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ARTICLE

Multiple founder effects and geographical clustering of *BRCA1* and *BRCA2* families in Finland

Laura Sarantaus[1], Pia Huusko[2], Hannaleena Eerola[3], Virpi Launonen[2], Paula Vehmanen[1], Katrin Rapakko[2], Elizabeth Gillanders[4], Kirsi Syrjäkoski[5], Tommi Kainu[5], Pia Vahteristo[1], Ralf Krahe[6], Kati Pääkkönen[6], Jaana Hartikainen[7], Carl Blomqvist[3], Tuija Löppönen[2], Kaija Holli[8], Markku Ryynänen[7], Ralf Bützow[1], Åke Borg[9], Brita Wasteson Arver[10], Eva Holmberg[11], Arto Mannermaa[7], Juha Kere[12], Olli-Pekka Kallioniemi[5], Robert Winqvist[2] and Heli Nevanlinna[1]

[1]Department of Obstetrics and Gynecology, and [3]Department of Oncology, Helsinki University Central Hospital; [2]Department of Clinical Genetics, University of Oulu and Oulu University Hospital, Finland; [4]Cancer Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA; [5]Laboratory of Cancer Genetics, Institute of Medical Technology, and [8]Department of Oncology, Tampere University Hospital; [6]Department of Medical Genetics, and [12]Finnish Genome Centre, University of Helsinki; [7]Unit of Clinical Genetics of the Department of Gynecology, Kuopio University Hospital and University of Kuopio, Finland; [9]Department of Oncology, University Hospital, Lund; [10]Department of Clinical Genetics and Institution of Molecular Medicine, CMM2, Karolinska Hospital, Stockholm; [11]Department of Clinical Genetics, Norrland University Hospital, Umeå, Sweden

In the Finnish breast and ovarian cancer families six *BRCA1* and five *BRCA2* mutations have been found recurrently. Some of these recurrent mutations have also been seen elsewhere in the world, while others are exclusively of Finnish origin. A haplotype analysis of 26 Finnish families carrying a *BRCA1* mutation and 20 families with a *BRCA2* mutation indicated that the carriers of each recurrent mutation have common ancestors. The common ancestors were estimated to trace back to 7–36 generations (150–800 years). The time estimates and the geographical clustering of these founder mutations in Finland are in concordance with the population history of this country. Analysis of the cancer phenotypes showed differential ovarian cancer expression in families carrying mutations in the 5' and 3' ends of the *BRCA1* gene, and earlier age of ovarian cancer onset in families with *BRCA1* mutations compared with families with *BRCA2* mutations. The identification of prominent and regional *BRCA1* and *BRCA2* founder mutations in Finland will have significant impact on diagnostics in Finnish breast and ovarian cancer families. An isolated population with known history and multiple local founder effects in multigenic disease may offer distinct advantages also for mapping novel predisposing genes. *European Journal of Human Genetics* (2000) **8**, 757–763.

Keywords: *BRCA1*; *BRCA2*; haplotype; founder mutations; breast cancer; ovarian cancer

Correspondence: Dr Heli Nevanlinna, Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Haartmaninkatu 2, FIN-00029 HUS, Finland. Tel: +358 9 471 72841; Fax: +358 9 471 72973; E-mail: heli.nevanlinna@hus.fi, and Dr Robert Winqvist, Department of Clinical Genetics, Oulu University Hospital, Kajaanintie 50, FIN-90220 Oulu, Finland. Tel: +358 8 315 3228; Fax: +358 8 315 3243; E-mail: robert.winqvist@oulu.fi
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Introduction

The cloning of *BRCA1*[1] and *BRCA2*,[2] the major known genes predisposing to early-onset breast cancer and ovarian cancer, has resulted in rapid identification of a large number of families with mutations in these genes.[3] Although both genes exhibit numerous distinct mutations, several alterations have been found recurrently in defined ethnic and geographic populations, especially in the Ashkenazim and in Iceland.[4–6] In Finland, 11 distinct *BRCA1* and seven *BRCA2* mutations have been detected,[7–9] and six of the *BRCA1* and five of the *BRCA2* mutations are recurrent. Some of these mutations are unique to Finland, while others have also been reported elsewhere in the world, like *BRCA2* 999del5, a strong founder mutation in Iceland as well.[4,6]

We have here investigated the mutation-associated haplotype conservation in Finnish *BRCA1* and *BRCA2* families. We have estimated the time since the common ancestor for the families segregating the same mutation and also studied the geographical distribution of the alterations in Finland. In addition, the breast and ovarian cancer phenotypes of the families were analysed.

