

Online Table. Genetic polymorphisms and their association with mammographic density.

Gene	Polymorphism	Chromosomal region	Amino acid change	rsID	Gene product function	Influence of polymorphism on enzyme	% relative change* in mammographic density	Homozygous variant carriers, n
Steroid hormone biosynthesis								
<i>CYP17A1</i>	+27T>C	10q24.3		743572	Mediates steroid 17 α -hydroxylase and 17,20-lyase activities to \uparrow production of estrone, 17 β -estradiol and testosterone ⁹⁸	Unlikely functional effect ⁵⁶	+9.1% ³⁹	48 all women
							-9.9% ⁴¹	76 all women
							-9.8% ⁴⁶	113 all women
							+24.0 ⁴³	69 premenopausal
							P=0.7 ⁴³	Postmenopausal N not stated
	-103G>T		Ser ⁶⁵ Ser	6163		Known?	-1.4% ⁵³	221 non-PMH
	-160C>T		His ⁴⁶ His	6162		Known?	-4.2% ⁵³	469 non-PMH
<i>CYP19A1</i> (aromatase)	(TTTA)n microsatellite	15q21.1		N/A	Converts testosterone to 17 β -estradiol and androstenedione to estrone	May alter splice site ⁶⁸ ; unlikely functional effect ⁵⁷	-6.6% with 10 repeat ⁴¹	7 all women
							+9.1% with 12 repeat ⁴¹	24 all women
							Lower MD with each copy of 8 repeat ³¹	All women N not stated
							Higher MD with each copy of 10 repeat ³¹	All women N not stated
	+268T>C			10046		Known?	-0.8% ⁴⁰	120 all women
							-13.6%*** ⁵³	298 non-PMH
							Higher MD with each copy of minor allele ³¹	All women N not stated
	+27(TCT)+/-			11575899		In LD with (TTTA)n microsatellite ⁷¹	+0.5% with insertion ⁵³	231 non-PMH
							-8.1% with deletion ⁵³	90 non-PMH
							Lower MD with deletion ³¹	All women N not stated

	17 other tagSNPs			Refer to ³¹		Known?	All P > 0.1 with each copy of minor allele ³¹	All women N not stated
<i>HSD3β1</i>	-429A>C	1p13.1	Asn ³⁶⁷ Thr	1047303	Catalyzes oxidation and isomerization of 3β-hydroxysteroid precursors into ketosteroids (progesterone, androgens)	Known?	-0.8% ³⁹	27 all women 23 Caucasians 4 African Americans
							-13.6%** ³⁹ +59.9%** ³⁹ -9.9%** ⁵⁰ -12.2%*** ⁵⁰ Not reported ⁵⁰	
<i>HSD17β1</i>	+220G>A	17q11-q21	Gly ³¹² Ser	605059	Converts estrone to 17β-estradiol and androstene-dione to testosterone	Creates <i>Bsp</i> UI site ⁵⁷ ; unlikely functional effect ⁷³	+9.9% ³⁹	96 all women
<i>SHBG</i>	-67G>A	17p13-p12		1799941	Specific plasma transport protein for testosterone and 17β-estradiol	Known?	+0.5% ⁵³	164 non-PMH
	+6G>A		Asp ³⁵⁶ Asn	6259			Creates an additional consensus site for N-glycosylation ⁹⁹ that ↑ protein half-life ¹⁰⁰ ; may ↑ SHBG	+23.0% ⁵³
Steroid hormone metabolism								
<i>CYP1A1</i>	+131A>G (also known as <i>m2</i>)	15q22-q24	Ile ⁴⁶² Val	1048943	Catalyzes estrone and 17β-estradiol preferentially to 2-OH catechol metabolites with lower activity for 4-OH metabolites ⁸⁶	Inconsistent: studies suggest ↑ enzyme activity ⁸⁴ and increased expression ⁸²	Not reported ⁴¹	All women N not stated
	T>C (also known as <i>m1</i>)						4646903	
<i>CYP1A2</i>	-154A>C (also known as CYP1A1*1F)	15q24		762551	Catalyzes estrone and 17β-estradiol preferentially to 2-OH catechol metabolites with	↑ inducibility; may ↓ bioactive estrogens ⁸²	-16.0%*** ⁴⁶	23 all women 16 premenopausal 18 cases
							-24.9%*** ⁴⁶ +2.9% ³⁸	

