**BRCA1/2 Mutations Appear Embryo-Lethal Unless Rescued by Low (CGG n<26) FMR1 Sub-Genotypes: Explanation for the “BRCA Paradox”?**

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**Abstract**

BRCA1/2 mutations and recently described constitutional FMR1 genotypes have, independently, been associated with prematurely diminished ovarian reserve. Whether they interrelate in distribution, and whether observed effects of BRCA1/2 and FMR1 on ovaries are independent of each other, is unknown. In a prospective comparative cohort study, we, therefore, investigated the distribution of constitutional FMR1 genotypes, normal (norm), heterozygous (het) and homozygous (hom), and of their respective sub-genotypes (high/low), in 99 BRCA1/2 mutation-positive women and 410 female controls to determine whether distribution patterns differed between study and control patients. In contrast to controls, BRCA1/2 carriers demonstrated almost complete absence of all constitutional FMR1 genotypes except for sub-genotypes with low (CGG n<26) alleles. Cross tabulation between BRCA1/2-positive patients and controls confirmed significant group membership, related to FMR1 distribution (P<0.0001). These results offer as most likely explanation the conclusion that BRCA1/2 mutations are embryo-lethal, unless rescued by low (CGG n<26) FMR1 sub-genotypes, present in approximately one quarter of all women. Women with low FMR1 sub-genotypes, therefore, should reflect increased BRCA1/2-associated cancer risks, while the remaining approximately 75 percent should face almost no such risks. If confirmed, this observation offers opportunities for more efficient and less costly BRCA1/2 cancer screening. The study also suggests that previously reported risk towards prematurely diminished ovarian reserve in association with BRCA mutations is FMR1-mediated, and offers a possible explanation for the so-called “BRCA paradox” by raising the possibility that the widely perceived BRCA1/2-associated tumor risk is actually FMR1-mediated.

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**Introduction**

The fragile X mental retardation 1 (FMR1) gene, located on the long arm of the X chromosome (Xq27.3) at base pairs 146,001,200 to 145,840,302, contains a repetitive DNA segment, the CGGn trinucleotide. The gene has, historically, primarily been investigated due to associated neuro-psychiatric risks at so-called premutation range CGG expansions (approximately CGG n=55–200) and at full mutation range (CGG n>200), the so-called fragile X syndrome [1].

In women, the premutation range genotype of FMR1 has for decades been known associated with greatly increased risk towards premature ovarian failure (POF), often also called primary ovarian insufficiency (POI) [2]. The gene until recently was, however, not known for any specific associated ovarian phenotypes. This changed with the description of newly described constitutional, so-called ovarian genotypes of FMR1, with distinct phenotypical ovarian aging patterns, associated with prematurely diminished functional ovarian reserve and other associations [3,4].

These newly described ovarian genotypes of FMR1 were based on definition of a normal CGG hetero range of 26–34 (median CGG n=10) [3], later confirmed to be identical in all races, though in outliers (het and hom genotypes and sub-genotypes) demonstrating distinct distribution differences between races [5,6]. The median of
reported independently for BRCA1/2 whether observed FMR1 genotypes and sub-genotypes. Because of the small number of FMR1 patients, they are not sub-divided into sub-genotypes in this study.

Their BRCA1/2 infertility patients, whose anonymized clinical information, distributions as a general population [5,6]. An infertile female population like the one presented here, previously was shown to demonstrate similar CGG count variations, and anonymity of patients.

The commonality of prematurely diminished ovarian reserve, reported independently for BRCA mutations and the FMR1 gene, therefore, led us to investigate to what degree BRCA1/2 and FMR1 genotypes and sub-genotypes interrelate in distribution, and whether observed BRCA effects on ovarian reserve may be FMR1-mediated. As this study will demonstrate, the relationship between BRCA1/2 and the FMR1 gene was found to be surprisingly interdependent, raising a number of new biological questions of importance.

Methods

Study Design

Coordination of research efforts between Austrian and U.S. centers involved one author (A.W.). BRCA1/2 and FMR1 data of Austrian BRCA1/2-positive patients were obtained in Austria, and without further analysis anonymized forwarded to New York investigators (D.H.B., A. K., N. G.) for statistical analyses.

Study Groups

The study involved two distinct patient populations: (i) 99 Austrian female BRCA1 or BRCA2 mutation-positive patients. Their BRCA1/2 testing was performed at the Medical University Vienna, Vienna, Austria, while their FMR1 assays were performed at the Medical University Graz, Graz, Austria. (ii) 410 female infertility patients, whose anonymized clinical information, including FMR1 testing results, were stored in the electronic research database of the Center for Human Reproduction in New York, U.S.A. An infertile female population like the one presented here, previously was shown to demonstrate similar CGG count distributions as a general population [5,6].

