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Gene Section

Review

ACVR1 (activin A receptor, type I)

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Identity

Other names: ACTRI, ACVR1A, ACVRLK2, ALK2, FOP, SKR1, TSRI

HGNC (Hugo): ACVR1

Location: 2q24.1

Local order: According to UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly, genes flanking ACVR1 in centromere to telomere direction on 2q24.1 are:
- PKP4 (plakophilin-4 isoform b),
- CCDC148 (coiled-coil domain-containing protein 148 isoform 1),
- UPP2 (uridine phosphorylase 2 isoform a),
- **ACVR1 (activin A receptor, type I),**
- ACVR1C (activin A receptor, type IC (ACVR1C),
- CYTIP (cytohesin 1 interacting protein),
- ERMN (ermin, ERM-like protein),
- and GALNT5 (UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 5 (GalNAc-T5).

DNA/RNA

Description

The human ACVR1 gene contains 11 verified exons and spans 139417 bp on chromosome 2q24.1, nucleotide position from 158592958 to 158732374.

Transcription

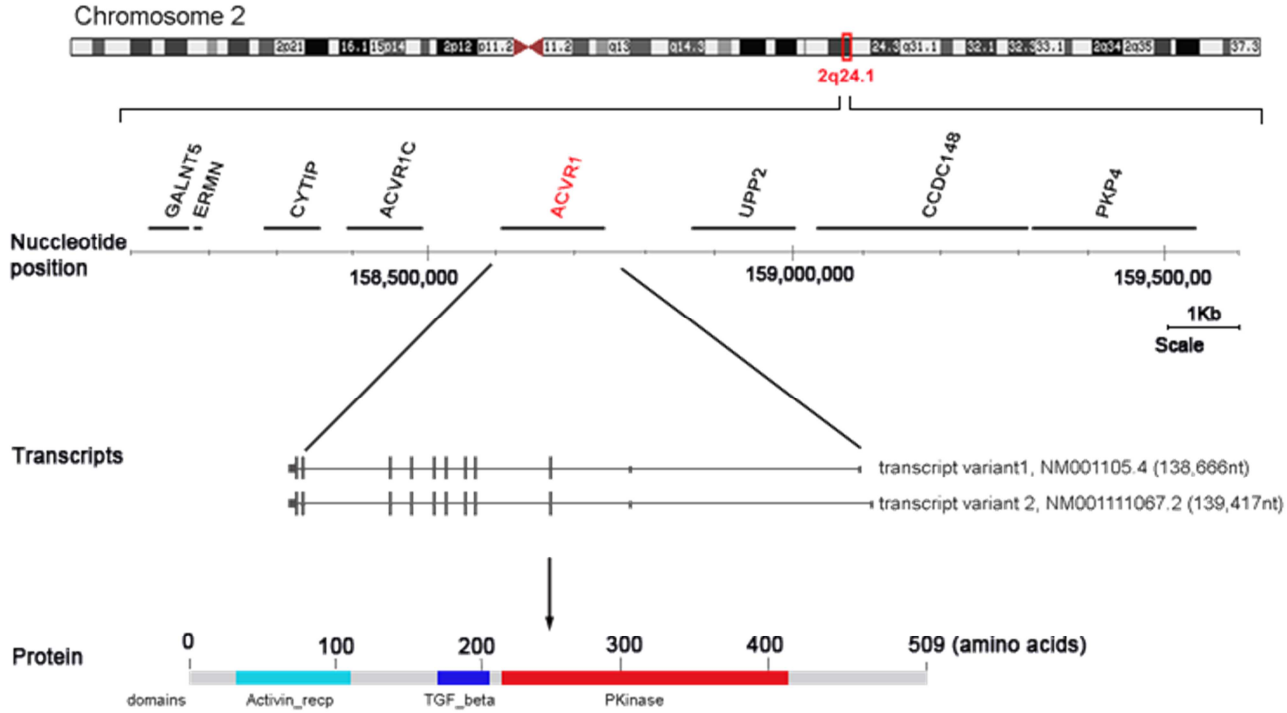
The two curated transcripts from ACVR1, mRNA variants 1 and 2, encode the same protein.
Associated RNA sequences are listed as follow: uc002tzn.3 and uc010fog.2 (UCSC genes); NM_001105.4 and NM_001111067.2 (RefSeq); OTTHUMT00000254927, OTTHUMT00000332969 and OTTHUMT00000402326 (Vega); ENST00000263640, ENST00000409283, ENST00000410057, and ENST00000434821 (Ensembl) and BC033867 (MGC).

