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**Identification of a novel *BRCA1* nucleotide
4803delCC/c.4684delCC mutation and a nucleotide
249T>A/c.130T>A (p.Cys44Ser) mutation in two Greenlandic
Inuit families: Implications for genetic screening of
Greenlandic Inuit families with high risk for breast and/or
ovarian cancer**

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Abstract Germ-line mutations in the tumour suppressor proteins *BRCA1* and *BRCA2* predispose to breast and ovarian cancer. We have recently identified a Greenlandic Inuit *BRCA1* nucleotide 234T>G/c.115T>G (p.Cys39Gly) founder mutation, which at that time was the only disease-causing *BRCA1/BRCA2* mutation identified in this population. Here we describe the identification of a novel disease-causing *BRCA1* nucleotide 4803delCC/c.4684delCC mutation in a Greenlandic Inuit with ovarian cancer. The mutation introduces a frameshift and a premature stop at codon 1572. We have also identified a *BRCA1* nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation in another Greenlandic individual with ovarian cancer. This patient share a 1-2 Mb genomic fragment, containing the *BRCA1* gene, with 4 Danish families harbouring the same mutation, suggesting that the 249T>A/c.130T>A (p.Cys44Ser) mutation originates from a Danish ancestor. We conclude that screening of Greenlandic Inuits with high risk of breast or ovarian cancer should include sequencing of the entire *BRCA1* gene.

Introduction

BRCA1 (MIM 113705) and *BRCA2* (MIM 600185) germ-line mutations predispose to hereditary breast and ovarian cancer, conferring a lifetime risk of approximately 80% for breast cancer and 20-50% for ovarian cancer in female carriers [1]. *BRCA1* and *BRCA2* are involved in a variety of cellular processes, including maintenance of genome stability [2, 3], DNA repair via homologous recombination [2, 3], transcriptional regulation [4], cell cycle control [5], chromatin remodelling [5] and ubiquitinylation [6]. Mutations are scattered throughout both genes and includes disease-causing mutations as well as unclassified variants (listed in Breast Cancer Information Core (BIC)). Moreover, several founder mutations have been reported in *BRCA1* and *BRCA2*, including the Icelandic *BRCA2* nucleotide 999del5, and the Ashkenazi Jews *BRCA1* nucleotide 185delAG mutations, which are found with frequencies between 0.6% to 1.0% in the population [7-10]. In Denmark multiple disease-causing *BRCA1/BRCA2* mutations have been identified [11-15]. However, only one disease-causing mutation (p.Cys39Gly) has been identified in Greenlandic Inuits [16]. This mutation was identified in 13 Greenlandic Inuit families with breast and/or ovarian cancer, and had not previously been identified in other populations. Mutation positive individuals shared a 4.5 Mb haplotype in the *BRCA1* region, indicating that the mutation in the *BRCA1* region happened once and segregated in the population as a founder mutation [16].

We now report the identification of another novel *BRCA1* nucleotide 4803delCC/c.4684delCC mutation in a Greenlandic Inuit with ovarian cancer, which results in a frameshift and a premature stop at codon 1572. Moreover, we have identified a nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation in a Greenlandic Inuit with ovarian cancer. However, SNP array analysis indicates that this mutation originates from a Danish ancestor. These findings have implications for the genetic testing of Greenlandic Inuits with high risk for breast or ovarian cancer, and we suggest that genetic screening of this group of patients should comprise sequencing of the entire *BRCA1* gene.

Patients and methods

Patients

Two Greenlandic Inuit families with ovarian and early breast cancer were identified (Fig. 1A and B). In one (family 97016), the proband was a 41 year-old woman recently diagnosed with ovarian cancer. The family had two cases of breast cancer (Fig. 1A). In the other family (family 84814), a 47-year old woman was diagnosed with ovarian cancer. This family had one case of breast cancer in a cousin (Fig. 1B). Following verbal and written consent, blood samples were collected and both probands underwent genetic testing. The family history was verified using the registry of the DBCG (Danish Breast Cancer Cooperative Group), hospital medical records and pathology reports, and genetic counselling was provided for the families.

