

Breast Cancer Research and Treatment

## Polygenic risk score is associated with increased disease risk in 52 Finnish breast cancer families

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Supplementary table 1 Study subjects

Genotyped study subjects	Total		3384
	BC patients‡		1802
Case-control data	Unselected BC patients†		1303 (175 / 87)
	Additional familial index cases†		378 (160 / 218)
	Healthy population controls		1272
52 breast cancer families	Genotyped family members	BC women‡	183
		Healthy women	246
		Men	64
	Registered family members	BC Women	110
		Healthy Women	1742
		Men	2140

† In parenthesis, the number of patients with a family history of breast cancer is reported separately for patients with one first degree relative with breast cancer and for patients with two or more first degree relatives with breast cancer.

‡ 63 patients from the 52 breast cancer families belonged to either unselected or familial cohorts of the case-control data set.

Supplementary table 2 Breast cancer families (the number of study subjects that passed genotyping quality control in parenthesis)

	All	BC cases	Healthy women	Men	Birth year of the youngest family member	Birth year of the oldest family member	Average follow-up age of genotyped healthy women	Average diagnosis age of genotyped breast cancer patients	BC cases born between 1930 and 1970	Healthy women born between 1930 and 1970	% of BC
7,5	106 (12)	14 (7)	46 (4)	46 (1)	1996 (1967)	1849 (1915)	53	62	10	28	26 %
Fam2	53 (13)	3 (3)	24 (8)	26 (2)	1986 (1974)	1892 (1923)	51.6	57	3	14	18 %
Fam3	41 (4)	8 (3)	15 (1)	18 (0)	1988 (1981)	1867 (1936)	30	48.3	6	3	67 %
Fam4	75 (20)	6 (5)	32 (15)	37 (0)	2001 (1975)	1848 (1907)	59.1	55.6	5	19	21 %
Fam5	81 (7)	4 (3)	41 (3)	36 (1)	1994 (1975)	1867 (1899)	69	61.3	3	30	9 %
Fam6	98 (13)	5 (4)	43 (8)	50 (1)	1983 (1962)	1859 (1916)	70.8	49.8	5	26	16 %
Fam7	50 (6)	5 (3)	25 (2)	20 (1)	1985 (1963)	1858 (1925)	66.5	57.7	5	20	20 %
Fam8	204 (22)	9 (4)	102 (16)	93 (2)	1995 (1974)	1800 (1920)	56.8	51.2	8	71	10 %
Fam9	197 (15)	5 (3)	96 (10)	96 (2)	1996 (1973)	1869 (1908)	65.9	57	5	59	8 %
Fam10	123 (11)	8 (4)	53 (3)	62 (4)	1992 (1969)	1858 (1921)	70.7	49.2	7	37	16 %
Fam11	30 (6)	3 (3)	14 (3)	13 (0)	1973 (1970)	1881 (1915)	50.3	46.3	3	8	27 %
Fam12	356 (14)	9 (6)	172 (7)	175 (1)	1994 (1950)	1821 (1912)	66.7	62.3	8	99	7 %
Fam13	73 (7)	4 (3)	32 (3)	37 (1)	1995 (1969)	1873 (1923)	56.3	52.3	3	18	14 %
Fam14	146 (10)	6 (4)	64 (4)	76 (2)	1989 (1967)	1858 (1934)	61.8	50.8	6	47	11 %
Fam15	269 (14)	17 (6)	129 (7)	123 (1)	1996 (1962)	1842 (1917)	68.1	59.5	13	72	15 %
Fam16	28 (12)	4 (3)	11 (8)	13 (1)	1989 (1960)	1889 (1913)	64.5	59	3	9	25 %
Fam17	111 (10)	9 (5)	50 (4)	52 (1)	1994 (1962)	1849 (1920)	65.2	59	9	29	24 %
