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REVIEW

BRCA mutations: is everything said?

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Abstract

Background Mutations in the BRCA1 and BRCA2 genes constitute a risk factor for breast cancer development. BRCA mutation research has been an active field since the discovery of the genes, and new mutations in both genes are constantly described and classified according to several systems.

Aim We intend to provide an overview of the current state of BRCA1 and BRCA2 mutation description and classification. We wanted to know whether there was a trend towards a more frequently described mutation type and what the proportion of pathogenic mutations was.

Results We found that, although new mutations are described each year as reflected in current database records, very few of them are reported in papers. Classification systems are highly heterogeneous and a consensus among them is still under development. Regarding their function, a large number of mutations are yet to be analyzed, a very complex task, due to the great number of possible variations and their diverse effect in the BRCA gene functions. After individual analysis, many variants of unknown significance turn out to be pathogenic, and many can disrupt interactions with other proteins involved in mechanisms such as DNA damage repair pathways. Recent data suggest that looking for mutation patterns or combinations would shed a wider light on BRCA-derived cancer susceptibility in the upcoming years.

Keywords Breast cancer risk · BRCA1 · BRCA2 · Mutation · Complex traits

What is said

Mutations in the aptly named Breast Cancer Susceptibility Genes, BRCA1 and BRCA2, are widely accepted as high-risk factors for breast cancer development. However, due to the sheer size of both genes and the complexity of their various functions, the mere presence of any mutation does not necessarily lead to a malfunctioning protein and, therefore, is not a direct indicator of cancer development. Consequently, a great amount of research has been put into analyzing the degree of cancer development risk associated with as many as possible BRCA mutations. This has proven a daunting task to the scientific community, not only due to the great number of possible variations, but due to the diverse effects that these mutations can have in the BRCA gene functions and the likelihood that they are benign or indeed malignant.

We reviewed journal articles published between the description of the BRCA genes in 1994, and 2017 in order to obtain an overview of the focus that the different types of BRCA mutation have received over time. It is important to

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point out that the present review is by no means a comprehensive recollection of all the described BRCA mutations, as a growing number of them are directly indexed in databases such as BIC [1] and ClinVar [2]; the reader is kindly directed to these repositories for data on the mutations themselves.

One of the main challenges that BRCA mutation analysis raises is their nomenclature. Although mutations are well-defined concepts [3, 4], researchers have pursued a classification that encompasses both the nucleotide changes per se and their effect in cancer development. As a result, BRCA mutation classification criteria include terms from DNA-, RNA-, and protein-level changes, such as 'insertion,' 'splice site mutation,' and 'frameshift,' respectively, along with indications of the associated cancer risk. This situation is often conflicting, since some of these categories overlap; for instance, splice site and frameshift mutations are essentially single-nucleotide insertions or deletions and are reported as such by some authors. Cancer development risk adds another layer of complexity to mutation classification: mutations can pose a high, uncertain, or no cancer risk, but the distinction requires careful analysis. Some mutation types are inherently deleterious—such as nonsense mutations–, while some others may or may not be—such as missense mutations—and therefore are labeled as uncertain; so a given mutation can fall into more than one category even under the same classification scheme, or be classified along with other non-related mutations, i.e., a single-nucleotide change that generates an amino acid change is a missense mutation, but if it represents little known cancer risk, it can also be considered uncertain and grouped together with a multiple nucleotide deletion in an intron. For example, Capalbo and colleagues [5] group nonsense, frameshift, and splicing site into a single 'truncating mutation' category, while Giannini and collaborators [6] include an 'intronic variants' category, which comprises single-nucleotide insertions, deletions, and substitutions. Both these schemes and many others found in similar works are sound and clearly explained within each paper, but the fact that they are not straightforward comparable makes it difficult to assess information about BRCA variants across different sources. Several classification systems that address this issues have been proposed, but an international consensus among research and clinical laboratories is yet to be reached [7, 8]. At the time of writing, even curated database entries display a number of equivalent nomenclatures for a single given mutation [1]. Efforts towards a more comprehensive and coordinated approach to BRCA mutation classification are being undertaken by organizations such as the Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA) [9] and the evidence-based network for the interpretation of germline mutant alleles (ENIGMA) [10]. These organizations collect and curate mutational data with the main intention of making it readily accessible though user-friendly repositories such as BRCA exchange (http://www.brcaexchange.org), building on the achievements of early databases such as the Catalogue of Somatic Mutations in Cancer COSMIC [11] and the Human Variome Project HGM [12]. Yet, true standardization still lies down the road.