BRCA1 and *BRCA2* screening

Genomic DNA was purified from 2 ml whole blood using the Maxwell 16 system (Promega) according to the manufacturer's instructions. As a first step, *BRCA1* exon 3 was amplified using intronic primer to examine for the Greenlandic *BRCA1* nucleotide 234 T>G/c.115 T>G (p.Cys39Gly) founder mutation. When negative for this screening, all other *BRCA1* and *BRCA2* exons were amplified using intronic primer pairs. PCR products were pre-screened by high-resolution melting curve analysis using the LightScanner (Idaho Technology) and variants were sequenced using an ABI3730 DNA analyzer (Applied Biosystems). Sequence variations were verified in a new blood sample. Moreover, genomic DNA was examined by MLPA analysis as recommended by the manufacturer (MRC-Holland). The *BRCA1* mutation is numbered according to Genbank accession number U14680 in which the A in the AUG start codon has number 120. Furthermore, the guidelines from the Human Genetic Variation Society (www.hgvs.org/mutnomen) were used.

In silico analysis

In silico prediction of the functional consequence of the *BRCA1* Cys44Ser missense variant was performed using SIFT (Sorting Intolerant From Tolerant): <http://blocks.fhcrc.org/sift/SIFT.html> [17] Polyphen: <http://coot.embl.de/PolyPhen/> [18] and PMut: <http://mmb2.pcb.ub.es:8080/PMut/> [19]. The mutation was introduced according to the guidelines of each programme and default settings were used in all predictions.

SNP chip analysis

Genomic DNA was applied to 250K *StyI* (~238.000 SNPs) SNP-microarray chips and processed according to the manufacturer's instructions (Affymetrix, UK). Briefly, 250 ng of genomic DNA was digested with *StyI* and ligated to adapters. Adapter ligated DNA was amplified, purified, fragmented and labeled with biotin and hybridized to the arrays for 18 hr. The Affymetrix 450 fluidics station and the Affymetrix 3000 G7 gene scanner were used to wash, stain and scan the arrays. The CEL files were analysed using the BRLMM algorithm from Affymetrix Genotyping analysis software (GTYPE).

In order to assess whether the mutation happens once or several times, we investigate the local relatedness across the genome using *Relate* [20]. The method estimates the local identical by descent (IBD) sharing in the presence of linkage disequilibrium using a hidden Markov model by conditioning on the 25 previous SNPs. Haplotype frequencies and allele frequencies were estimate using the five affected individuals plus an additional 60 unrelated HapMap CEPH (Centre d'Etude du Polymorphisme Humain) individuals. SNPs with more than 5% missing data or a minor allele frequency of less than 1% were excluded from the analysis. Genetic distances were used instead of physical distances inferred from the Kong genetic map [21].

Results

The proband from family 97016, which was diagnosed with ovarian cancer at the age of 41, was referred to genetic counselling, since her deceased mother was diagnosed with breast cancer before the age of 40, and her deceased aunt was diagnosed with breast cancer at 55 years of age (Fig. 1A). The proband from family 84814, which was diagnosed with ovarian cancer at the age of 47, was referred to genetic counselling, since her cousin had breast cancer. Her mother died at the age of 34 of unknown reason, while the father is unknown (Fig. 1B). Both probands underwent genetic testing. The probands were first examined for the Greenlandic *BRCA1* nucleotide 234T>G/c.115T>G (p.Cys39Gly) founder mutation. However, both were negative for this mutation. Due to the family history, the proband from family 97016 underwent whole screening of both *BRCA1* and *BRCA2*. The analysis demonstrated a *BRCA1* exon 16 nucleotide 4803delCC/c.4684delCC mutation (Fig. 2A) not previously described in the BIC database or the literature. The mutation introduces a frameshift and a premature stop at codon 1572. In family 84814, the analysis of *BRCA1* exon 3 identified a nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation (Fig. 2B). This mutation is reported once in the BIC database as a variant of unknown significance. To indicate whether the mutations could be disease-causing, three different protein prediction programmes [17-19] were used to predict the functional consequence of the *BRCA1* p.Cys44Ser mutation. All three protein prediction programmes estimated the *BRCA1* p.Cys44Ser mutation to be pathogenic. We have previously identified the p.Cys44Ser mutation in 4 Danish families. Since the paternal side of patient with the nucleotide 249T>A/ c.130T>A (p.Cys44Ser) mutation is unknown, a SNP array analysis was performed to determine if the mutation represented a Danish founder mutation. If the *BRCA1* mutation is a founder mutation, we would expect the carriers to share as least one allele identical by descent (IBD) around the *BRCA1* gene. Fig. 3 shows the average IBD sharing between the 5 mutation carriers on chromosome 17. The probability of IBD sharing for the *BRCA1* gene is shown in Fig. 4. Four out of the five carriers, including the Greenlandic individual, all have high probability of being IBD in the gene. Accordingly, we infer that the *BRCA1* nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation represent a Danish founder mutation. The last individual only shows high probability with one of the other individual and this region is only 1-2 Mb long and too short to infer relatedness between the other three individuals.

