Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

ESRRG (estrogen-related receptor gamma)

Rebecca B Riggins

Department of Oncology, Georgetown University, 3970 Reservoir Road NW, E407 Research Bldg, Washington, DC 20057, USA (RBR)

Published in Atlas Database: October 2009

Online updated version : http://AtlasGeneticsOncology.org/Genes/ESRRGID45840ch1q41.html
DOI: 10.4267/2042/44822

Identity

Other names: ERR3; ERRG2; FLJ16023; KIAA0832; NR3B3; DKFZp781L1617

HGNC (Hugo): ESRRG

Location: 1q41

DNA/RNA

Description

The ESRRG gene encompasses 587 kb of sequence on the minus strand. ERRgamma transcript variant 1 contains 7 exons, while variants 2, 3, and 4 contain 6 exons.

Transcription

ERRgamma has 4 coding and 1 (presumed) non-coding transcript variants. ERRgamma transcript variant 1 (NCBI, NM_001438) is the longest isoform, while ERRgamma transcript variant 2 (NM_206594) utilizes an alternate 5' UTR and lacks the first 23 amino acids of the coding sequence of variant 1 (Heard et al., 2000). In 2006, a third splice variant (ERRgamma3, NM_206595) was identified (Kojo et al., 2006). This isoform has 3 novel amino-terminal exons and lacks Exon F, which contains the second zinc-finger binding motif within the DNA binding domain of the receptor. Consequently ERRgamma3 cannot stimulate transcription from an estrogen response element (ERE)-driven reporter construct, although it can modulate the activity of other nuclear receptors, such as estrogen receptors alpha and beta (ERalpha, ERbeta), thyroid hormone receptor (TR), and glucocorticoid receptor (GR) (Kojo et al., 2006). ERRgamma4 (NM_001134285), similar to variant 2, uses an alternate 5' UTR and also encodes a shorter protein isoform than variant 1. ERRgamma5 (NR_024099) is transcribed but presumed to be non-coding.

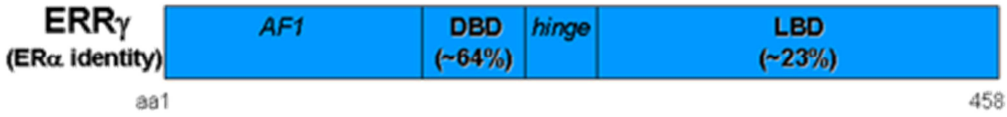
Protein

Note

The domain structure of ERRgamma is typical for a member of the nuclear receptor superfamily. ERRgamma and its family members (ERRalpha and ERRbeta) are most similar to the classical estrogen receptors alpha and beta (ERalpha, ERbeta).

Description

AF1: Like most nuclear receptors, the activation function -1 (AF1) domain of ERRgamma participates in the regulation of transcription by the receptor. It is the region to which several coactivators can bind (see below), as well as the site of post-translational modification.



Schematic of ERRgamma domain structure. aa = amino acid, and numbers correspond to the ERRgamma1 isoform; AF1 = activation function-1 ; DBD = DNA binding domain ; LBD = ligand binding domain; (%) denotes amino acid identity to estrogen receptor alpha (ERalpha).

Phosphorylation of the family member ERRalpha at serine 19 has recently been shown to direct subsequent SUMOylation at a nearby lysine (residue 14), and that this series of post-translational modifications is in fact inhibitory for receptor transcriptional activity (Vu et al., 2007). While ERRgamma lacks a serine residue in this position, in March of 2008 Tremblay et al. confirmed ERRalpha phosphorylation at serine 19 and reported that ERRgamma transcriptional activity can also be inhibited by SUMOylation of lysine 40 that is directed by phosphorylation of serine 45 (Tremblay et al., 2008). The authors went on to identify protein inhibitor of activated signal transducer and activator of transcription gamma (PIAS4) as a functional E3 ligase for the family member ERRalpha, and hypothesized that PIAS4 and the SUMO-conjugating enzyme Ubc9 are responsible for the modification of ERRgamma as well.