Fam18	36 (3)	3 (3)	13 (0)	20 (0)	1995 (1943)	1896 (1925)	-	56	3	9	25 %
Fam19	79 (8)	5 (3)	32 (3)	42 (2)	1996 (1959)	1888 (1923)	64	50.7	5	28	15 %
Fam20	32 (5)	3 (3)	12 (1)	17 (1)	1981 (1968)	1898 (1939)	43	47.3	3	10	23 %
Fam21	39 (6)	6 (3)	16 (2)	17 (1)	1990 (1962)	1857 (1923)	66	51.7	6	10	38 %
Fam22	79 (12)	6 (4)	38 (7)	35 (1)	1990 (1976)	1884 (1922)	59.4	61.5	6	23	21 %
Fam23	26 (4)	4 (3)	8 (1)	14 (0)	1984 (1959)	1866 (1928)	47	57.7	4	2	67 %
Fam24	129 (17)	6 (3)	69 (14)	54 (0)	1995 (1960)	1844 (1920)	60.6	66	5	55	8 %
Fam25	91 (12)	7 (3)	39 (8)	45 (1)	1995 (1962)	1850 (1917)	63.8	59.3	7	27	21 %
Fam26	170 (16)	6 (4)	81 (7)	83 (5)	1992 (1968)	1857 (1925)	68.1	48.2	6	49	11 %
Fam27	30 (6)	4 (3)	14 (3)	12 (0)	1964 (1964)	1858 (1915)	73	54.3	3	7	30 %
Fam28	28 (6)	4 (3)	10 (2)	14 (1)	1977 (1964)	1882 (1915)	71	55.3	4	8	33 %
Fam29	32 (6)	6 (2)	9 (2)	17 (2)	1992 (1956)	1843 (1925)	65.5	64.5	4	6	40 %
Fam30	65 (11)	4 (3)	32 (7)	29 (1)	1991 (1969)	1869 (1924)	62.1	52.3	4	17	19 %
Fam31	88 (7)	4 (3)	33 (2)	51 (2)	1995 (1939)	1875 (1912)	79	63.7	3	24	11 %
Fam32	171 (4)	5 (2)	78 (2)	88 (0)	1996 (1971)	1859 (1926)	50.5	53	3	49	6 %
Fam33	74 (9)	5 (3)	29 (4)	40 (2)	1988 (1978)	1881 (1909)	52.5	53.3	3	19	14 %
Fam34	21 (7)	4 (3)	6 (1)	11 (3)	1993 (1943)	1874 (1905)	95	64	3	5	38 %
Fam35	111 (7)	5 (3)	50 (4)	56 (0)	1994 (1974)	1878 (1909)	62.5	52	4	34	11 %
Fam36	120 (15)	7 (3)	50 (11)	63 (1)	1996 (1960)	1882 (1923)	64.2	45.3	6	36	14 %
Fam37	48 (5)	6 (3)	15 (1)	27 (1)	1993 (1974)	1863 (1940)	36	52	5	8	38 %
Fam38	174 (11)	7 (3)	82 (5)	85 (3)	1993 (1964)	1868 (1907)	70.2	43.3	6	50	11 %
Fam39	225 (10)	5 (4)	111 (4)	109 (2)	1995 (1967)	1872 (1935)	53	46.8	5	69	7 %
Fam40	62 (9)	5 (4)	25 (3)	32 (2)	1994 (1968)	1874 (1925)	56.3	59.8	5	18	22 %
Fam41	34 (9)	4 (4)	17 (5)	13 (0)	1989 (1965)	1878 (1919)	59.8	60	4	11	27 %
Fam42	39 (7)	5 (4)	16 (2)	18 (1)	1977 (1966)	1884 (1923)	54.5	52.8	4	13	24 %
Fam43	36 (8)	4 (3)	12 (1)	20 (4)	1976 (1976)	1870 (1927)	50	55.3	3	4	43 %
Fam44	24 (9)	4 (3)	9 (3)	11 (3)	1961 (1961)	1888 (1918)	76.3	56	4	8	33 %
Fam45	22 (8)	4 (4)	7 (3)	11 (1)	1992 (1980)	1896 (1941)	46	46	4	4	50 %
Fam46	43 (13)	7 (5)	19 (8)	17 (0)	1988 (1982)	1883 (1920)	49.8	50.4	7	9	44 %
Fam47	43 (11)	7 (5)	15 (6)	21 (0)	1987 (1975)	1908 (1935)	52.8	50	7	10	41 %
Fam48	22 (6)	3 (3)	10 (3)	9 (0)	1998 (1975)	1913 (1940)	46.3	54.7	3	4	43 %
Fam49	22 (7)	3 (3)	8 (4)	11 (0)	1990 (1979)	1901 (1906)	51.2	47.7	3	4	43 %
Fam50	28 (6)	5 (3)	12 (2)	11 (1)	1974 (1974)	1860 (1943)	51	46.3	4	5	44 %
Fam51	33 (4)	4 (3)	11 (1)	18 (0)	1982 (1982)	1874 (1940)	29	44.7	4	5	44 %
Fam52	36 (9)	7 (3)	12 (6)	17 (0)	1991 (1979)	1872 (1926)	53.5	47.3	6	10	38 %
Summary	4353 (489)	293 (183)	1949 (244)	2111 (62)	2001 (1982)	1800 (1899)	60.3	54.1	183	992	16 %