Discussion

Individuals from Greenland with hereditary breast and/or ovarian cancer are screened for *BRCA1/BRCA2* mutations at Rigshospitalet, Copenhagen, Denmark. We previously reported the *BRCA1* nucleotide 234T>G/c.115T>G (p.Cys39Gly) mutation, which - at that point - was the only disease-causing mutation identified in this population [16]. The first individual with this mutation was identified in 2001 and was a woman with breast cancer at the age of 43. But it was first until later, when the mutation was identified in other patients, we realized that this mutation was exclusively identified in Greenlandic Inuit's and that the mutation represented a Greenlandic founder mutation [16]. The finding suggested that screening of the mutation in the whole population could be warranted [16], but due to difficulties in collection of blood samples this is not feasible. We have - until now - screened 51 Greenlandic breast and/or ovarian cancer families and have identified the nucleotide 234T>G/c.115T>G (p.Cys39Gly) mutation in 18 of these families, which primarily includes high-risk breast and/or ovarian cancer families.

Here, we report a novel *BRCA1* nucleotide 4803delCC/c.4684delCC mutation in a Greenlandic high risk family. The mutation introduces a frameshift and a premature stop at codon 1572, resulting in the deletion of 292 amino acid residues of BRCA1, including the C-terminal BRCT domain, which is involved in protein-protein interaction [22]. It is currently not known whether this mutation introduces nonsense-mediated decay (NMD). Moreover, we identified a *BRCA1* nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation in another Greenlandic family. This mutation changes the amino acid residue cysteine, which is polar, to a serine, which is hydrophobic. Cys-44 is highly conserved [16] and resides in the RING domain of BRCA1, which is involved in protein-protein interaction [23, 24]. The RING domain is characterized by a pattern of seven highly conserved cysteines and one highly conserved histidine residue forming two distinct Zn²⁺ binding sites, termed site I and II [25, 26]. Mutations in the conserved residues in the RING domain disrupt the ubiquitin ligase activity of BRCA1 by interfering either with the heterodimerization between BRCA1 and BARD1 or by changing the ubiquitin ligase activity by disturbing the binding of E2 proteins like UbcH5c to the BRCA1/BARD1 complex [6, 27, 28]. Indeed, *in silico* analysis using the SIFT, Polyphen or PMut software all regarded the BRCA1 p.Cys44Ser mutation as disease-causing. We have moreover only observed the mutation in breast and/or ovarian cancer families, and not in 200 healthy adult Danish controls (blood donors). Other mutations have been reported on this position, including p.Cys44Phe, p.Cys44Tyr and p.Cys44Ala and functional and *in silico* studies supports that they are disease-causing [6, 27, 29].

The identification of the novel *BRCA1* nucleotide 4803delCC/c.4684delCC mutation has led us to consider the optimal screening strategy in the Greenlandic population. Screening of individuals from Greenland for *BRCA1/BRCA2* mutations have until now - as a first step -

included examination of the *BRCA1* nucleotide 234T>G/c.115T>G (p.Cys39Gly) mutation. However, due to the finding in this report we now suggest that whole sequencing of the *BRCA1* gene should be performed in high risk families. We have retrospectively screened the remaining thirty-one *BRCA1* nucleotide 234T>G/c.115T>G (p.Cys39Gly) negative individuals, but have not found other disease-causing mutations in either *BRCA1* or *BRCA2* than the ones described in this paper.