DBD: The greater than 60% identity between the DNA binding domains (DBDs) of ERRgamma and ERalpha (see figure) results in ERRgamma being able to bind the estrogen response element (ERE: AGGTCA...TGACCT). However, ERRgamma also binds to what was originally identified as the consensus sequence for steroidogenic factor 1 (SF1, SFRE: TCAAGGTCA) (Horard and Vanacker, 2003).

LBD: A key difference between ERRgamma and most members of the nuclear receptor superfamily is the regulation of its transcriptional activity. There is only about 23% sequence identity between classical ERalpha and ERRgamma in the ligand binding domain (LBD) (see figure). Therefore, while ERalpha (like most nuclear receptors) is dependent upon ligand for full activation, ERRgamma and the other members of the ERR family exhibit constitutive transcriptional activity. None of the ERR family members are affected by estradiol (E2) stimulation because their LBDs cannot accommodate E2 binding (discussed in Ariazi and Jordan, 2006). However, ERRgamma transcriptional activity at EREs and SFREs can be inhibited by 4-hydroxytamoxifen (4HT) and the synthetic estrogen diethylstilbestrol (Greschik et al., 2002; Greschik et al., 2004; Yu and Forman, 2005). In contrast, 4HT-bound ERRgamma acquires the ability to positively regulate transcription at activator protein-1 (AP1) sites (Huppunen et al., 2004), but the mechanism by which this occurs is not clear. ERRgamma constitutive activity can be enhanced or stabilized by the synthetic agonist GSK4716 (Yu and Forman, 2005; Zuercher et al., 2005), the endocrine disruptor Bisphenol A (BPA) (Matsushima et al., 2007; Takayanagi et al., 2006), and a variant of this compound (4-alpha-cumylphenol) (Matsushima et al., 2008). ERRgamma constitutive activity has also recently been shown to be inhibited by kaempferol, a dietary flavonoid (Wang et al., 2009).

Coactivators/Corepressors: Like other nuclear receptors, ERRgamma transcriptional activity is modulated by binding to other proteins that can serve as coactivators or corepressors. Coactivators and corepressors bind directly to nuclear receptors, most often within the carboxyl-terminal activation function-2 (AF2) domain that participates in ligand-binding but some can exert their effects by binding to the amino-terminal AF1 domain or the flexible hinge region of the receptor (Hall and McDonnell, 2005). Among the coactivators that have been demonstrated to bind and activate ERRgamma are PPARGC1A (also known as PGC-1alpha), TLE1, NCOA1, NCOA2 and, under certain circumstances, NRIP1 (Gowda et al., 2006; Sanyal et al., 2004). PPARGC1A is best known as a coactivator for peroxisome proliferator-activated receptor gamma, but it is also able to enhance ERRgamma activity in an AF1-dependent manner (Hentschke et al., 2002). TLE1 can also enhance ERRgamma activity by binding to its AF1 domain, and the coactivator function of TLE1 in this context is unique because this protein typically functions as a repressor for Drosophila and mammalian high mobility group (HMG) box transcription factors. TLE1 also has no known interactions with classical ERalpha or any other nuclear receptor (Hentschke and Borgmeyer, 2003). In contrast, NCOA1 and NCOA2 are well-known AF2-dependent coactivators of ERalpha and other nuclear receptors, including ERRgamma (reviewed in Hall and McDonnell, 2005).

Expression

In fetal and adult human tissues, ERRgamma1 and ERRgamma2 are most highly expressed in the heart, brain, kidney, and skeletal muscle (Heard et al., 2000), while ERRgamma3 expression appears to be restricted to the prostate and adipose tissue (Kojo et al., 2006). Interestingly, in the mouse ERRgamma is also expressed in these tissues but is even more abundant in the brain stem and spinal cord (http://www.nursa.org/10.1621/datasets.02001).