For the purpose of this review, we classified BRCA mutations in six broad categories according to their effect in mRNA processing and/or in the protein translation: indel (short insertions or deletions, thus including frameshift mutations), missense, nonsense, splice site (disruption of the consensus splice sites), large rearrangements (insertion or deletion of more than 12 nucleotides, or chromosomal aberrations); additionally, we listed variants with no evident effect in mRNA or protein as VUS (variants of unknown significance). Through the PubMed.org portal, we searched the Medline database for papers in English published from 1994 to 2017, using three-word queries comprising 'BRCA1' or 'BRCA2,' each of the aforementioned mutation types and the word 'mutation' (e.g., BRCA1 nonsense mutation); we carefully read each resulting paper and computed the number of novel described mutations, listing them as indel, missense, nonsense, spliced site, large rearrangement, or VUS after detailed analysis. For the sake of clarity, we list all the reviewed papers in additional files and cite only highlights in this text. We wanted to know how many mutations were described in published papers each year to gain insight about how much attention was paid to each mutation type over time.

We found a total of 1272 BRCA1 and 1320 BRCA2 (Fig. 1) mutations described in the reviewed papers and were struck by these numbers since the BIC database currently lists 15,311 BRCA1 and 14,016 BRCA2 mutations [1, 2]. It is indeed possible that our queries did not detect every single mutation ever published and thus that we are underestimating the number of published mutations, though we find it unlikely that our search ignored published works on around 90% of the listed variants. It is far more likely that most of the newly discovered mutations are directly uploaded to databases such as BIC. The complete list of reviewed papers and the number of novel mutations described in each one is shown in Additional File 1.

In our search, single-nucleotide mutations were the most reported, and their proportion was very similar in both BRCA 1 and 2. Indels, together with missense, nonsense, and splice mutations, accounted for 67% of the BRCA1 and 56% and BRCA2 mutations, while around 33% and 45% were of unknown significance (Fig. 1). Conversely, a review of early BRCA mutation data [13] reported 254 BRCA1 mutations, around 80% of which were small indels or nonsense mutations, and just 8% were of unknown significance. This suggests that mutation detection has advanced at a higher pace than mutation evaluation has. We think that this creates a substantial

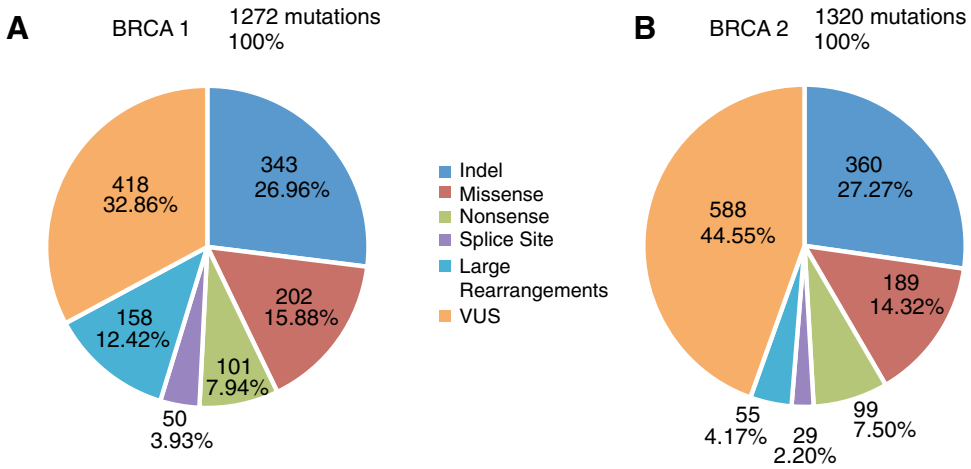

Fig. 1 Proportion of BRCA 1 (**a**) and BRCA 2 (**b**) mutations classified according to their effect in mRNA processing and/or in the protein translation

information gap because, as the number of mutations increases in the form of database entries, the in-depth information about them—available in the form of research papers—is proportionately lower.