An initial statistical analysis of the Austrian data set, because of here reported rather extraordinary findings, raised questions about reproducibility of Austrian and U.S. FMR1 results. The Austrian laboratory was, therefore, requested to provide random anonymized results of a patient population reflecting the whole CGG spectrum. When the U.S. investigators analyzed these 105 additional controls, FMR1 genotypes and sub-genotypes did not differ significantly in either median or distribution between 25th and 75th percentiles from infertile U.S. controls, thus confirming reproducibility and compatibility of Austrian and U.S. FMR1 analyses.

Laboratory Analyses

BRCA1/2 and FMR1 analyses of the Austrian study group were performed in Vienna (BRCA1/2) and Graz (FMR1), Austria, respectively. Until and inclusive of 2008, BRCA1/2 analyses were performed by denaturation high performance liquid chromatography, as previously reported by the laboratory [9]. After 2008, DNA sequencing, with use of chain-terminating inhibitors, was utilized [10].

FMR1 analyses in Austria were performed by Southern blot hybridization and polymerase chain reaction (PCR), as previously reported from this laboratory [11]. New York FMR1 analyses were performed by commercial assays, as previously reported [3-6].

Austrian FMR1 data were reported for both alleles as CGGn, and in New York converted to the recently reported format of ovarian genotypes and sub-genotypes [3,4,6]. In brief, it is based on a normal range of CGGn = 26–34, with median of 30 repeats. Women, therefore, can have the following genotypes: normal (norm) if both alleles are in normal range; heterozygous (het), if one allele is in and one outside of normal range; and homozygous (hom) if both alleles are outside normal range. Het and hom genotypes can then be further subdivided, depending whether abnormal alleles are above (high) or below (low) normal range into het-norm/high and het-norm/low and hom-high/high, hom-high/low and hom-low/low sub-genotypes. Because of the small number of hom patients, they are not sub-divided into sub-genotypes in this study.

Institutional Review Board (IRB) Approvals

The Ethikkommission der Medizinischen Universita¨t Wien, an IRB at the University Vienna, Austria, approved analysis of BRCA1/2 patients. Written consents were obtained from all participants. The CHR’s IRB (Institutional Review Board, the Center for Human Reproduction) approved data analysis of the U.S. control group. CHR patients, at time of initial consultation, sign an informed consent, which allows for review of medical records for research purposes as long as patient anonymity and confidentiality of the medical record are maintained. These conditions were met, and the study, therefore, qualified for expedited review. Patients, undergoing FMR1 testing at CHR, in addition, sign a genetic testing-specific consent, and all clinical and research staff at CHR, in concordance with federal HIPAA rules, in writing commit to maintaining confidentiality of medical record and anonymity of patients.

Statistical Analyses

Proportions of FMR1 genotypes and sub-genotypes were compared between the two study groups using cross-tabulations and calculations of Chi-square and Cramer’s V statistics. When comparing CGGn as a continuous function between the groups, nonparametric testing was used because CGGn in populations tends to be positively skewed. Mann-Whitney U tests were conducted to evaluate differences between the two groups on median change in CGGn of both alleles.

All statistical calculations were performed utilizing SPSS, version 18 (Chicago, Illinois).

Results

Controls demonstrated a similar FMR1 genotype and sub-genotype distribution to previously reported populations [4,6] (Figure 1), with normal (norm), heterozygous (het) and homozygous (hom) genotypes of 58.0, 36.1 and 5.9 percent, respectively. The expected distribution was also observed with sub-genotypes, with het-norm/high at 15.6 and het-norm/low at 20.5 percent, each, and also follows that in general populations [4,6].

Table 1 offers a detailed description of BRCA1/2 mutations in the study group. BRCA1/2 carriers presented with distinctively different FMR1 genotype and sub-genotype distributions (Figure 1): An overwhelming majority of BRCA1/2 carriers exhibited the het-norm/low FMR1 sub-genotype (74.0% BRCA1 and 83.7% BRCA2,
respectively). Combined, 78.8 percent of women who were BRCA1 or BRCA2 positive, thus, exhibited the het-norm/low FMR1 sub-genotype. In further stark contrast to controls, none of the BRCA1/2 carriers demonstrated the het-norm/high FMR1 sub-genotype.

BRCA1/2-positive patients also demonstrated almost no norm genotypes, by far the most prevalent genotype in controls (Figure 1) and in previously investigated populations [4,6]: Only 10.0 and 2.0 percent of BRCA1 and BRCA2 patients, respectively (combined 6.1%), demonstrated a norm FMR1 genotype.