Localisation

Endogenous ERRgamma is localized to the nucleus in human breast cancer (Park et al., 2005) and prostate tissue (Yu et al., 2007), and transfected, exogenous ERRgamma is also found in the nucleus of tissue culture cells (Yasumoto et al., 2007).

Function

Molecular function: transcription factor activity, steroid hormone receptor activity, steroid binding, protein binding, zinc ion binding.

Biological processes: transcription, positive regulation of transcription (DNA-dependent).

As a member of the nuclear receptor superfamily, ERRgamma is a transcription factor. In the mouse, homozygous knockout of ERR results in death on or about postnatal day 1 caused by severe cardiac defects (Alaynick et al., 2007). This is due to a key metabolic defect whereby the animals are unable to switch from deriving energy from carbohydrates in utero to lipids as a neonate because ERRgamma controls the

transcription of essential genes that regulate oxidative metabolic processes (Giguere, 2008).

Homology

ERRgamma is highly conserved among several species. At the amino acid level, human ERRgamma is 100% identical to rat, mouse, and cow ERRgamma, and 99.78% identical to dog and chimpanzee ERRgamma.

Mutations

Germinal

Two recent studies have identified single nucleotide polymorphisms (SNPs) in ERRgamma. In a genome-wide association study searching for genes linked to Type 2 diabetes in an Amish population, Rampersaud et al. identified the non-coding rs2818781, which is present in an intron of ERRgamma2 and ERRgamma3 (Rampersaud et al., 2007). The T vs. C allele confers an increased risk for Type 2 diabetes (O.R. 1.61, p=0.003), and is also significantly associated with elevated glucose area under the curve (GAUC), a measure of impaired glucose tolerance collected during the oral glucose tolerance test (OGTT).

Two different SNPs in ERRgamma have been linked to breast cancer risk in a population of Thai women (Sangrajrang et al., 2009). The non-coding rs1857407 is located in an intron of ERRgamma1, ERRgamma2, and ERRgamma3, and heterozygotes for the G vs. A allele have a reduced breast cancer risk (O.R. 0.72, p=0.022). This risk reduction is even more pronounced in post-menopausal women (O.R. 0.69, p=0.043). In contrast, homozygote carriers of the CC (vs. TT) allele of rs945453 have an elevated breast cancer risk (O.R. 1.66, p=0.034), though this shows no significant association with pre- vs. post-menopausal status. This SNP leads to a synonymous change (serine-to-serine) at position 318 for ERRgamma1, and 295 for ERRgamma2, ERRgamma3, and ERRgamma4.

Implicated in

Breast cancer

Note

In 2002 Ariazi et al. published a study of ERRgamma family expression in 38 breast tumors as compared to normal mammary epithelial cells (MECs) (Ariazi et al., 2002). ERRgamma mRNA expression is nearly 4-fold higher in these tumors than in the MECs and is positively associated with ERalpha and progesterone receptor (PR) expression. It was therefore concluded that the correlation of ERRgamma with ERalpha and PR in breast tumors suggests that ERRgamma expression is an indicator of good prognosis in breast cancer (Ariazi et al., 2002), given that women with ER+/PR+ breast tumors are excellent candidates for adjuvant endocrine therapy with aromatase inhibitors or antiestrogens such as Tamoxifen (TAM).

However, TAM therapy is ineffective in approximately 30% of patients with ER+/PR+ breast tumors, and the majority of women who initially respond to TAM but go on to acquire resistance to this and other endocrine agents do so without complete loss of ERalpha expression (Clarke et al., 2001). Moreover, 4-hydroxytamoxifen (4HT)-bound ERRgamma is known to activate transcription at AP1 sites, and elevated AP1 activity has been linked to TAM resistance in multiple in vitro (Dumont et al., 1996; Zhou et al., 2007) and in vivo (Johnston et al., 1999; Schiff et al., 2000) studies. In light of this, we were intrigued to find that that endogenous expression of ERRgamma is upregulated during the acquisition of TAM resistance by the ER+/PR+ SUM44 breast cancer cell line (Riggins et al., 2008). We subsequently demonstrated that overexpression of ERRgamma confers Tamoxifen (TAM) resistance to this and another ERalpha+ breast cancer cell line, and that ERRgamma-driven AP1 activation plays a dominant role in the resistance phenotype.