Large rearrangements, ranging from deletions of more than a few nucleotides to complex chromosomal aberrations, were not reported for BRCA genes until 1997 [14]. It has been established that BRCA1 is much more prone to genomic rearrangements due to the high number of *Alu* repeats in its sequence, and that therefore many more of them are detected in BRCA1 than in BRCA2 [15]. Our data maintain this proportion, though large rearrangements only represent 12% and 4% of the published BRCA1 and BRCA2 mutations (Fig. 1).

When looking at the yearly cumulative number of mutations (Fig. 2), other than a 3-year delay in the start of BRCA2 mutation publishing, we found a steady increase in virtually every mutation category. The slope change seen in the VUS mutants is the effect of a single paper by Borg and colleagues that reported 128 BRCA1 and 229 BRCA2 VUS found in a 2103 patient cohort [16]. This was an unexpected result, as we had anticipated a trend towards the detection of one or more mutation classes, perhaps due to the discovery or popularization of new detection techniques. However, our data showed that reports about BRCA mutations have maintained a relatively steady pace.

Throughout these years, several authors have reviewed BRCA mutations from different perspectives [13, 17–20]; one of the most recent is particularly interesting, as it shows that BRCA1/2 pathogenetic mutations—and thus mutation-associated cancer risk—are differentially distributed by ethnicity [21]. Nevertheless, all these works list a substantial number of mutations as unclassified variants or VUS. In our own literature review, this category accounted for 32% and 44% of the reported mutations for BRCA1 and BRCA2, respectively. This term rather imprecise, as different authors apply different criteria.

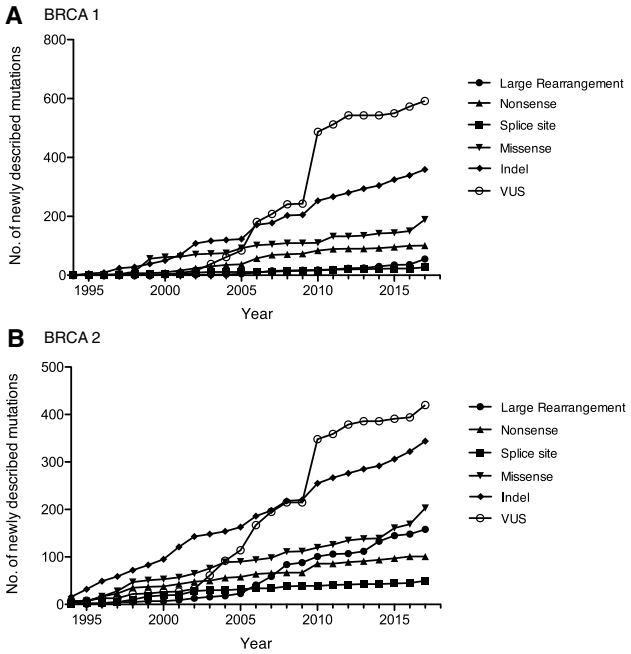

Fig. 2 Cumulative number of BRCA 1 (**a**) and BRCA 2 (**b**) new mutations described yearly from 1994 to 2018, classified according to their effect in mRNA processing and/or in the protein translation

Broadly, mutations with an unknown effect on protein function are classified as VUS [18]; this typically includes mutations that do not generate a stop codon or a sensible amino acid change, but silent mutations and intronic variants fit the description as well and thus may or may not be included depending by some authors. For example, Maillet and collaborators [22] describe intronic variants present as polymorphisms or VUS only based on whether they were present in more or less than 1% of their sample; i.e., single base changes such as IVS20+45T>C—present in > 5% of the cases—were classified as polymorphisms, while variants such as IVS12+24A>G—with potentially similar function

but present in < 1% of the population—were classified as VUS; at the time of writing, neither of these two variants is listed in BRCA Exchange (direct search on 05/18, http://www.brcaexchange.org).