Supplementary table 3 Odds ratios (OR) used for calculating the PRS and imputed values for missing genotypes (BC: breast cancer)

Variant	OR	Imputed value: BC cases	Imputed value: healthy controls
rs10069690	1.024	0.6101	0.6013
rs1011970	1.05	0.37468	0.36467
rs1045485	0.964	0.19358	0.19449
rs10472076	1.042	0.75922	0.74716
rs10759243	1.054	0.68355	0.65097
rs10771399	0.863	0.1396	0.15802
rs10941679	1.12	0.58574	0.54783
rs10995190	0.856	0.33451	0.38736
rs11075995	1.037	0.63637	0.62156
rs11199914	0.94	0.79022	0.81524
rs11242675	0.943	0.79171	0.81524
rs11249433	1.099	0.74367	0.70178
rs11571833	1.261	0.01817	0.01702
rs11780156	1.069	0.2755	0.25041
rs11814448	1.218	0.02431	0.02755
rs11820646	0.956	0.89152	0.92869
rs12022378	1.081	0.38358	0.36386
rs12422552	1.033	0.38589	0.40113
rs12493607	1.053	0.80468	0.77877
rs12662670	1.139	0.09063	0.08752
rs12710696	1.039	0.6551	0.6691
rs1292011	0.922	0.74169	0.77229
rs132390	1.109	0.06322	0.06321
rs13281615	1.095	0.80322	0.75859
rs13329835	1.076	0.51187	0.53809
rs13387042	0.879	0.8961	0.95543
rs1353747	0.921	0.0925	0.10292
rs1432679	1.067	0.8313	0.80941
rs1436904	0.947	0.64085	0.65397
rs1550623	0.945	0.26654	0.28201
rs16857609	1.072	0.60907	0.57942
rs17356907	0.908	0.7147	0.69935
rs17529111	1.046	0.53738	0.51864
rs17817449	0.93	0.84999	0.82563
rs17879961	1.363	0.08091	0.06088
rs2016394	0.95	0.95459	0.97648
rs204247	1.05	0.88414	0.859
rs2046210	1.047	0.47649	0.45057
rs2236007	0.92	0.41049	0.34279
rs2363956	1.026	0.85273	0.8363
rs2380205	0.977	0.86862	0.88169
rs2588809	1.067	0.27496	0.26499
rs2736108	0.938	0.4377	0.46515
rs2823093	0.927	0.41467	0.44282
rs2943559	1.133	0.06773	0.06333
rs2981579	1.252	0.93066	0.82415
rs3760982	1.055	0.78763	0.81752
rs3803662	1.226	0.77407	0.67883
rs3817198	1.074	0.4859	0.46272
rs3903072	0.944	1.03803	1.02755
rs4245739	1.029	0.35538	0.3282
rs4808801	0.935	0.7936	0.81442
rs4849887	0.919	0.12936	0.13128
rs4973768	1.094	0.92438	0.87805
rs527616	0.957	0.9564	0.91248