Material and methods

Families studied

Altogether 26 Finnish breast or breast–ovarian cancer families carrying recurrent *BRCA1* mutations and 20 families with *BRCA2* mutations were studied for haplotype conservation, and 34 *BRCA1* and 37 *BRCA2* families for the cancer phenotype. The families had previously been ascertained and mutations identified[7–9] in four University Hospitals in Finland (Helsinki, Oulu, Tampere, and Kuopio, additional unpublished data). The permission for the genetic analysis was obtained by written informed consent. The family data were collected by interviewing the index patients as well as by searching church parish records and population registry data. Cancer diagnoses and ages at onset were obtained from hospital records, death certificates or family questionnaires. The diagnoses were confirmed through the Finnish Cancer Registry whenever possible. The study was approved by ethical committees of the hospitals and appropriate permissions were obtained from the Ministry of Social Affairs and Health in Finland. For comparison of the mutation-associated haplotypes of the *BRCA1* 3744delT mutation in Finland and Sweden,[10] samples from four Swedish families were also included.

Mutations studied

The *BRCA1* and *BRCA2* mutations identified in Finland and the recurrent *BRCA1* and *BRCA2* mutations studied in the haplotype analysis are indicated in Table 1. Mutation-specific breast and ovarian cancer phenotypes are also shown in Table 1.

Table 1 Mutations and phenotypes of the *BRCA1* and *BRCA2* families in Finland

Gene and mutation	*No. of families in Finland*	*No. of female breast cancer cases[b] (mean age at dg)[c]*	*No. of ovarian cancer cases[b] (mean age at dg)[c]*	*Reported outside Finland*
BRCA1				
Ex 11, 1924delA	1	1 (44)	–	No
Ex 11, 2803delAA	2	3 (56)	2 (62)	the Netherlands[30]
Ex 11, 3604delA[a]	6	7 (45)	10 (46)	Belgium, the Netherlands[30]
Ex 11, 3744delT[a]	8	7 (45)	10 (49)	Sweden[10]
Ex 11, 3904C→A	1	3 (49)	3 (59)	Yes[3]
Ex 11, 4153delA	1	1 (32)	1 (48)	Latvia, Poland, Russia, Sweden[3,28,37]
Int 11, 4216nt-2A→G[a]	9	24 (43)	8 (52)	No
Ex 13, 4446C→T[a]	3	23 (46)	8 (53)	Belgium, Canada, France, UK, USA[3,28,29]
Ex 17, 5145del11	1	4 (37)	–	No
Ex 20, 5370C→T[a]	3	12 (49)	3 (67)	Austria[31]
Ex 20, 5382insC	1	2 (57)	1 (40)	Austria, Belgium, Canada, France, Germany, Hungary, Israel, Italy, Latvia, the Netherlands, Russia, UK, USA[3,28,37]
Total	36	87 (46)	46 (51)	
BRCA2				
Ex 9, 999del5	13	52 (47)	6 (60)	Iceland[6]
Ex 11, 4081insA	1	2 (67)	2 (60)	No
Ex 11, 6495/6496G→C, delCA	1	3 (52)	–	No
Ex 11, 6503delTT[a]	3	8 (57)	4 (62)	Belgium, the Netherlands, Sweden, UK, USA[32,33]
Ex 15, 7708C→T[a]	8	26 (45)	4 (56)	No
Ex 18, 8555T→G[a]	5	12 (49)	1 (60)	No
Int 23, 9346nt-2A→G[a]	9	20 (52)	4 (66)	No
Total	40	123 (48)	21 (61)	

[a]mutations studied in the haplotype analysis; [b]in families included in the phenotype analysis; [c]not available for all cases; dg=diagnosis.