The hom genotype was mildly overrepresented in BRCA1 and BRCA2 carriers (16.0% and 14.3%, respectively; combined, 15.2%). Numbers were, however, too small for meaningful assessments of individual hom sub-genotypes, and this group of patients was, therefore, collapsed. Controls had not been investigated for BRCA1/2.

In comparing distribution of FMR1 genotypes and sub-genotypes between BRCA1/2 patients and controls (with hom sub-genotypes collapsed), group membership was significantly related [χ²(6, N = 614) = 158.71; P < 0.0001]. Non-parametric testing (Mann-Whitney U test) confirmed statistically significant differences in median change for CGGₙ on the low count allele of the FMR1 gene between both patient groups; with follow up tests (Dunn’s Method) indicating significant differences between groups (Figure 2a & b).

For the lower CGGₙ allele, in most cases representative of a low FMR1 genotype/sub-genotype, values amongst the two groups were also significantly different [Mann-Whitney U = Mean Rank BRCA1 83.37low, 296.44high, Z = -13.10; P = 0.001]: The higher count CGGₙ allele, mostly representing high FMR1 genotypes/sub-genotypes, varied amongst the two groups as well (Mann-Whitney U = Mean Rank BRCA1 231.18low, 260.75high, Z = -0.069; P = 0.07) but failed to reach statistical significance (Figure 2a). Figure 2 presents distributions of individual CGGₙ in both study groups.

Discussion

This study was initiated to determine whether prematurely diminished functional ovarian reserve in women with BRCA1/2 mutations, was, as had been suggested, a newly discovered association with BRCA1/2 [8] or due to overlapping associations with FMR1 genotypes and sub-genotypes, previously demonstrated to affect ovarian reserve [3-6]. Here reported finding answered this question rather unequivocally by demonstrating that BRCA1/2 mutations were, practically, almost exclusively only associated with the het-norm/low FMR1 sub-genotype. Since this sub-genotype has been associated with prematurely diminished ovarian reserve and lower pregnancy chances with IVF in all races [4,6], it appears likely that the reported association of BRCA1 with premature diminished ovarian reserve [8] is actually FMR1-mediated.

The here observed distribution of FMR1 genotypes and sub-genotypes in BRCA1/2 carriers came, however, as a complete surprise since no other previously investigated patient population
had demonstrated a FMR1 genotype/sub-genotype distribution as here observed amongst BRCA1/2 carriers. The most likely explanation for complete absence of het-norm/high, minimal presence of norm genotypes and highly excessive presence of het-norm/low FMR1 sub-genotypes in BRCA1/2-positive women is principal embryo-lethality of BRCA1/2 mutations. Only if a human embryo carries a low (CGG \(_n\), \(\leq 26\)) sub-genotype allele is such an embryo able to overcome the BRCA1/2-associated embryo lethality. Such low sub-genotypes can be present in het-norm/low, hom-low/low and hom-high/low FMR1 sub-genotypes, combined, representing approximately 25 percent of all women (Figure 1) [4,6]. In other words, only approximately one in four human embryos with BRCA1/2 mutations will survive—a previously unreported cause of human embryo mortality.

An alternative explanation for here reported findings would be that BRCA1/2 mutations, somehow, are able to influence CGG triple nucleotide repeats (CGG\(_n\)) on the FMR1 gene. Such an explanation, however, appears unlikely. BRCA1/2 mutations have never before in humans been reported to be embryo-lethal. Some homozygous BRCA1/2 mouse models, however, proved embryo-lethal, though with great variability in phenotypes and in rescue of embryonic lethality on a p53-null background [12]. BRCA1/2 genetically interacts with the p53 pathway, at least partially explaining the so-called “BRCA paradox,” defined by BRCA-deficient tumor cells rapidly proliferating, while BRCA-deficient embryos suffer from proliferation defects [12] (for further detail see later). In animal experiments, p53-nullizygousity can rescue some BRCA1 mouse mutants [13–15] but may only delay lethality [16,17]. The possibility of BRCA1/2 being embryo lethal in humans, therefore, appears realistic.