Ovarian cancer

Note

In a study of ovarian cancer specimens, normal ovaries, and ovarian cancer cell lines, Sun et al. showed that ERRgamma expression is significantly greater in ovarian cancer relative to normal tissue (Sun et al., 2005). However, patients whose tumors were positive for ERRgamma had significantly improved disease-free survival, and ERRgamma expression was not correlated with serum levels of CA-125, a tumor marker used to monitor ovarian cancer recurrence.

Endometrial cancer

Note

In 2006, Gao et al. reported that ERRgamma mRNA expression was significantly higher in ERalpha-positive endometrial carcinoma than normal endometrial tissues, although patients with ERRgamma-positive tumors had a reduced occurrence of lymph node metastases (Gao et al., 2005).

Prostate cancer

Note

In cell culture models of prostate cancer, stable overexpression of ERRgamma has been shown to inhibit cell proliferation and survival in vitro and in in vivo xenograft tumor models (Yu et al., 2007). This occurs via cell cycle arrest at the G1/S phase transition, which is induced by upregulation of the cell cycle inhibitors p21 and p27. ERRgamma activates transcription at both the p21 and p27 promoters, which may suggest that ERRgamma has tumor suppressor activities in prostate cancer.

References

Dumont JA, Bitonti AJ, Wallace CD, Baumann RJ, Cashman EA, Cross-Doersen DE. Progression of MCF-7 breast cancer

cells to antiestrogen-resistant phenotype is accompanied by elevated levels of AP-1 DNA-binding activity. Cell Growth Differ. 1996 Mar;7(3):351-9

Johnston SR, Lu B, Scott GK, Kushner PJ, Smith IE, Dowsett M, Benz CC. Increased activator protein-1 DNA binding and c-Jun NH2-terminal kinase activity in human breast tumors with acquired tamoxifen resistance. Clin Cancer Res. 1999 Feb;5(2):251-6

Heard DJ, Norby PL, Holloway J, Vissing H. Human ERRgamma, a third member of the estrogen receptor-related receptor (ERR) subfamily of orphan nuclear receptors: tissue-specific isoforms are expressed during development and in the adult. Mol Endocrinol. 2000 Mar;14(3):382-92

Schiff R, Reddy P, Ahotupa M, Coronado-Heinsohn E, Grim M, Hilsenbeck SG, Lawrence R, Deneke S, Herrera R, Chamness GC, Fuqua SA, Brown PH, Osborne CK. Oxidative stress and AP-1 activity in tamoxifen-resistant breast tumors in vivo. J Natl Cancer Inst. 2000 Dec 6;92(23):1926-34

Clarke R, Skaar TC, Bouker KB, Davis N, Lee YR, Welch JN, Leonessa F. Molecular and pharmacological aspects of antiestrogen resistance. J Steroid Biochem Mol Biol. 2001 Jan-Mar;76(1-5):71-84

Ariazi EA, Clark GM, Mertz JE. Estrogen-related receptor alpha and estrogen-related receptor gamma associate with unfavorable and favorable biomarkers, respectively, in human breast cancer. Cancer Res. 2002 Nov 15;62(22):6510-8

Greschik H, Wurtz JM, Sanglier S, Bourguet W, van Dorsselaer A, Moras D, Renaud JP. Structural and functional evidence for ligand-independent transcriptional activation by the estrogen-related receptor 3. Mol Cell. 2002 Feb;9(2):303-13