With so many possibilities under the same term, it is hard to gauge the pathogenicity of VUS. At first sight, intronic variants contrast starkly with indels that generate a stop codon and thus a truncated protein; but intron retention—a possible outcome of a given intronic variant—can generate an extremely long mRNA that would be subject to degradation, rendering this variant as deleterious as the previously mentioned indel. A number of published studies attempt to re-classify VUS according to their pathogenicity, as we found in our literature search. We computed the previously described VUS that were classified as pathogenic or benign and found that roughly half of the assessed VUS in both BRCA1 (49%) and BRCA2 (45%) resulted pathogenic (Fig. 3, Additional file 2). This is hardly an encouraging scenario, as it indicates that VUS simply may or may not be pathological.

The methods employed by authors to establish VUS pathogenicity varied widely and included in vivo and in silico approaches. For instance, Lee and collaborators [23] performed structural and transcriptional analysis on 117 BRCA1 variants; Steffensen et al. [24] employed a minigene system to characterize 13 BRCA1 variants; Easton and coworkers [25] assessed 1433 BRCA1 and BRCA2 through a logistic-regression analysis.

Our literature search evinced great need for a standardized method of pathogenicity evaluation of BRCA mutants. As is the case with mutation classification, virtually each research group has established its own methodology for cancer risk assessment and, due to the great number of VUS and the interest in analyzing each one of them, these data are not routinely validated in more than one laboratory. Notably, every VUS re-classification study left a number of them still unclassified. Moreover, a database compiling re-classified VUS—designated Ex-UVs by the authors—has been proposed. It included data on variants assessed in published papers and was intended to be updated yearly [26]. At the time of writing, the database is not available through the provided links.

What is not said. Yet

BRCA proteins exert their function in transcription and cell cycle regulation and DNA damage repair [extensively reviewed in 27, 28] through the formation of large complexes with a large network of associated proteins, including but not limited to ATM/ATR, CHK2, BARD1, Rb1, p53, and RAD51. BRCA cancer-associated mutations, especially those located in the BRCT domain (such as c.3607C>T, c.3700_3704del, c.3756_3759del, c.3839_3843delinsAGGC), disrupt its interactions with one or multiple members of these complexes, decreasing the efficiency of DNA repair mechanisms and thus its tumor-suppressive effect [29].

This year, Knijnenburg and colleagues found a characteristic pattern of alterations in 276 genes associated with the eight major DNA damage response pathways (NHEJ, TLS, BER, FA, NER, MMR, DR, HDR) for each of the 33 assessed cancer types ($n = 9125$ cases). BRCA 1 and 2 were among the top 20 more frequently mutated genes, and among the 48 potential cancer drivers as per the combined result of five driver identification algorithms [30]. It has been previously demonstrated that the accumulation of small genomic changes can lead to alterations in complex traits [31]; therefore, we find it very plausible that the effects of BRCA variations lie in its interaction network and that the known direct associations between single BRCA mutations and cancer development are the exception rather than the rule.

Recent research offers at least two lines of evidence that support this idea. First, current data still underestimate the effect of single-nucleotide variants in splicing, and thus in