					lower activity for 4-OH metabolites ⁸⁶		+39.7%** ³⁸	18 controls
<i>CYP1B1</i>	+251G>C	2p21	Val ⁴³² Leu	1056836	Catalyzes estrone and 17β-estradiol preferentially to 4-OH catechol metabolites with lower activity for 2-OH catechol metabolites ⁸⁵	↑ enzyme activity; may ↓ bioactive estrogens and ↑ potentially carcinogenic 4-OH metabolites ^{85, 86}	-3.2% ⁴¹	148 all women
							-25.8%** ⁴⁰	47 cPMH
							+7.4% ⁴⁶	32 all women
							-23.4% ³⁷	37 ePMH
							+110%** ³⁷	13 epPMH
+143C>G			Arg ⁴⁸ Gly	10012		Inconsistent: ↑ expression or no effect on enzyme activity (reviewed in ¹⁰¹)	-3.8% ⁵³	237 non-PMH
							-4.4% ⁵³	102 non-PMH
+356G>T			Ala ¹¹⁹ Pro	1056827		Known?	-3.8% ⁵³	273 non-PMH
<i>COMT</i>	-12G>A	22q11.21	Val ¹⁵⁸ Met	4680	Methylates and inactivates 2- and 4-OH catechol estradiol and catechol estrone ⁵⁸	↓ enzyme activity; may ↑ catechol estrogen metabolites ⁵⁸	+4.5% ³⁹	82 all women
							+34.7%** ³⁹	19 cPMH
							-5.8% ⁴¹	149 all women
							-23.3%** ⁴¹	63 n/pPMH
							-15.0%** ⁴⁶	58 all women
							-20.7%** ⁴⁶	46 premenopausal
							-40.0%** ⁴²	38 premenopausal
							P = 0.76 ⁴²	Postmenopausal N not stated
							+62% ³⁷	25 ePMH
							+22.5% ³⁶	3 epPMH
							+2.0% ⁵³	329 non-PMH
							-3.5% ³⁸	42 cases
							+6.3% ³⁸	47 controls
+14.2% ⁵⁰	All women N not stated							
						P > 0.1 ⁵⁰	Pre or postmenopausal N not stated	
-98A>G				6269		Known?	-10.9% ⁵³	202 non-PMH
-104C>T			His ⁶² His	4633		Known?	+5.2% ⁵³	340 non-PMH

	-76C>G +701A>G		Leu ¹³⁶ Leu	4818 737865		Known? Alters DNA protein binding; Up-regulates membrane-bound COMT expression ⁵⁵	-12.8% ⁵³ Lower MD with each copy of minor allele*** ⁵⁵ P = 0.88 ⁵⁵	187 non-PMH 402 postmenopausal 136 premenopausal	
<i>UGT1A1</i>	(TA) _n TAA repeat	2q37		N/A	Glucuronidation of 17β-estradiol (with less affinity for estrone), 2-OH and 4-OH catechol estradiol and 2-OH and 4-OH catechol estrone for excretion ¹⁰²	↓ promoter activity with increasing <i>n</i> repeats; may ↓ glucuronidation ¹⁰²	-0.8% ⁴¹	51 all women	
							+32%*** ⁴¹ +56.8%*** ⁴¹	31 postmenopausal 12 cPMH	
							-22.8% ³⁷ -23.9% ³⁶	14 ePMH 3 epPMH	
<i>AKR1C4</i>	+931C>G	10p15-p14	Leu ³¹¹ Val ¹⁰³	17134592	3α-hydroxylation of ketosteroids to yield inactive metabolites for conjugation and elimination ¹⁰⁴	↓ enzyme activity by 66-80%; may ↑ progesterone or androgen levels ¹⁰³	+27.9% for heterozygotes ³⁶	25 ePMH	
							+632%*** ³⁷	1 epPMH	
Nuclear receptors and transcription factors									
<i>ESR1</i>	-351A>G (also known as Xba I, where A = x allele; G = X allele)	6q25.1		9340799	Binds 17β-estradiol and acts as a transcription factor ¹⁰⁵	Unlikely ⁵⁷	-2.0% with XX genotype ⁵³	280 non-PMH	
							+13.8% with xx genotype*** ⁴⁷	71 non-PMH	
	-397C>T (also known as Pvu II, where C = P allele; T = p allele)				2234693	Unlikely ⁶⁰	+9.4% with pp genotype*** ⁴⁷	155 non-PMH	
							Slower decline with x allele*** ⁵²	634 cPMH	
<i>PGR</i>	+331G>A	11q22-q23		N/A	Nuclear receptor; trans-activates progesterone-responsive genes	Creates a unique transcription start site; favours ↑ transcription of PGR β isoform ⁶⁴	Slower decline with GG genotype*** ⁵²	623 cPMH	
	<i>PROGINS</i> : -48C>T +72G>T		His ⁷⁷⁰ His Val ⁶⁶⁰ Leu Alu insertion sequence	1042839 1042838		Loss of ligand binding and transcriptional activity ⁶⁵	No difference in density decline by genotype ⁵²	703 cPMH	