In summary, we have identified two additional *BRCA1* mutations in Greenlandic Inuits. While the novel nucleotide 4803delCC/c.4684delCC mutation is found in an Inuit family, the nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutation could be a Danish derived mutation. We conclude that screening of Greenlandic Inuits with high risk for breast- and/or ovarian cancer should include sequencing of all *BRCA1* exons.

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Figure legends

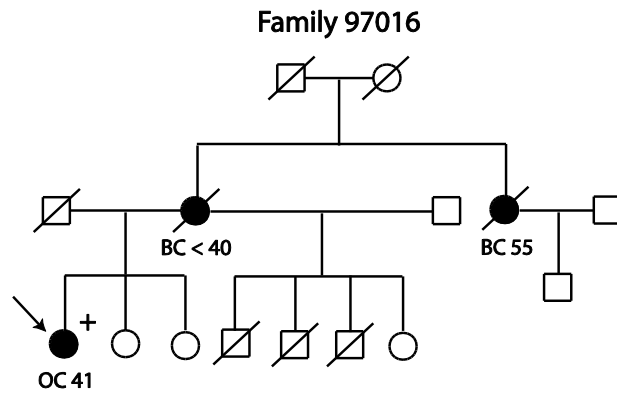
Fig. 1 Family pedigrees. (A) shows the pedigree from family 97016, while (B) show the pedigree from family 84814. Breast and ovarian cancer are indicated as well as the age at diagnosis. Diagonal slash indicates deceased, while the proband is indicated with an arrow. Mutation positive individuals are indicated with +.

Fig. 2. Identification of the *BRCA1* nucleotide 4803delCC/c.4684delCC and the nucleotide 249T>A/c.130T>A (p.Cys44Ser) mutations. DNA was purified from the patients and the *BRCA1* and/or *BRCA2* genes were amplified using intronic primer pairs flanking each exon. For total *BRCA1/BRCA2* screening, the PCR products were pre-screened by high-resolution melting curve analysis followed by sequenced. The *BRCA1* nucleotide 4803/c.4684delCC identified in family 97016 (A) and the nucleotide 249T>A/c.130T>A identified in family 84814 (B) are shown.

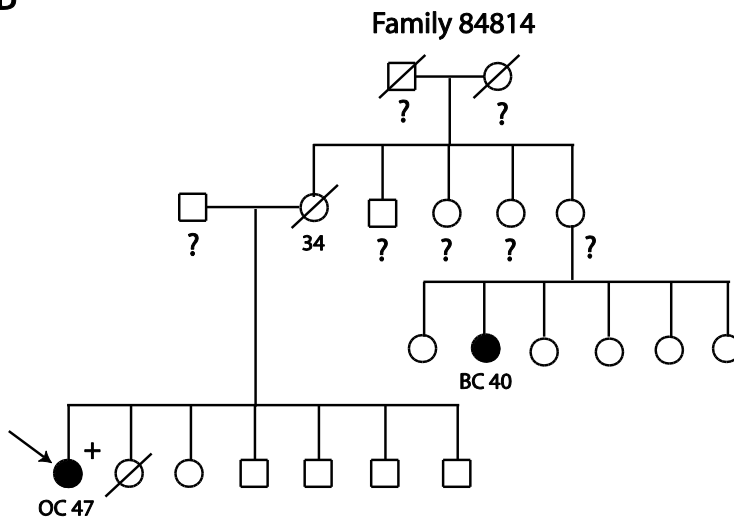
Fig. 3. Average identical by descent (IBD) sharing across chromosome 17 between all five p.Cys44Ser mutation carriers. Each orange dot represents the average IBD sharing for a single SNP. The *BRCA1* gene is indicated as the green dot with the highest IBD sharing peak directly above it.

Fig. 4. Pairwise identical by descent (IBD) sharing probabilities at the *BRCA1* gene between each possible pair of the five p.Cys44Ser mutation carriers. The four Danish and one Greenlandic individuals are indicated.