Genotyping

Eleven polymorphic microsatellite markers spanning 26 cM around *BRCA1*[11–15] on chromosome 17q21 and 17 polymorphic microsatellite markers spanning 36 cM around *BRCA2*[16–18] on chromosome 13q12 were used for genotyping (Figure 1). Primer sequences for markers D13S260 through D13S267 were positioned and marker order and physical distances were determined using Sequencher v3.0 (Gene Codes Corporation, Ann Arbor, MI, USA) and the genomic sequence[19] for this region. Physical distances for markers D13S260 through D13S267 were converted to centiMorgans assuming 1 cM = 0.5 Mb, which was the average observed ratio at this region.

For 17q21 markers PCR products were labelled with [α-^{32}P]-dCTP and separated by denaturing polyacrylamide gel (7%) electrophoresis. Biomax X-ray films (Kodak, NY, NY, USA) were used for autoradiography. Allele sizes were determined using M13mp18 marker (Sequenase Kit, USB, Cleveland, OH, USA).

For 13q12 markers forward PCR primers were fluorescent dye labelled with either FAM, HEX or TET (PE Applied Biosystems, Foster City, CA, USA). The amplification products were separated on an ABI 377 instrument (PE Applied Biosystems), and genotype data were analysed using GeneScan 3.1 and Genotyper 2.0 software from PE Applied Biosystems. Allele sizes were matched according to the genotype of CEPH reference individual 134702 (PE Applied Biosystems).

In order to define the allele frequencies in the Finnish population, 42 and 96 healthy individuals were genotyped for chromosome 17q21 and 13q12 markers, respectively.

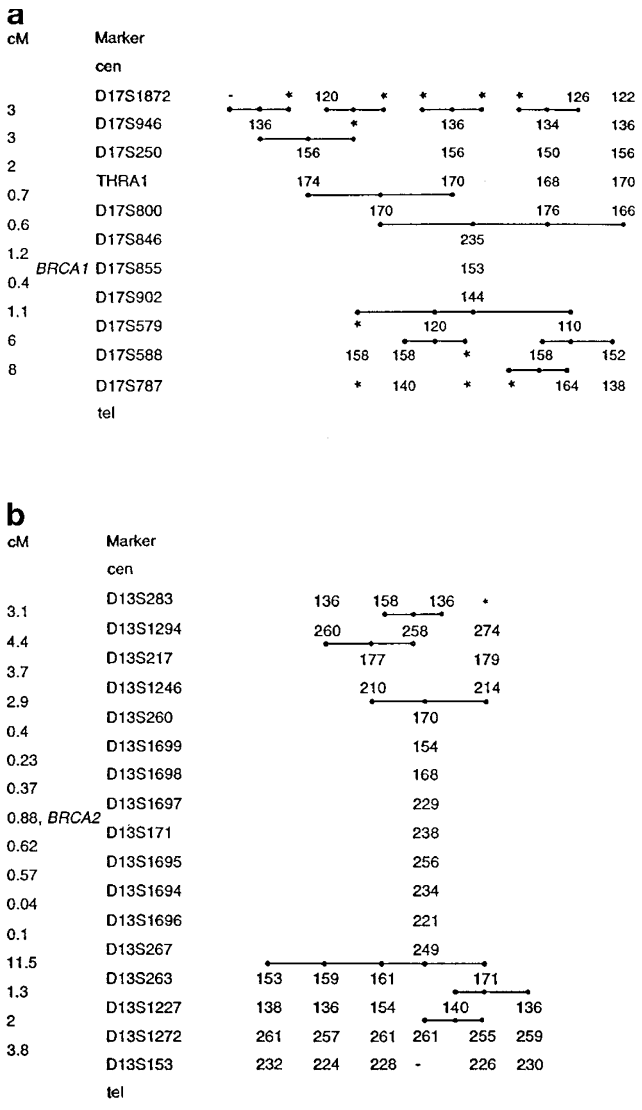

Figure 1 A haplotype reconstruction for **a** *BRCA1* 3744delT and for **b** *BRCA2* 9346nt-2A G. The order of markers studied and their relative distances in cM are on the left; the historical recombinations are on the right. Alleles are designated according to their size in base pairs * = ambiguous allele; – = unknown allele.