Variant	OR	Imputed value: BC cases	Imputed value: healthy controls
rs554219	1.26	0.34046	0.28145
rs6001930	1.134	0.32737	0.30551
rs616488	0.942	0.65331	0.67747
rs6472903	0.912	0.37148	0.39497
rs6504950	0.934	0.57171	0.59968
rs6678914	0.989	0.89415	0.87277
rs6762644	1.066	0.85116	0.81442
rs6828523	0.906	0.21983	0.24635
rs704010	1.07	0.69023	0.66018
rs7072776	1.058	0.52146	0.49433
rs720475	0.945	0.47917	0.50081
rs7726159	1.036	0.65545	0.64611
rs7904519	1.058	0.92817	0.90032
rs8170	1.031	0.4507	0.43112
rs865686	0.898	0.63281	0.68613
rs889312	1.118	0.50056	0.46434
rs941764	1.064	0.64325	0.67397
rs9693444	1.073	0.71198	0.67504
rs9790517	1.048	0.51781	0.49311
rs999737	0.924	0.41343	0.43355

Supplementary table 4 Odds ratios (OR) with 95% confidence intervals (CI) for breast cancer associated with the PRS and three moderate penetrance mutations within the breast cancer families.

	OR	95% CI	p-value
PRS	1.59	[1.28 – 1.98]	2.9E-5
<i>CHEK2</i> :c.1100delC	4.51	[2.59 – 7.85]	9.4E-8
<i>PALB2</i> :c.1592delT	6.40	[3.07 – 13.3]	6.6E-7
<i>FANCM</i> :c.5101C>T	3.78	[2.55 – 5.59]	2.5E-11

Supplementary table 5 Proportion of estrogen receptor positive (ER+) and negative (ER-) breast cancer in categories of PRS-quintiles

		PRS-quintiles					P for trend
		0-20	20-40	40-60	60-80	80-100	
Sporadic breast cancer cases	ER+	92 (78%)	113 (84%)	162 (86%)	177 (86%)	278 (91%)	0.00082
	ER-	26 (22%)	22 (16%)	27 (14%)	29 (14%)	29 (9%)	
Breast cancer index cases with positive family history of breast cancer	ER+	28 (74%)	55 (82%)	75 (74%)	120 (84%)	216 (86%)	0.023
	ER-	10 (26%)	12 (18%)	26 (26%)	23 (16%)	36 (14%)	
Breast cancer patients of the 52 breast cancer families	ER+	4 (40%)	15 (83%)	21 (72%)	20 (74%)	42 (76%)	0.22
	ER-	6 (60%)	3 (17%)	8 (28%)	7 (26%)	13 (24%)	

**Supplementary figure 1** PRS distribution of healthy population controls and a) different patient groups of the case-control data, b) healthy and affected members of breast cancer families, c) affected members of the breast cancer families depending the number (0, 1, 2, more) of affected first-degree relatives. For better visualization the number of healthy population controls is divided by two in b) and by ten in c). (Distribution mean is marked with dashed line; BC = breast cancer)

- population controls
- sporadic breast cancer
- breast cancer index cases from small families
- breast cancer index cases from large families

- population controls
- healthy female relatives from the 52 families
- breast cancer cases from the 52 families

- population controls
- breast cancer cases with no affected 1<sup>st</sup> dg relatives
- breast cancer cases with 1 affected 1<sup>st</sup> dg relative
- breast cancer cases with two affected 1<sup>st</sup> dg relatives
- breast cancer cases with more than 2 affected 1<sup>st</sup> dg relatives