A

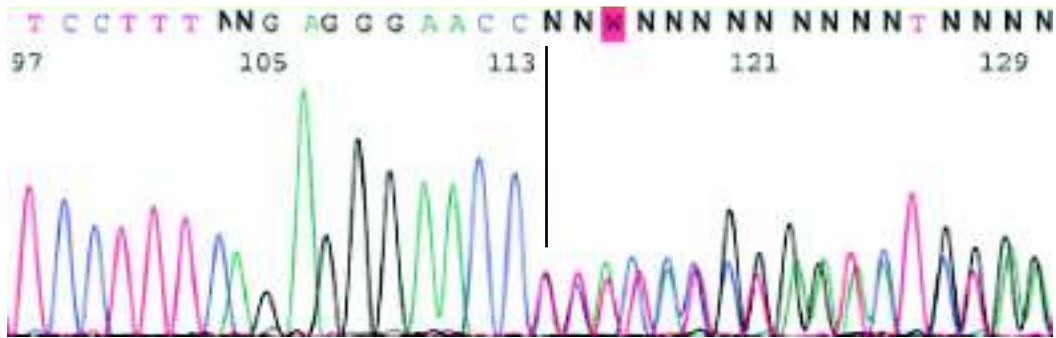


B



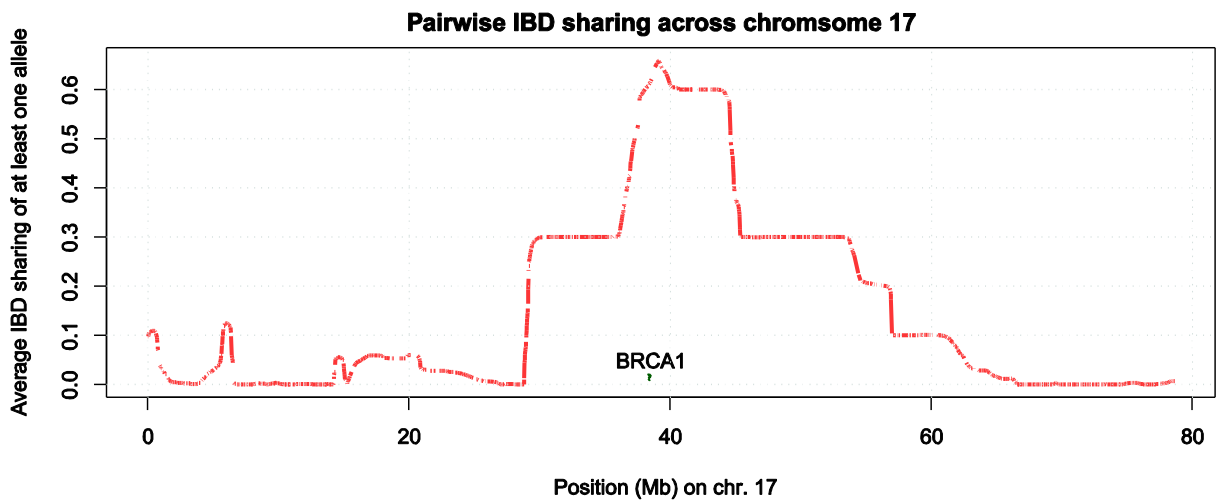
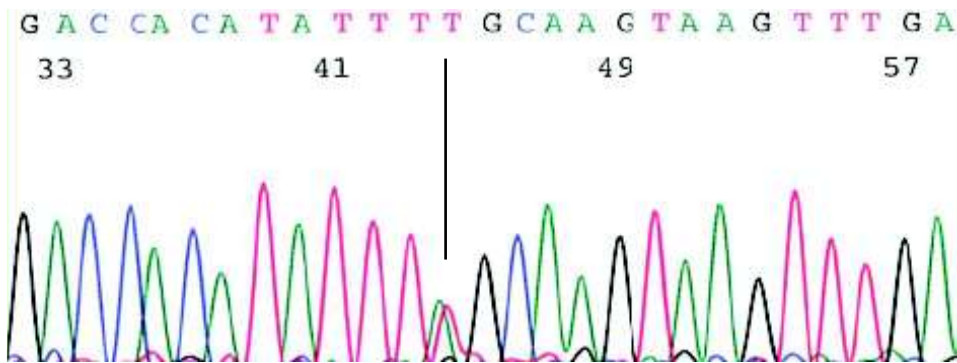
A