This then raises the next important question: how do low FMR1 sub-genotypes (CGG \(_n\), \(\leq 26\)) rescue embryos from BRCA1/2 lethality? The answer will require a better understanding of the FMR1 gene. Ovarian function associations of het sub-genotypes have been reasonably well defined [3,4,6]. The much rarer, hom sub-genotypes are less well defined and, here, had to be collapsed

### Table 1. Individual BRCA1/2 mutations in study group.

| Mutation type (n = 64) | Frequency count |
|------------------------|-----------------|
| 1023delG               | 1               |
| 1135insA               | 1               |
| 1546dupCT              | 1               |
| 185delAG               | 1               |
| 1914del4               | 1               |
| 2041insA               | 2               |
| 2798delGAAA            | 1               |
| 3137delTTCA            | 3               |
| 3427delA               | 1               |
| 3473delGA              | 1               |
| 3600del11              | 2               |
| 3773delTT              | 1               |
| 4088delA               | 1               |
| 4143delT               | 1               |
| 4233insA               | 1               |
| 4512insT1428           | 1               |
| 4992del13              | 1               |
| 5343del5insG           | 1               |
| 5382insC               | 3               |
| 557ins25               | 1               |
| 5869delAAAT            | 2               |
| 5873C>A (S1882X)       | 2               |
| 5910C>G (Y1894X)       | 1               |
| 6174delT               | 1               |
| 6536G-A (S2130X)       | 1               |
| 6580delGT              | 1               |
| 6803del14              | 1               |
| 6869insC               | 1               |
| 703+3A>G (IVS5+3A>G)   | 1               |
| 7124insA               | 1               |
| 795delT                | 4               |
| 7994insS               | 2               |
| 8034-2A-G (IVS16-2A>G) | 1               |
| 8074delT               | 1               |
| 8230A-T (R2686X)       | 1               |
| 8592G-A (W2788X)       | 10              |
| 8715+1G>A (IVS19+1G>A) | 1               |
| 886delGT               | 2               |
| 8893-1G>A (IVS21-1G>A) | 5               |
| 9325insA               | 1               |
| 9610C>T(R3128X)        | 1               |
| 962del4                | 1               |
| 9900insA               | 1               |
| C61G                   | 2               |
| del20–24               | 1               |
| del5–14                | 1               |
| dup11B                 | 1               |
| dup2                   | 1               |
| dup23                  | 1               |
| E755X                  | 1               |

### Table 1. Cont.

| Mutation type (n = 64) | Frequency count |
|------------------------|-----------------|
| IV516-2A>G             | 1               |
| IV516+3G>C             | 1               |
| IV520-1G>C             | 1               |
| IV52-1G>C              | 1               |
| K1772X                 | 1               |
| L1086X                 | 1               |
| L639X                  | 1               |
| Q1395X                 | 3               |
| Q1424X                 | 1               |
| Q2563X                 | 5               |
| R1203X                 | 2               |
| R1751X                 | 2               |
| R71M                   | 1               |
| W321X                  | 1               |

None of the BRCA1/2 mutations demonstrated significant associations with FMR1. The single mutation noted in 10 patients was in 9 women associated with a het-norm/low FMR1 sub-genotype.
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into a single group with potentially functionally opposing sub-genotypes.

Evolutionary, the norm genotype of FMR1, with both alleles in normal range (CGG \( n = 26-34 \)), appears to represent the original (”ur”) FMR1 gene. Whether one or both alleles mutated outside of normal range, then determined het and hom genotypes. Expansions beyond CGG \( n > 34 \) generated high sub-genotypes, primarily known for neuro-psychiatric risks in association with traditional premutation and full mutation genotypes [1,2,18]. Contractions to CGG \( n < 26 \) resulted in low sub-genotypes, with, as here demonstrated, rescue ability from embryo lethality by BRCA1/2 mutations but increased risk towards autoimmunity [4,6].

It is remarkable that not a single BRCA1/2 patient demonstrated in this study a high (CGG \( n > 34 \)) sub-genotype, strongly suggesting that high FMR1 sub-genotypes do not protect from embryo lethality. This is, however, not the first observation where low and high sub-genotypes of the FMR1 gene denote opposing effects: het-norm/high was shown to be protective against autoimmunity, while het-norm/low promoted significant autoimmune risk [4,6]. Since higher prevalence of autoimmunity in women has remained unexplained [19], the FMR1 gene may have here an additional role to play.