Protein

Note
Consensus coding sequence (CDS) unique identifier number: 2206.1_prot.
Protein associated sequences: NP_001096.1 and NP_001104537.1 (RefSeq), OTTHUMP00000162806, OTTHUMP00000204626, and OTTHUMP00000240120 (Vega), ENSP00000263640,ENSP00000387273, ENSP00000387127, and ENSP00000405004 (Ensembl).

Description

The ACVR1 gene encodes a transmembrane protein which is a member of bone morphogenetic protein (BMP) type I receptors included in the TGF-B receptors subfamily.
The protein contains 509 amino acids residues and comprises a single transmembrane and three conserved domains, including:
- Activin-recp domain: a specific hydrophilic Cys-rich ligand-binding domain characterized by 9 amino acid cysteine box, with the consensus CCX{4-5}CN and 7 extracellular residues preceding the cysteine box.



Physical mapping of ACVR1 gene on chromosome 2q24.1. The two curated transcript variants (NM_001105.4 and NM_001111067.2) of ACVR1 encode the same protein of 509 amino acids containing a single transmembrane and three conserved domains (cyan - Activin receptor, blue - TGF-beta and red - Pkinase domains). (UCSC Genome Browser on Human, assembly GRCh37/hg19).

- TGT_beta_GS domain: the GS motif is characterized by the highly conserved GSGSGLP signature in the cytoplasmic juxtamembrane region immediately preceding the protein's kinase domain. This motif is found in the transforming growth factor beta (TGF-beta) type I which regulates cell growth and differentiation.
- Catalytic domain of Protein Kinases: this domain catalyzes the transfer of the gamma-phosphoryl group from ATP to serine/threonine on protein substrates.

Protein kinases regulate many cellular processes including proliferation, division, differentiation, motility, survival, metabolism, cell-cycle progression, cytoskeletal rearrangement, immunity, and neuronal functions.

Expression

This gene is ubiquitously expressed in normal parenchymal cells, endothelial cells, fibroblasts and tumor-derived epithelial cells (http://www.informatics.jax.org/marker/MGI:87911).

By using a polymerase chain reaction (PCR)-based strategy, Dijke et al. (1993) characterized cDNA clones encoding four putative transmembrane protein serine/threonine kinases, named as activin receptor-like kinases (ALK) -1, -2, -3 and -4. The ALKs have approximately 40% sequence identity to activin receptor type II and activin receptor type IIB, transforming growth factor-beta (TGF-beta) type II receptor and Daf-1 in the kinase domains. Since the sequence identities were higher (60-79%) between ALK-1, -2, -3 and -4, the authors suggested that they form a subfamily among the putative receptor serine/threonine kinases.

Further, in this study it was observed that the expression of mRNA in human tissues varied for the different ALKs; ALK-2 (nowadays, ACVR1) and ALK-4 showed ubiquitous tissue expression patterns, whereas the distribution of other members, such as ALK-1 and ALK-3, varied strongly between different tissues with more restricted expression patterns.