BRCA1 nt 4803delCC

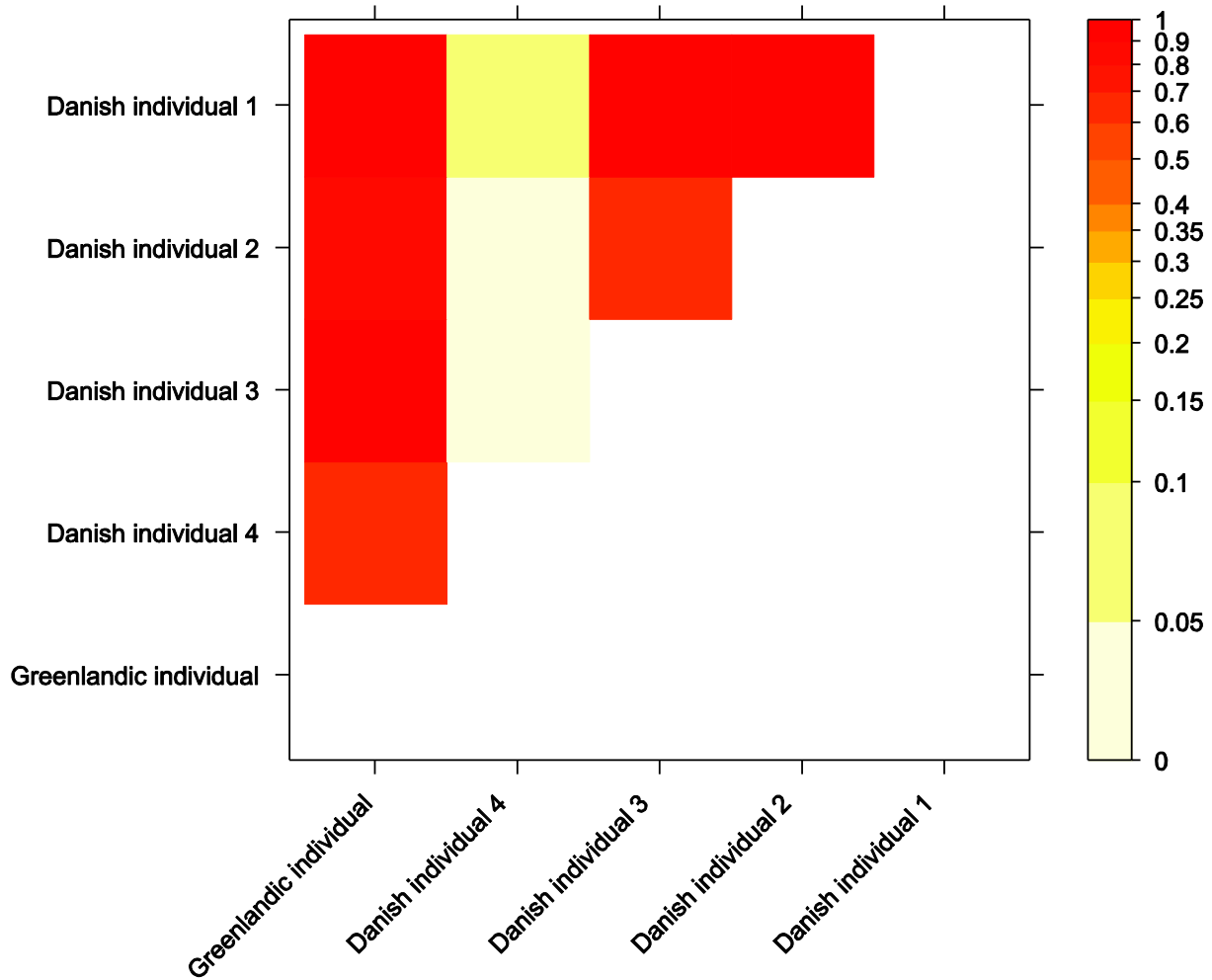


B

BRCA1 nt 249 T>A, p.Cys44Ser



Pairwise relatedness (sharing at least one chromosome IBD)



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BREAST CANCER RESEARCH AND TREATMENT

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