Haplotyping and estimation of the time since common ancestors (spreading of the mutations)

The haplotypes were constructed by Genehunter program and/or manually. Historical recombinations were reconstructed assuming minimal parsimony. Starting from the site of the mutation and moving outwards in both directions, historical recombinations were noted as the branching of the haplotype when two or more different alleles were observed for a marker. Examples of such recombinational histories for the *BRCA1* 3744delT and *BRCA2* 9346nt-2A G chromosomes are depicted in Figure 1.

The number of generations (g) since the common ancestor of the families studied, denoted in the following as the time since spreading of the mutation, was estimated by the Luria-Delbrück equation[20] of $p_{excess} = \alpha(1-\theta)^g$, where $\alpha = 1$ (all chromosomes carry the same mutation), θ refers to the recombination fraction between the mutation and marker locus, and $p_{excess} = (p_{affected} - p_{normal})/(1 - p_{normal})$, where $p_{affected}$ = fraction of the ancestral chromosomes (allele) of all affected chromosomes and p_{normal} = frequency of the same allele in normal population chromosomes. The average of the estimations was considered as the most likely time since the common ancestor. Alternatively, a modification was applied where p_{excess} value for each marker was the minimum and maximum fraction of chromosomes carrying the most common shared allele for that marker based on the branched haplotype tree.

Phenotype analysis

Thirty-four families with a *BRCA1* and 37 with a *BRCA2* mutation were examined for breast and ovarian cancer phenotype. All cancer cases in the families were included in the phenotype study, with the exception of those who were known not to be *BRCA1* or *BRCA2* mutation carriers.

Correlation between the position of the mutation (5' versus 3' end of the gene) and the breast and ovarian cancer phenotype in the *BRCA1* families was analysed using Fisher's exact test. Only one of the *BRCA2* mutations (6503delTT) is located in the ovarian cancer cluster region (OCCR),[21] which does not allow assessment of the genotype–phenotype correlation. The variation of the age at diagnosis was analysed for both genes and both phenotypes by unpaired *t*-test. Cumulative age-specific percentages of age at onset for breast and ovarian cancer using 5-year intervals were determined for the *BRCA1* and *BRCA2* families as well as the general population.[22]

Results and discussion

Haplotype analysis

The haplotype analysis showed that the carriers of each recurrent mutation have common ancestors. Variation in the length of the shared haplotype indicates that distinct mutations probably started to spread at different time periods, which is also supported by the geographical distribution of the mutations and their relationship to the population history and settlement of the country. The conserved core haplotypes as well as the time estimates and geographical distribution of the origins of the families are shown in Figure 2. Both methods used for estimating the time since the spread of the mutations began gave consistent results. The estimates derived from using the population-based allele frequencies were within the range of minimum and maximum values derived from the modification using information from the branched haplotype tree.

Recently, recombination suppression in a region of 200–400 kb including and immediately adjacent to *BRCA1* has been reported.[23] The Luria-Delbrück calculation uses data from observed historically recombined chromosomes. The generation estimates are based on the average value of all recombined markers studied and the common haplotypes extended outside the suppression region. Thus the short suppressed region that does not recombine essentially looks like a 'point' in the genome and is expected to have little effect on the time estimates here. Interestingly, more extensive variation of the alleles was denoted in this study than reported by Liu and Barker.[23] Among the five different *BRCA1* mutation haplotypes, four different alleles were present in the intragenic marker D17S855 within the reported recombination suppression region.