	+72G>T		Val ⁶⁶⁰ Leu	1042838		Known?	+28.4% ³³	30 non-PMH	
<i>AR</i>	(CAG)n repeats	Xq11.2-q12		N/A	Binds testosterone (androgens); transactivates androgen-responsive genes ⁷⁸	AR alleles containing longer CAG repeat lengths are less active ^{76, 77}	-2.5% with long repeat allele ⁴¹	116 all women	
							+2.3% with long repeat allele ⁴⁰ +61.1% with long repeat allele** ⁴⁰	145 all women 27 epPMH	
<i>AIB1</i>	(CAG)n repeats	20q12		N/A	A steroid receptor coactivator that facilitates transcription of target gene by the estrogen receptor ^{106, 107}	↑ poly-glutamate length may decrease AIB1 stability ¹⁰⁸	+8.3% with short repeat allele ⁴¹ +20.3% with short repeat allele** ⁴¹	125 all women 91 postmenopausal	
Cell proliferation and growth									
<i>IGF-1</i>	(CA)n repeat	12q22-q23		N/A	Encodes peptide growth hormones that promote cellular proliferation	Unknown; ≥19 repeats may ↓ promoter activity or be in LD with an unmeasured polymorphism; may ↓ serum IGF-1 levels ¹⁰⁹	+0.4% with 19 CA repeat allele ⁴⁵	All women N not stated	
	8470 bp 3' of STP G>A			2946834			Known?	-17.7%** ³⁰	117 all women
								Not significant by menopausal status ³⁰ +6.5%** ³²	Pre or postmenopausal N not stated 192 premenopausal
	-178C>G			1520220			Known?	-29.7%** ³⁰	36 all women
								Not significant by menopausal status ³⁰	Pre or postmenopausal N not stated
								+1.6% ³² +30.9%** ⁵⁴	58 premenopausal 18 premenopausal
	-17526T>C			7965399			Known?	-27.9% ³⁰	2 all women
Not significant by menopausal status ³⁰ -0.9% for TC/CC genotypes ³²					Pre or postmenopausal N not stated 155 premenopausal				
+4996C>A			1019731	Known?	-3.3% ³⁰ Not significant by menopausal status ³⁰	23 all women Pre or postmenopausal N not stated			

	-26989G>A			2373722		Known?	+8.6% ³² -26.6%*** ³⁰	36 premenopausal 7 all women
	8 other tagSNPs			Refer to ³⁰			Not significant by menopausal status ³⁰	Pre or postmenopausal N not stated
	+1830T>C			6220		Known?	Not significant ³⁰	N varies from 19-270 all women
	A>G			5742612		Known?	+6.7%*** ³² +23.3%*** ⁵⁴	143 premenopausal 38 premenopausal
	C>A			1549593		Known?	+41.2% ⁵⁴	2 premenopausal
	A>G			7956547		Known?	-5.9% ⁵⁴ +11.0% ³⁰ Not significant by menopausal status ³⁰	11 premenopausal 20 all women Pre or postmenopausal N not stated
	T>C			7136446		Known?	+7.6%*** ³²	110 premenopausal
	10 other tagSNPs			Refer to ³²		Known?	-7.8% for TT ³² -8.2% for TC ³² -4.6% for CC** ³²	256 pre to postmenopause 289 pre to postmenopause 99 pre to postmenopause
<i>IGFIR</i>	G>A	15q26.3	Glu ¹⁰¹³ Glu	2229765	Encodes IGF-I receptor	Known?	Not significant ³²	N varies from 20-300 premenopausal
<i>IGFBP-1</i>	-574G>A	7p13-p12		1065780	Encodes circulatory binding proteins of IGF-1; sequesters IGF-1 from interacting with its cell-surface receptor	No functional impact ¹¹⁰	+8.7% ⁵⁴	148 premenopausal
	4 other tagSNPs			Refer to ³⁰		Known?	+14.5%*** ³⁰ Not significant by menopausal status ³⁰	158 all women Pre or postmenopausal N not stated
<i>IGFBP-3</i>	-202C>A	7p13-p12		2854744		Known?	Not significant ³⁰	N varies from 1-120 all women
						↑ promoter activity; may ↑ serum IGFBP-3 levels ⁶⁷	+20.0%*** ⁴⁵ +26.2%*** ⁴⁵ +14.9% ⁴⁸ +4.0% ⁴⁸ +8.8% ⁵⁰	All women N not stated Premenopausal N not stated 41 premenopausal 39 postmenopausal
							P > 0.1 ⁵⁰	All women N not stated Pre or postmenopausal N not stated