Localisation

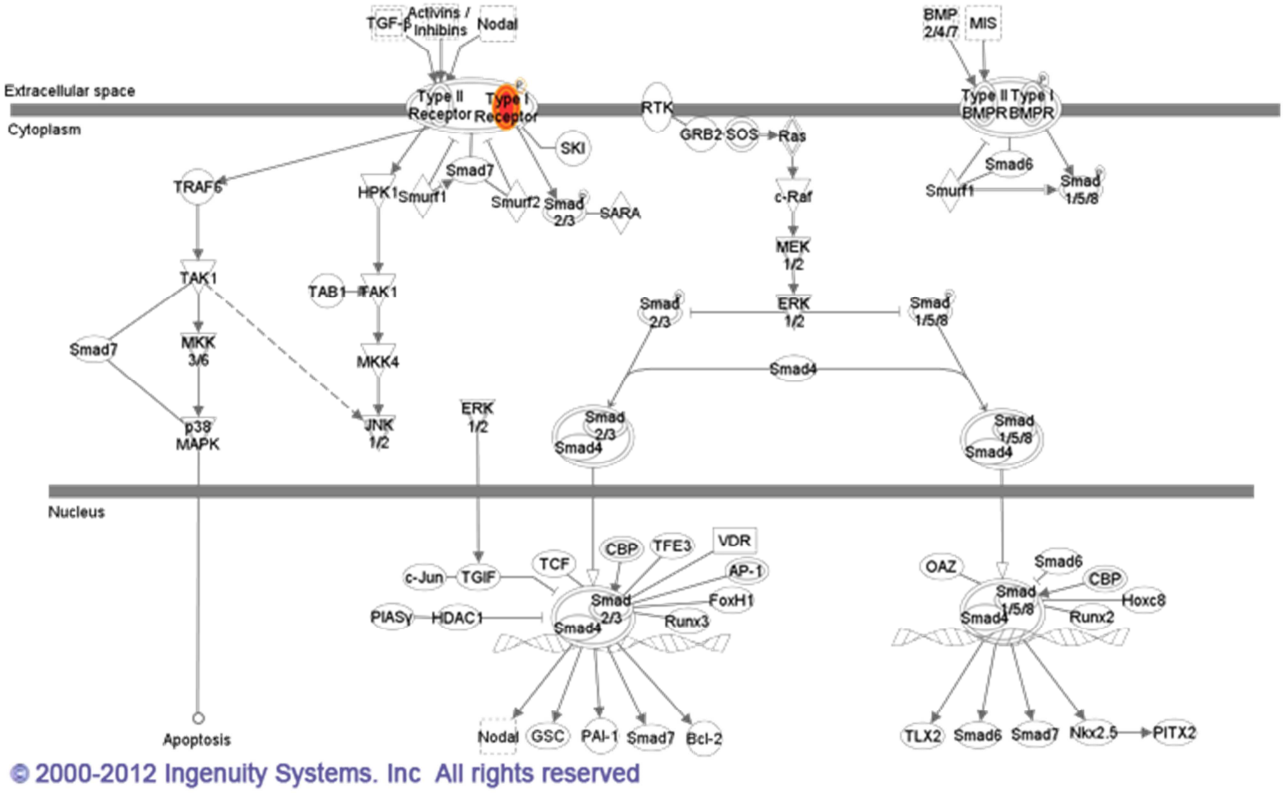
ACVR1 is a single-pass type I membrane protein.

Function

Activins are dimeric factors belonging to the transforming growth factor-b (TGF-beta) family, which also includes the TGF-beta and the bone morphogenetic proteins (BMPs) (Attisano et al., 1996).

At first, the ACVR1 was identified as an activin type I receptor for its ability to bind activin in concert with ActRII or ActRIIB. ACVR 1 is also identified as a BMP type I receptor, and has demonstrated its ability to form a complex with either the BMP-2/7-bound BMPR-II or ACVR2A/ACVR2B (Liu et al., 2002).

The activin A type I receptor is essential for activin signaling, while type II receptors are required for binding ligands.



TGFβ signaling. TGFβ signaling involves a heteromeric complex involving type II (RII) and type I (RI) serine/threonine kinase receptors, resulting in the activation of type I receptor (red). Once activated, type I receptor subsequently phosphorylates the intracellular proteins of at least two interacting signaling cascades: the canonical Smad pathway and the p38 mitogen-activated protein kinase (p38 MAPK) pathway. The networks were generated through the use of IPA (Ingenuity Systems).

On ligand binding, forms a stable complex, resulting in phosphorylation of type I receptors by type II receptors. Once phosphorylated, the complex activates intracellular signaling mediated by the Smad proteins and several non-Smad signaling pathways. Smads interact with Smad4 and translocate to the nucleus where they regulate gene expression (see diagram).

Homology

ACVR1 belongs to the protein kinase superfamily, TKL Ser/Thr protein kinase family, TGFB receptor subfamily. These receptors are composed of a ligand-binding extracellular domain with cysteine-rich region, a transmembrane domain, and a cytoplasmic domain with predicted serine/threonine specificity (HomoloGene).

The ACVR1 gene is conserved in chimpanzee, rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, fruit fly, and mosquito.

Mutations

Note

Human ACVR1 was indicated as a candidate gene to Fibrodysplasia Ossificans Progressiva (FOP) by Shore et al. (2006). This condition is an autosomal dominant disorder of connective tissue characterized by congenital malformations of the great toes and progressive heterotopic ossification of muscles, tendon, ligament, and fascia. In this first study (Shore et al., 2006), the FOP phenotype was linked to markers located in the 2q23-q24 interval; interestingly, an identical heterozygous mutation (617G>A; R206H) in the glycine-serine (GS) activation domain of ACVR1 gene was detected in all affected individuals examined.