The *BRCA1* mutation 3744delT (haplotype reconstruction shown in Figure 1a) was estimated to have started to spread 23–36 generations (500–700 years) ago. The alleles in the short conserved haplotype (1.6 cM) of the seven Finnish and four Swedish families analysed are rare (estimated haplotype frequency in the Finnish population 0.57%), supporting the common origin of the families. According to the church records, a majority of the Finnish families have lived in Central Ostrobothnia for at least 300 years, whereas the Swedish ones come from the opposite side of the Gulf of Bothnia. Thus, the mutation could have been brought across the sea from Sweden to Finland, along with Swedish settlers.[24]

The origins of the families with the 4216nt-2A→G mutation also cluster in Central Ostrobothnia and further in Central Finland inhabited after the fifteenth century, during the more permanent settlement of central and northern parts of the country.[24,25] This mutation is unique to the Finns, and although it is the most frequent *BRCA1* mutation in Finland, we estimated that the spread of this mutation started fairly recently (less than 10 generations ago).

The 4446C→T mutation is reported frequently in the Breast Cancer Information Core database (BIC),[3] and has been detected at least in Belgium, Canada, France, the UK and the USA. Several distinct disease-linked haplotypes segregating with this mutation indicate independent origins of the same mutation.[26–29] In Finland, the three kindreds share a 7.9 cM core haplotype and the origins of the families cluster in a remote geographical location in Southern Karelia, near the Russian border. This particular mutation could be a distinct mutational event in Finland, supporting the hypothesis of a hotspot site. The 3604delA has also been reported several times in BIC,[3] and has previously been found in Belgium and the Netherlands.[30] The geographical location of all the families in the most southern and coastal part of Finland may suggest that the mutation originated from Central Europe. Besides Finland, 5370C→T has been identified in Austria.[31]

The *BRCA2* mutation 9346nt-2A→G (haplotype reconstruction shown in Figure 1b) has been found in nine different families, and represents an alteration unique to the Finns. The spread of this mutation was estimated to have started 7–11 generations (150–200 years) ago. This is also supported by the distribution of the origins of the families in the northern and eastern parts of the country that were settled after the fifteenth century, followed by regional population expansions in the seventeenth century.[24]

The 7708C→T mutation, which is also unique to the Finns, seems to be of older origin (200–400 years) with dispersed geographical pattern both in the regions of older as well as more recent inhabitation. The 8555T→G mutation is also unique to Finland, and all the families originate from Pirkanmaa. Although this part of the country was inhabited early in our population history, this mutation is not widespread but has remained as a regional founder mutation for 7–9 generations.

The geographical distribution of 6503delTT is quite similar to that of 9346nt-2A→G as both mutations have spread into the late settlement area. 6503delTT has been listed several times in BIC[3] and families with this mutation have been reported in Belgium, the Netherlands, Sweden, the UK, and the USA.[3,32,33] The conserved haplotype of the Finnish families includes completely different allele sizes from those

reported elsewhere, indicating distinct origins of the 6503delTT mutation.[33]

Phenotypic studies have suggested that *BRCA1* mutations in families with a high proportion of ovarian cancer tend to be located at the 5' end, whilst families exhibiting predominantly breast cancer seem to have mutations at the 3' end of the gene.[34] A significant correlation between the location of the *BRCA1* mutation and the cancer phenotype was also