							-0.4% ³⁰ Not significant by menopausal status ³⁰	202 all women Pre or postmenopausal N not stated
	G>A			2132572		Known?	-2.3% ⁵⁴	188 premenopausal
	G>C			2471551		Known?	+1.9% ⁵⁴	39 premenopausal
	C>T			3110697		Known?	+2.9% ⁵⁴	27 premenopausal
						Known?	+3.4% ⁵⁴	114 premenopausal
							-6.4% ³⁰ Not significant by menopausal status ³⁰	195 all women Pre or postmenopausal N not stated
	7 other tagSNPs			Refer to ³⁰		Known?	Not significant ³⁰	N varies from 35-148 all women
<i>IRS1</i>	G>A	2q36	Gly ⁹⁷¹ Arg	1801278	Encodes insulin receptor substrate 1, a downstream signaling molecule of IGF1R	Impairs insulin-stimulated signaling ¹¹¹	+29.4% ⁵⁴	2 premenopausal
<i>PIK3CB</i>	Promoter T>C	3q22.3		361072	Encodes phosphoinositide-3-kinase, catalytic, β polypeptide, a major effector of insulin action	Impairs PIK3CB expression; may promote insulin resistance ¹¹²	-9.9%** ⁵⁴	161 premenopausal
<i>GHI</i>	-75G>A	17q24.2	Val ²⁶ Val	6171 ¹¹³	Encodes growth hormone	May \downarrow promoter activity or be in LD with an unmeasured polymorphism; may \downarrow GH1 levels ¹¹⁴	+13.1%** ⁴⁴	280 all women
	-57G>T		Gly ³⁰ Gly	2665802 ¹¹³			+20.6%** ⁴⁴	137 premenopausal
							+18.7%** ⁴⁴	57 all women
							+22.5%** ⁴⁴	25 premenopausal
<i>GHRHR</i>	+169G>A	7p14	Ala ⁵⁷ Thr	4988496 ¹¹³	G-protein-linked receptor expressed in the pituitary; binds GHRH to \uparrow GH production	\uparrow sensitivity of GHRHR to bind GHRH; may \uparrow GH secretion ¹¹⁵	+0.7% with ≥ 1 A allele ⁴⁴	43 all women
<i>HER2</i>	A>G	17q21.1	Val ⁶⁵⁵ Ile	1801200	Encodes a epidermal growth factor (EGF)	Known?	-8.4% ³⁰	All women N not stated

					receptor family member; enhances kinase-mediated (mitogen) signaling pathways		P > 0.1 ⁵⁰	Pre or postmenopausal N not stated
Tumor suppressors								
<i>BRCA1/BRCA2</i>	>750 protein-truncating mutations ⁸⁰	17q21/13q12.3		N/A	Tumor suppressors	Known?	No difference in density between mutation positive and negative cases ^{33, 36, 49} Higher density in mutation positive cases** ^{34, 35}	N varies from 9 to 206
DNA repair								
<i>XPD</i>	A>C	19q13.3	Lys ⁷⁵¹ Gln	17359310	Nucleotide excision repair cross-complementing 2 gene involved in DNA repair	May ↑ repair of X-ray induced DNA damage ¹¹⁶	+1.3% ⁵⁰ P > 0.1 ⁵⁰	All women N not stated Pre or postmenopausal N not stated
<i>XRCC3</i>	T>C	14q32.3	Thr ²⁴¹ Met	861539	X-Ray Repair Cross-Complementing 3 gene involved in DNA homologous recombinational repair	Predicted to abolish a putative phosphorylation site ¹¹⁷	-1.6% ⁵⁰ P > 0.1 ⁵⁰	All women N not stated Pre or postmenopausal N not stated
Genome Wide Association Study Candidates								
?	A>C	5q		889312		Known?	-18.2% ⁵¹	49 all women
<i>FGFR2</i>	T>C	10q26		2981582	Encodes fibroblast growth factor receptor 2 that interacts with FGF to influence mitogenesis and differentiation.	Known?	No change ⁵¹	76 all women
?	T>C	16q		3803662		Known?	+5.5% ⁵¹	58 all women
<i>LSP1</i>	T>C	11p15.5		3817198	Encodes lymphocyte-specific protein 1; may regulate neutrophil motility,	Known?	+11.2% ⁵¹	54 all women

					adhesion to fibrinogen matrix proteins, and transendothelial migration			
?	A>G	8q		13281615		Known?	+11.9% ^{§1}	116 all women
?	A>G	2q		13387042		Known?	-0.8% ^{§1}	109 all women

cPMH = current postmenopausal hormone users; p/nPMH = past or never; ePMH = estrogen only; epPMH = estrogen and progestin.

* Comparing relative percent change in mammographic density (MD) between homozygous variant (hv) genotype and homozygous wildtype (hwt) genotype using the formula: $(MD_{hv} - MD_{hwt} / MD_{hwt}) * 100$. Those associations that were significant at $P < 0.05^{**}$ or $0.05 \leq P \leq 0.1^{***}$ are indicated.