experimental design; SMW: experimental design, data analysis and interpretation, manuscript writing.

Funding The study was supported by grants from the University of Macau (SRG2017-00097-FHS, MYRG2019-00018-FHS), a start-up fund from the Faculty of Health Sciences, University of Macau, and a grant from the Macau Science and Technology Development Fund (085/2017/A2) (SMW), and the Shanghai General Hospital Start-up Fund (02.06.01.20.01) (HD).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Shanghai City Ethics Committee for Clinical Research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data generated from the study are available as supplementary tables 1-5.

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