Germinal

DNA sequencing of all ACVR1 protein-coding exons and splice junctions identified a heterozygous mutation (the transition 617G>A; R206H) in affected members of five families evaluated by linkage analysis, and in 32 out of 32 sporadic FOP patients with classical clinical features (Shore et al., 2006). Recurrent associations betweem R206H mutation and FOP were subsequently confirmed in unrelated sporadic FOP patients (Lin et al., 2006; Nakajima et al., 2007; Bocciardi et al., 2009; Kaplan et al., 2009; Lee et al., 2009; Sun et al., 2009; Carvalho et al., 2010; Du et al., 2010; Guo et al., 2010; Dandara et al., 2012; Eresen Yazicioglu et al., 2013 ; Morales-Piga et al., 2012).

Additional ACVR1 missense mutations were described in atypical FOP patients. These patients were defined based on the classic features of FOP plus one or more atypical features (FOP plus) and included patients showing variations in one or both of the two classic clinical signs of FOP. The new mutations detected were transitions 587T>C(L196P) (Gregson et al., 2011; Ohte et al., 2011), 982G>A(G328R) (Kaplan et al., 2009), 983G>A(G328E) (Kaplan et al., 2009; Petrie et al., 2009), 1097G>A(G356D) (Fukuda et al., 2008; Furuya et al., 2008; Kaplan et al., 2009) as well transversions 605G>T(R201I) (Pietrie et al., 2009; Barnett et al., 2011), 774G>C(R258S) (Bocciardi et al., 2009; Morales-Piga et al., 2012), 774G>T(R258S) (Rabti et al., 2010; Morales-Piga et al. 2012; Eresen Yazicioglu et al., 2013), 974G>C(G325A) (Whyte at al., 2012) and 1124G>C(R375P) (Kaplan et al., 2009).
Protein structure homology modeling predicts that each of the amino acid substitutions of the TGF-beta-GS motif or the kinase domain of the activin A receptor I in FOP patients are gain-of-function mutations that activates the ACVR1 protein to enhance receptor signaling pathway (Kaplan et al., 2009).

Somatic

Somatic mutations of ACVR1 gene were described in primary ovary and colon cancer as well as in melanoma cell line (Font: COSMIC Project - Catalogue of Somatic Mutations in Cancer, online data available in COSMIC).