Hentschke M, Süsens U, Borgmeyer U. PGC-1 and PERC, coactivators of the estrogen receptor-related receptor gamma. Biochem Biophys Res Commun. 2002 Dec 20;299(5):872-9

Hentschke M, Borgmeyer U. Identification of PNRC2 and TLE1 as activation function-1 cofactors of the orphan nuclear receptor ERRgamma. Biochem Biophys Res Commun. 2003 Dec 26;312(4):975-82

Horard B, Vanacker JM. Estrogen receptor-related receptors: orphan receptors desperately seeking a ligand. J Mol Endocrinol. 2003 Dec;31(3):349-57

Greschik H, Flaig R, Renaud JP, Moras D. Structural basis for the deactivation of the estrogen-related receptor gamma by diethylstilbestrol or 4-hydroxytamoxifen and determinants of selectivity. J Biol Chem. 2004 Aug 6;279(32):33639-46

Huppunen J, Wohlfahrt G, Aarnisalo P. Requirements for transcriptional regulation by the orphan nuclear receptor ERRgamma. Mol Cell Endocrinol. 2004 Apr 30;219(1-2):151-60

Sanyal S, Matthews J, Bouton D, Kim HJ, Choi HS, Treuter E, Gustafsson JA. Deoxyribonucleic acid response element-dependent regulation of transcription by orphan nuclear receptor estrogen receptor-related receptor gamma. Mol Endocrinol. 2004 Feb;18(2):312-25

Gao M, Wei LH, Sun PM, Zhao D, Wang JL, Wang ZQ, Zhao C. [Expression of estrogen receptor-related receptor isoforms in endometrial carcinoma tissues and its clinical significance]. Zhonghua Fu Chan Ke Za Zhi. 2005 Nov;40(11):756-60

Hall JM, McDonnell DP. Coregulators in nuclear estrogen receptor action: from concept to therapeutic targeting. Mol Interv. 2005 Dec;5(6):343-57

Sun P, Sehouli J, Denkert C, Mustea A, Könsgen D, Koch I, Wei L, Lichtenegger W. Expression of estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor biomarkers in ovarian cancer cells. J Mol Med. 2005 Jun;83(6):457-67

Yu DD, Forman BM. Identification of an agonist ligand for estrogen-related receptors ERRbeta/gamma. Bioorg Med Chem Lett. 2005 Mar 1;15(5):1311-3

Zuercher WJ, Gaillard S, Orband-Miller LA, Chao EY, Shearer BG, Jones DG, Miller AB, Collins JL, McDonnell DP, Willson TM. Identification and structure-activity relationship of phenolic acyl hydrazones as selective agonists for the estrogen-related orphan nuclear receptors ERRbeta and ERRgamma. J Med Chem. 2005 May 5;48(9):3107-9

Ariazi EA, Jordan VC. Estrogen-related receptors as emerging targets in cancer and metabolic disorders. Curr Top Med Chem. 2006;6(3):203-15

Gowda K, Marks BD, Zielinski TK, Ozers MS. Development of a coactivator displacement assay for the orphan receptor estrogen-related receptor-gamma using time-resolved fluorescence resonance energy transfer. Anal Biochem. 2006 Oct 1;357(1):105-15

Kojo H, Tajima K, Fukagawa M, Isogai T, Nishimura S. A novel estrogen receptor-related protein gamma splice variant lacking a DNA binding domain exon modulates transcriptional activity of a moderate range of nuclear receptors. J Steroid Biochem Mol Biol. 2006 Mar;98(4-5):181-92

Takayanagi S, Tokunaga T, Liu X, Okada H, Matsushima A, Shimohigashi Y. Endocrine disruptor bisphenol A strongly binds to human estrogen-related receptor gamma (ERRgamma) with high constitutive activity. Toxicol Lett. 2006 Dec 1;167(2):95-105