Similar observations were recently also made for the polymorphic CAG repeat unit, which encodes an uninterrupted polyglutamine (polyQ) tract in the N-terminal transactivation domain of the androgen receptor. This is another prominent gene, characterized by ability to expand or contract trinucleotide repeat sequences from a normal range of CAG \( n = 6-35 \) [20]. Like with the FMR1 gene, initial investigations only considered the gene’s expansion risk to be clinically significant. A recent study, however, for the first time found shorter CAG repeats associated with cryptorchidism risks [20].
Located at the 5′ untranslated exon 1 on the X chromosome at Xq27.3, a region now considered associated with autoimmune risks [21], the FMR1 gene appeared positioned at crossroads of autoimmunity and reproduction [4]. Based on here reported data the gene, now, however, appears located at triple crossroads of autoimmunity, cancer, and reproduction. Here is why: Lifetime risk for breast cancer of 1 per 8.2 women (12.2% per woman) increases in presence of BRCA1/2 mutations approximately fivefold to ca. 60 percent [22]. BRCA1/2 mutations, thus, account for 5–10 percent of all breast cancers [23]. Lifetime ovarian cancer risk of ca. 1.4 percent in presence of BRCA1/2 mutations increases 10.7- to 28.6-fold to a 15 to 40 percent range [22]. BRCA1/2, thus, accounts for 10 to 15 percent of all ovarian cancer risk [23], with other cancers also demonstrating increased prevalence in association with BRCA1 (uterine cervix and corpus, pancreas and colon) [24,25] and BRCA2 (pancreas, stomach, gallbladder, bile ducts and malignant melanoma) [26].

Because of high costs, BRCA1/2 mutation screening is currently restricted to families at excessive risk for breast and ovarian cancers. Here presented data, if confirmed, suggest a potentially restricted to families at excessive risk for breast and ovarian cancers also demonstrating increased prevalence in association with BRCA1 (uterine cervix and corpus, pancreas and colon) [24,25] and BRCA2 [pancreas, stomach, gallbladder, bile ducts and malignant melanoma] [26].

The estimated population frequency for BRCA1/2 mutations (0.024 to 0.04%) in recessive and polygenic models, respectively [27], is held responsible for 5 to 10 percent of all breast cancers and 10 to 15 percent of all ovarian cancer risk [23]. Extrapolating, the het-norm/low FMR1 sub-genotype, representing approximately 78.8 percent of BRCA1/2 patients, spread over only ca. a quarter of all women, would reflect 3.95 to 7.9 percent of all breast and 7.9 to 11.9 percent of ovarian cancer risk, concentrated in only approximately a quarter of the female population.

Het-low FMR1 sub-genotypes, hom-low and hom-low/low, in this study not separately assessed, likely, would add a few percentage points. FMR1 genotypes and sub-genotypes [6] and prevalence of BRCA1/2 mutations [28–30] vary in different races/ethnicities. Interestingly, so do female cancers [31,32], autoimmunity [33] and female infertility prevalence [4]. It is tempting to hypothesize that these observations may be associated.

Since BRCA in normal cells induces growth arrest, while promoting tumor formation in BRCA mutation carriers, Evers and Jonkers pointed at the likely presence of secondary suppressor mutations, which may overcome BRCA-associated arrests during BRCA-associated tumorigenesis in association with the so-called “BRCA paradox” [12]. With FMR1 apparently at crossroads of reproduction, immunology and cancer, it is tempting to hypothesize about such, each other opposing, functions for the two het sub-genotypes of FMR1, het-norm/high and het-norm/low. Within such a context low FMR1 alleles not only may overcome embryo lethality (i.e., growth arrest) in human embryos but may also have a similar function in the induction of BRCA1/2-associated malignancies by overcoming the natural growth arrest functions of BRCA1/2 by inducing tumor growth. Appropriate studies in BRCA1/2-associated tumor models, therefore, would be of interest.

Confirming such a growth arrest-reversing function of low FMR1 alleles would, of course, have major relevance for the current understanding of tumor induction and diagnostic tumor risk assessments. Most importantly, however, one would have to conclude that in so-called BRCA1/2-associated tumors [like in premature decreased ovarian reserve] low FMR1 alleles, and not BRCA mutation, are the real culprits. Finally, confirmation of such an FMR1 function would rekindle decades-old considerations about common biological processes in pregnancy and malignancy [34,35].

Here investigated patients were European and American, and, therefore, may reflect genetic diversities. Furthermore, their retroactive evaluations may have resulted in selection biases. Assay performance in different laboratories may have resulted in divergent results between study groups. Similarities in FMR1 genotype and sub-genotype distribution between Austrian and US, control groups (for detail see Materials and Methods), however, practically rule out significant statistical impacts from laboratory or patient variability.

Remarkable statistical clarity of here reported results, therefore, strongly supports reported assertions, suggesting major new biological and clinical importance for FMR1 and BRCA1/2 mutations, deserving of further exploration.

Author Contributions

Conceived and designed the experiments: AW DHB NG. Performed the experiments: DHB AK. Analyzed the data: DHB AK AW NG. Contributed reagents/materials/analysis tools: MKT CFS KW. Wrote the paper: NG. Contributed to availability of Austrian patient data: MKT CFS KW. Coordination between Austrian and US investigators: AW.

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