Implicated in

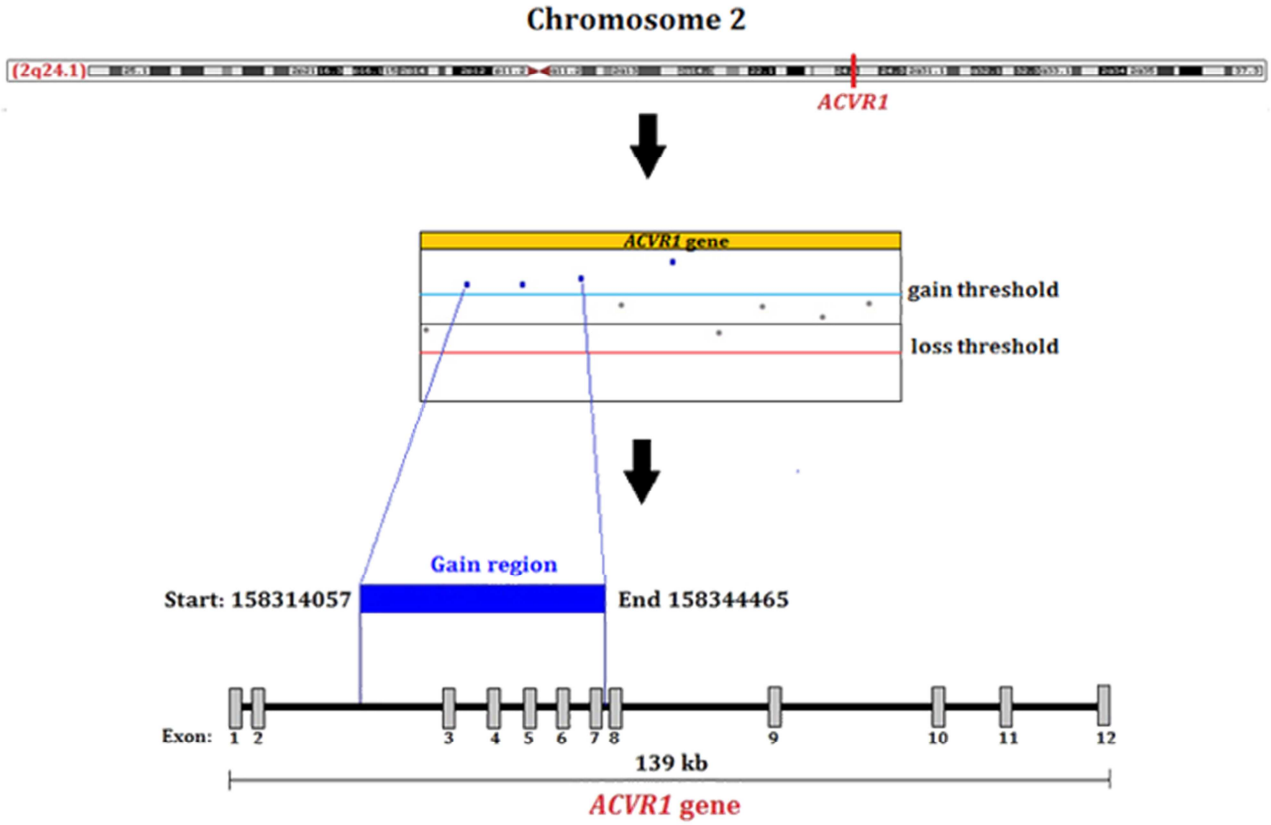
Head and neck cancer

Note

The ACVR1 gene is mapped in a region frequently related in gains detected by chromosomal CGH and array-CGH analysis in several cancer types. Ambrosio et al. (2011) reported that copy number alterations of 2q24.1 were associated with ACVR1 overexpression and with longer overall survival in laryngeal carcinomas.

Prognosis

In the study of Ambrosio et al. (2011), it was described at first that oral cavity, laryngeal and pharyngeal carcinomas presented ACVR1 overexpression in agreement with 2q24 gains and amplifications detected by FISH analysis.
No statistical association was observed between its expression and clinicopathological parameters; however, when laryngeal carcinomas were considered separately, multivariate analysis revealed that ACVR1 overexpression was associated with longer overall survival, suggesting that this gene is a putative prognostic marker in laryngeal squamous cell carcinoma.



Illustrative scheme showing an intragenic region of ACVR1 copy number gains in oropharyngeal carcinoma after array-Comparative Genomic Hybrydization (aCGH) analysis. The gain region comprises a 30Kb segment of ACVR1 gene covered by three consecutive probes (blue dots) (personal communication).

Cytogenetics

Twenty-eight samples of squamous cell carcinoma were evaluated by fluorescence in situ hybridization (FISH) using the probes RP11- 546J1 (2q24) and RP11-21P18 (internal control).

Significant gains at 2q24 were detected in most cases at frequencies varying from 3 to 35% (Ambrosio et al., 2011).

Prostate cancer

Note

In prostate cancer cell lines (Pca cells), it has been proposed that endoglin abrogates TGFβ-mediated increases in cell motility.

Craft et al. (2008) demonstrated that both Smad1 and ACVR1/ALK2 are necessary for endoglin-mediated suppression of cell motility and that constitutively active ACVR1/ALK2 was sufficient to restore a low-motility phenotype in endoglin deficient cells.

Futher, by using RT-qPCR, it was detected that ACVR1/ALK2 was expressed at high levels in PCa cells, and was increased four fold compared to ALK5 expression in both PC3 and PC3-M cells. Subsequently, Romero et al. (2010) provided new evidences for a novel Smad-independent TGF-β effector that regulates cell migration via phosphorylation of endoglin by ACVR1.

According to the authors, upon TGF-β1 stimulation, ALK5 phosphorylates Smad2 and Smad3 with a negative impact on ACVR1/ALK2-Smad1, Smad5 and Smad8 signaling.

Thus, ACVR1/ALK2 phosphorylates endoglin as an alternative substrate; while after BMP7 stimulation, ACVR1/ALK2 phosphorylates endoglin without a requirement for ALK5 participation.

Colon cancer

Note

It has been suggested that Activin receptor 2 (ACVR2) is commonly mutated in microsatellite unstable (MSI) colon cancers, leading to protein loss, signaling disruption, and to a larger tumors. Thus, Jung et al. (2009) examined activin signaling disruption of three components of this pathway in microsatellite stable (MSS) colon cancers, including ACVR1, ACVR2 and pSMAD2 protein expression analysis and loss of heterozigosity assays.