Alaynick WA, Kondo RP, Xie W, He W, Dufour CR, Downes M, Jonker JW, Giles W, Naviaux RK, Giguère V, Evans RM. ERRgamma directs and maintains the transition to oxidative metabolism in the postnatal heart. Cell Metab. 2007 Jul;6(1):13-24

Matsushima A, Kakuta Y, Teramoto T, Koshiba T, Liu X, Okada H, Tokunaga T, Kawabata S, Kimura M, Shimohigashi Y. Structural evidence for endocrine disruptor bisphenol A binding to human nuclear receptor ERR gamma. J Biochem. 2007 Oct;142(4):517-24

Rampersaud E, Damcott CM, Fu M, Shen H, McArdle P, Shi X, Shelton J, Yin J, Chang YP, Ott SH, Zhang L, Zhao Y, Mitchell BD, O'Connell J, Shuldiner AR. Identification of novel candidate genes for type 2 diabetes from a genome-wide association scan in the Old Order Amish: evidence for replication from diabetes-related quantitative traits and from independent populations. Diabetes. 2007 Dec;56(12):3053-62

Vu EH, Kraus RJ, Mertz JE. Phosphorylation-dependent sumoylation of estrogen-related receptor alpha1. Biochemistry. 2007 Aug 28;46(34):9795-804

Yasumoto H, Meng L, Lin T, Zhu Q, Tsai RY. GNL3L inhibits activity of estrogen-related receptor gamma by competing for coactivator binding. J Cell Sci. 2007 Aug 1;120(Pt 15):2532-43

Yu S, Wang X, Ng CF, Chen S, Chan FL. ERRgamma suppresses cell proliferation and tumor growth of androgen-sensitive and androgen-insensitive prostate cancer cells and its implication as a therapeutic target for prostate cancer. Cancer Res. 2007 May 15;67(10):4904-14

Zhou Y, Yau C, Gray JW, Chew K, Dairkee SH, Moore DH, Eppenberger U, Eppenberger-Castori S, Benz CC. Enhanced NF kappa B and AP-1 transcriptional activity associated with antiestrogen resistant breast cancer. BMC Cancer. 2007 Apr 3;7:59

Giguère V. Transcriptional control of energy homeostasis by the estrogen-related receptors. Endocr Rev. 2008 Oct;29(6):677-96

Matsushima A, Teramoto T, Okada H, Liu X, Tokunaga T, Kakuta Y, Shimohigashi Y. ERRgamma tethers strongly bisphenol A and 4-alpha-cumylphenol in an induced-fit manner. Biochem Biophys Res Commun. 2008 Aug 29;373(3):408-13

Riggins RB, Lan JP, Zhu Y, Klimach U, Zwart A, Cavalli LR, Haddad BR, Chen L, Gong T, Xuan J, Ethier SP, Clarke R. ERRgamma mediates tamoxifen resistance in novel models of invasive lobular breast cancer. Cancer Res. 2008 Nov 1;68(21):8908-17

Tremblay AM, Wilson BJ, Yang XJ, Giguère V. Phosphorylation-dependent sumoylation regulates estrogen-related receptor-alpha and -gamma transcriptional activity through a synergy control motif. Mol Endocrinol. 2008 Mar;22(3):570-84

Sangrajrang S, Sato Y, Sakamoto H, Ohnami S, Laird NM, Khuhaprema T, Brennan P, Boffetta P, Yoshida T. Genetic polymorphisms of estrogen metabolizing enzyme and breast cancer risk in Thai women. Int J Cancer. 2009 Aug 15;125(4):837-43

Wang J, Fang F, Huang Z, Wang Y, Wong C. Kaempferol is an estrogen-related receptor alpha and gamma inverse agonist. FEBS Lett. 2009 Feb 18;583(4):643-7

This article should be referenced as such:

Riggins RB. ESRRG (estrogen-related receptor gamma). Atlas Genet Cytogenet Oncol Haematol. 2010; 14(8):753-757.