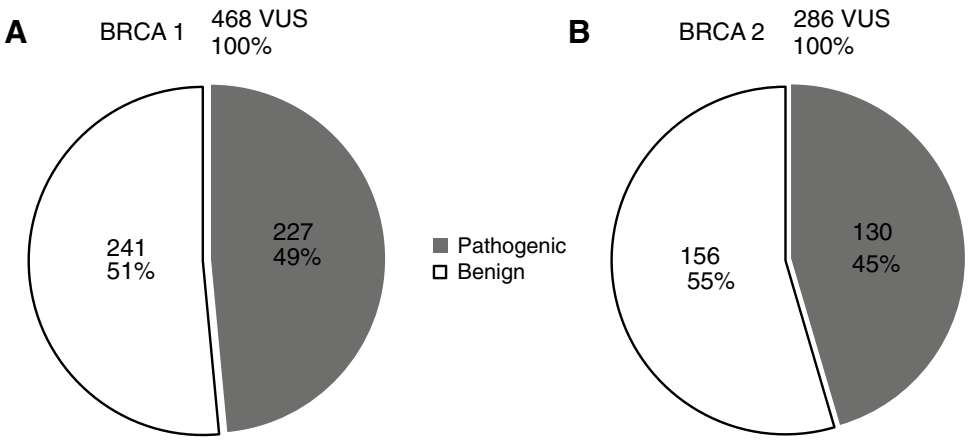

Fig. 3 Proportion of cancer risk of BRCA 1 (**a**) and BRCA 2 (**b**) VUS, analyzed from 1994 to 2018

the production of new protein isoforms or the balance of the known ones, as demonstrated in studies of the BRCA2 [32] and MLH1 [33] genes. For instance, the BRCA1 alternative splicing isoform BRCA1-Δ11q was detected as a result of the 2288delT, 2529C>T, and 3960C>T mutations and conferred PARP inhibition and cisplatin resistance to the cells that express it [34], but the BIC database lists only the latter two as deleterious while offering no record of the first one (direct search on 05/18, research.nhgri.nih.gov/projects/bic) and BRCA Exchange only lists 2529C>T as 'not yet reviewed' (direct search on 05/18, brcaexchange.org). The 2288delT variant has been previously observed: it shows differential localization compared to the full-length BRCA1 protein [35] and its presence, together with Gadd45a deficiency, leads to centrosome duplication and genomic stability [36]. Interestingly, Elstrodt and colleagues [37] had found the 2288delT variant in a single case and reported it as deleterious without further investigating its mechanisms. Considering this, it is only reasonable to wonder whether a given BRCA mutation can associate with cancer development only in a determinate context of particular alleles of the interacting proteins; this way, conflicting results on the cancer risk of BRCA variants would be the result of different interaction patterns. This idea would also explain why a number of variants remain unclassified after experimental analysis: they are not being analyzed in the appropriate context.

Second, Doss and colleagues [38] recently modeled the BRCA2 and its interacting partners PALB2 and RAD51 in silico. They represented in silico the alternative conformations that resulted from a number of single-nucleotide polymorphisms on both proteins and analyzed amino acids relevant for their function. Their analyses revealed substantial differences in the binding dynamics of both pairs of mutant proteins, suggesting that the effect of a mutation in BRCA2 or PALB2 alone (or in BRCA2 or RAD51 alone) would not have a pronounced change in the binding dynamics. This strongly suggests that the analyzed BRCA2 and PALB2 mutations rely on one another to be deleterious, i.e., that what is in fact deleterious is the combination of both mutations.

Certainly, the most studied BC predisposition genes have been BRCA1/2 and their clinical validity has been established as well, but besides them, germinal mutations in other genes are involved in BC development. Mutations in genes such as TP53, CDH1, PTEN, STK11, and NF1 with high penetrance and MLH1, MSH2, MSH6, PMS2, MEN1, and PPMID with low penetrance have already been individually associated to cancer development [39]. Likewise, loss-of-function mutations in PALB2 also confer the higher risk (6 times in carriers more than non-carriers) although this mutation may overlap with BRCA mutations [40]. Similarly, RAD51C pathogenic variant c.404G>A and RAD51D pathogenic variant c.694C>T are involved in predisposition to BC and ovarian cancer; it has been even suggested to include these genes in genetic testing performed in hereditary breast and ovarian cancer patients [41, 42].

We think that rather than only perfecting the mathematical model of combined risk, future research will assess the molecular interactions that drive carcinogenesis and propose interactions derived from specific haplotypes as cancer development markers. This interaction or haplotype markers would be more robust, since they would necessarily be based on the functional data that several authors of single-gene association papers still regard as lacking.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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