Letter to the Editor

The BRCA1 S1715N mutation segregates with breast and ovarian cancer in an extended family pedigree

To the Editor:

Classification of rare germ line sequence variants in the BRCA1 gene is important for prophylactic treatment decisions of patients affected with breast and/or ovarian cancer and to identify at risk family members. Missense mutations are difficult to classify since the effect of amino acid substitutions on protein function is often unknown. In the absence of a published consensus regarding the pathogenicity of a particular missense variant, clinicians are unable to advise patients regarding prophylaxis and family related risks. One such mutation is the substitution of serine to asparagine at BRCA1 codon 1715. This variant is known as S1715N (protein) and 5263G>A (DNA) in the Breast Cancer Information Core database (BIC: http://research.nhgri.nih.gov/bic/) and by Human Genome Variation Society (HGVS: http://www.hgvs.org/mutnomen/) recommendations, it is described as p.Ser1715Asn (protein) and c.5144G>A (DNA). The serine residue at codon 1715 is located within a functionally important BRCA1 C-terminal (BRCT) domain in exon 18 of BRCA1 (1). In silico and in vitro studies suggest that any amino acid substitution at S1715 would impact negatively on

Fig. 1. Pedigree of family segregating S1715N with breast and/or ovarian cancer.
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Table 1. Summary of *in vitro* functional evidence supporting pathogenicity of S1715N

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<td>Measured the thermodynamic stability of the BRCA1 BRCT domains.</td>
<td>S1715C, S1715N and S1715R found to be very destabilizing.</td>
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<td>Assayed the structure and function of missense variants in the BRCA1 BRCT domains.</td>
<td>S1715N and S1715R found to have strong negative functional effect.</td>
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<td>Inferred the disease relevance of BRCA1 unclassified variants from data derived from an <em>in vitro</em> functional assay.</td>
<td>S1715N and S1715R shown to have a high posterior probability of being damaging (0.9994 and 0.9997 respectively).</td>
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**BRCA1** protein structure and function (2–6). Although experimental evidence strongly points to a deleterious effect, *in vivo* support is needed for the hypothesis that S1715N is pathogenic. In this communication, we present a large family showing co-segregation of the S1715N variant with breast and/or ovarian cancer. We propose that sufficient evidence now exists to conclude that S1715N is a clinically significant, pathogenic mutation in **BRCA1**.

The family is a kindred of British descent. The consultant (Fig. 1, IV:3) was diagnosed with the so-called ‘triple negative’ (estrogen receptor negative, progesterone receptor negative and HER2/neu receptor negative) invasive breast cancer at the age of 47. Her mother had a diagnosis of breast cancer at age 53, and ovarian cancer at age 80. Due to her personal and family history of breast cancer, the consultant agreed to bidirectional Sanger sequencing of **BRCA1** and **BRCA2**. This analysis revealed a c.5144G>A:p.Ser1715Asn variant in exon 18 of **BRCA1**. Subsequently, a sister (Fig. 1, IV:2) was diagnosed with invasive breast cancer at age 51. **BRCA1** targeted sequencing of the sibship revealed that she as well as her unaffected brother carried the S1715N variant. Extended family history on the maternal side was taken and it was discovered that a maternal relative (Fig. 1, III:6) had been diagnosed with serous ovarian cancer. This patient’s subsequent genetic analysis revealed that she also had S1715N. Her daughter, IV:12, who was affected with breast cancer, also carried the variant. Thus five affected females, including the deceased obligate carrier III:2, were found to carry S1715N in this family. Using the co-segregation analysis method of Mohammadi et al. (7) to determine the likelihood ratio (LR) of S1715N, we calculated the LR to be 80.7 in favour of causality, a strongly positive finding for a single family.

It is interesting to note that II:4 appears to have been a non-penetrant female carrier by descent. She was reported to have undergone a total abdominal hysterectomy and bilateral salpingo-oophorectomy at the age of 41. Although the reasons for these surgical interventions are unknown, it is expected that they would have substantially reduced the risk of a subsequent breast or ovarian cancer diagnosis (8).

S1715N has been reported multiple times in both BIC and the Leiden Open Variation Database (LOVD: http://www.lovd.nl/2.0); however, the classifications assigned to this variant are inconsistent and vary from benign to deleterious. We have reviewed the medical literature and found multiple independent *in vitro* functional studies (summarized in Table 1) that clearly support *in silico* predictions that S1715 is a critical **BRCA1** amino acid. When our family is considered in light of these findings, we believe that the accumulation of evidence is now sufficient to consider S1715N causative of susceptibility to breast and/or ovarian cancer. Patients found to have S1715N should therefore be counselled regarding their prophylactic options and family members offered targeted genetic testing, if desired.

**Acknowledgements**

The authors wish to thank the subject family for their willingness to share this pedigree and information for this publication.

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