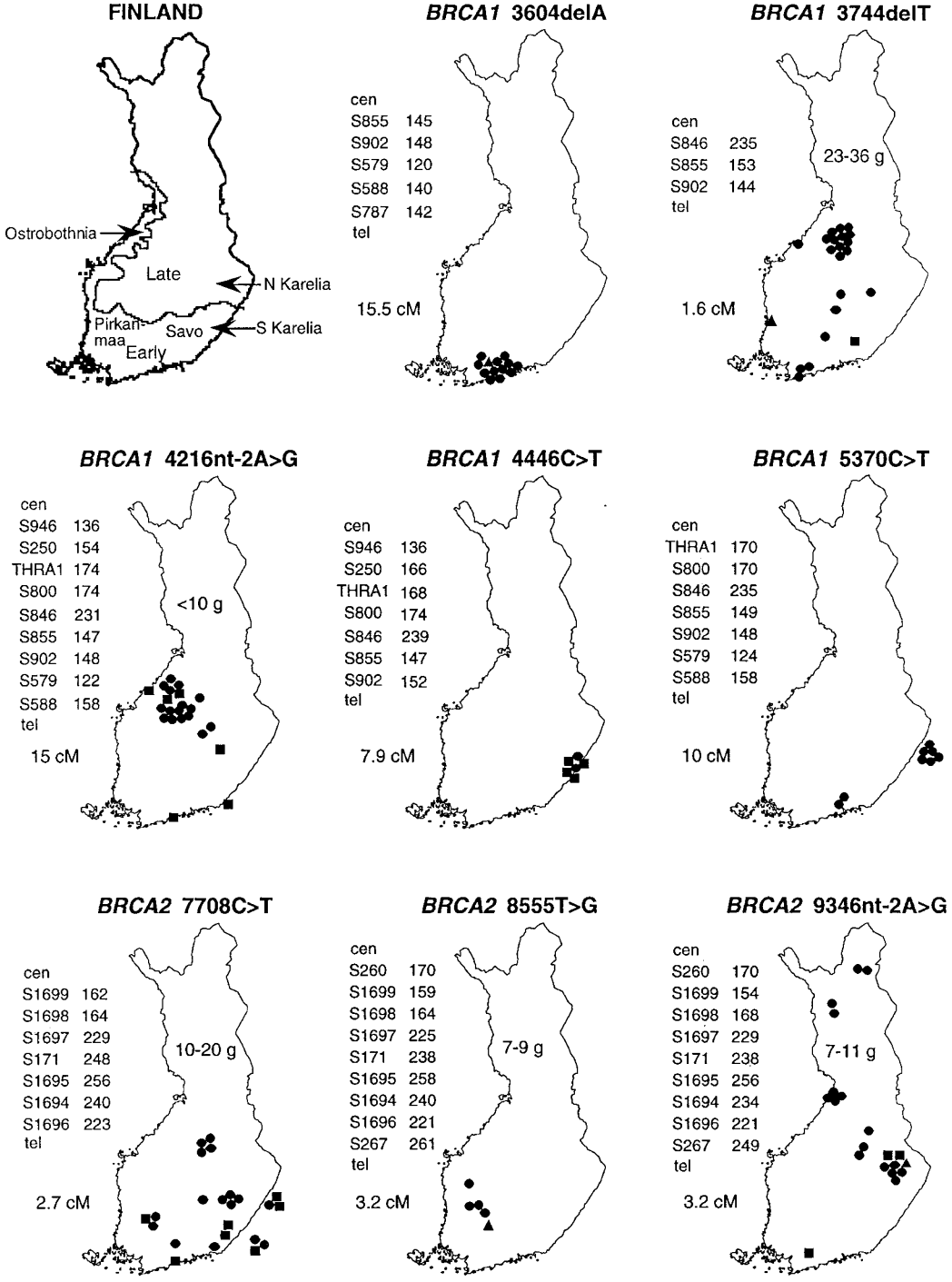

Figure 2 Maps of Finland showing early and late settlement areas and geographical distribution of the ancestry of recurrent *BRCA1* and *BRCA2* mutations. Birthplaces of grandparents, when known, are marked by black circles. Otherwise, birthplaces of parents (black squares) or index persons (black triangles) are shown. The conserved core haplotypes (alleles designated according to their size in base pairs) and the estimations of the number of generations (*g*) since the common ancestor are indicated.

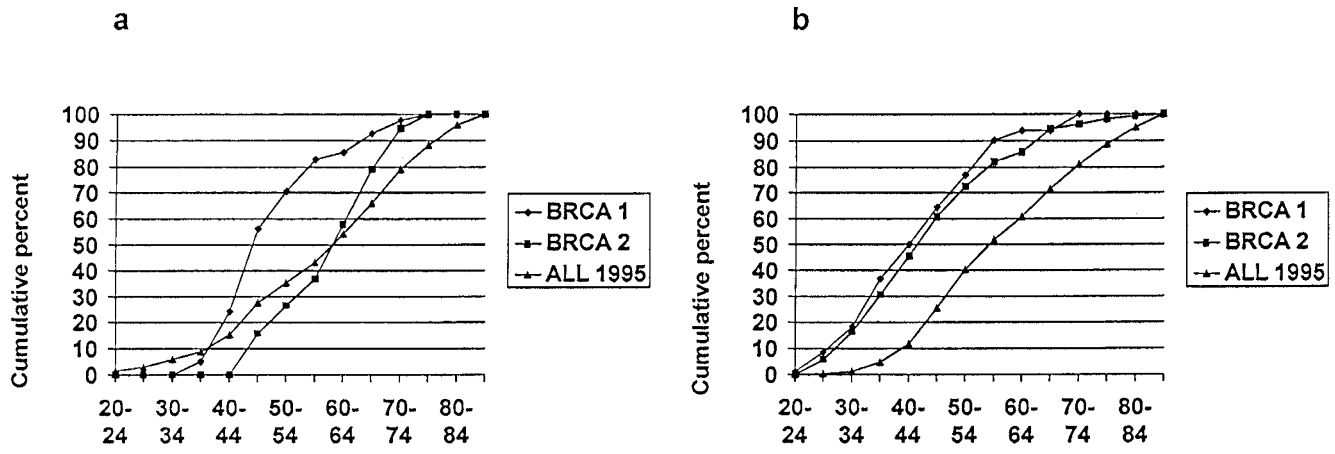

Figure 3 **a** Cumulative age-specific percentages of age at onset for ovarian cancer and **b** breast cancer in *BRCA1* and *BRCA2* families. All 1995 means all ovarian **a** and breast **b** cancer cases diagnosed in Finland in the year 1995.[22]

found here. The proportion of ovarian cancer was significantly higher ($P = 0.001$, Fisher's exact test), with a 2.3-fold difference, in families carrying mutations in exon 11 compared to the families with mutations 3' of this exon. Altogether, phenotype information was available from 34 *BRCA1* families and 37 *BRCA2* families, and ovarian cancer was present in 74% and 43%, respectively (Table 1). The age at ovarian cancer onset was significantly earlier in the *BRCA1* families (mean 51 years) than in the *BRCA2* families (mean 61 years) ($P < 0.0005$, unpaired *t*-test), with almost 60% of the *BRCA1* cases diagnosed before age 50 (Figure 3a). However, the distribution of diagnostic ages for breast cancer was similar in the *BRCA1* (mean 46 years) and *BRCA2* (mean 48 years) families (Figure 3b). Identification of larger number of individuals with these prevalent founder mutations in Finland will facilitate analysis of mutation-specific cancer risks and phenotypes. This will affect the clinical management of families carrying these mutations. Furthermore, environmental or other genetic factors modifying the cancer risks can ideally be studied in a genetically homogeneous population, especially in families carrying identical mutations.

In Finland the 11 known recurrent *BRCA1/2* mutations cover 84% of all *BRCA1* and *BRCA2* families found in screening the entire genes.[7–9] Whilst an unknown fraction, perhaps as high as almost 40% of mutations, may remain undetected by any mutation detection method,[35] linkage analysis in 24 of our large mutation-negative families suggested possible linkage to either *BRCA1* or *BRCA2* in only 4 (17%) (Kainu T *et al*, 2000, unpublished data). Thus, the major Finnish founder mutations may already have been identified. The high coverage of the founder mutations in Finland has also significant impact on diagnostics, which can first be based on direct screening of these mutations. Especially in some parts of the country, the mutation spectrum is very narrow and specific, whereas in the capital region of Helsinki, almost all Finnish mutations have been detected. Finally, the observation of multiple local founder effects in a multigenic disease provides support for the concept that an isolated population with known history may offer distinct advantages also for mapping novel predisposing genes.[36]

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