Only a small percentage of MSS colon cancers lost expression of activin signaling members: of a total of 51 tumors analysed, only 2 samples (4%) lost ACVR1 expression. The authors suggested that, loss of ACVR2, ACVR1 and pSMAD2 expression may occur in a subset of MSS tumors, possibly indicating the abrogation of the normal growth suppressive activity of activin signaling. Furthermore, the authors suggested that activin signaling could be inactivated by distinctive mechanisms in MSI and MSS colon cancers.

Ovarian cancer

Note

Herrera et al. (2009) demonstrated that BMP9 acts as a proliferative factor for immortalized ovarian surface epithelial cells and ovarian cancer cell lines, signaling predominantly through an ACVR1/Smad1/Smad4 pathway rather than through ALK1, the major BMP9 receptor in endothelial cells. In addition, it was observed that ovarian cancer cell lines gained autocrine BMP9 signaling and that 25% of epithelial ovarian cancers express BMP9, whereas normal human ovarian surface epithelial specimens do not. These data indicate that BMP9 signaling through ACVR1 may be a novel therapeutic target in ovarian cancer.

Breast cancer

Note

Bone morphogenetic proteins (BMP) are thought to be associated with breast cancer promotion and progression. Takahashi et al. (2008) reported that activin decreased ESR1 mRNA expression, while BMP6 and BMP7 impaired steroid sulfatase expression in MCF-7 cells. It was suggested that the difference of BMP responsiveness could be related to the fact that estradiol decreased the expression levels of BMPR1A, BMPR1B, ACVR2A, and ACVR2B but did not affect ACVR1 and BMPRII. Thus, estradiol rapidly could activate MAPK phosphorylation including extracellular signal-regulated kinase 1/2, p38, and stress-activated protein kinase/c-Jun NH2-terminal kinase pathways and BMP6, BMP7, but activin could preferentially inhibit estradiol-induced p38 phosphorylation. In this study, it was also demonstrated that SB203580 (a selective p38 MAPK inhibitor) effectively suppressed estradiol-induced cell mitosis, suggesting that p38 MAPK plays a key role in estrogen-sensitive breast cancer cell proliferation. The authors suggested that the inhibitory effects of BMP6 and BMP7 on p38 signaling and steroid sulfatase expression could lead to the suppression of estrogen-induced mitosis of breast cancer cells.

Recently, Slattery et al. (2012) evaluated the possible association between genetic variation in BMP-related genes and the risk of breast cancer development among Hispanic (2111 cases, 2597 controls) and non-Hispanic White (NHW) (1481 cases, 1586 controls) women. Interestingly, after adjustment for multiple comparisons, specific SNPs of ACVR1 gene was modestly associated with breast cancer risk according to the ER and PR status of the tumors.

Eigth out of 16 single nucleotide polymorphisms (SNPs) of the ACVR1 gene were associated with ER+PR+ tumors, although the level of association was modest with ORs between 1.19 and 1.33. Further, four and one ACVR1 SNPs were associated with ER+PR- and ER-PR- tumors, respectively. The rare A-T

haplotype of rs4380178 and rs17182166 of this gene was associated with an OR of 1.51 (95% CI 1.14, 2.00). The polymorphisms ACVR1 rs1220134 and ACVR2A rs10497025 were associated with reduced breast cancer risk. However, for the ACVR1 rs17182166 polymorphism, the association was stronger with ER- as well ER-PR- tumors.

Polycystic ovary syndrome

Note

Polycystic ovary syndrome (PCOS) is an endocrinological condition associated with infertility and metabolic abnormalities. Considering that members of the transforming growth factor beta family, anti-Müllerian hormone (AMH) and bone morphogenetic proteins (BMPs) inhibit FSH sensitivity, it has been proposed that TGF-beta signalling may contribute to the aberrant follicle development in women with PCOS. Kevenaar et al. (2009) evaluated seven ACVR1 single nucleotide polymorphisms in 359 PCOS patients and 30 normo-ovulatory as well as in 3543 population-based control women. Although the polymorphisms rs1220134, rs10497189 and rs2033962 and their corresponding haplotypes did not differ between cases and controls, it was detected and associated with AMH levels in PCOS women. The authors suggested that genetic variants of ACVR1 may be associated with AMH levels and follicle number in PCOS women, contributing to abnormal folliculogenesis in PCOS patients.

To be noted

Note

ACVR1 as therapeuthic target in FOP patients. Although the regulation of ACVR1/Alk-2 gene expression is still poorly understood, it was well establisehd that ACVR1 mutations in FOP patients result in constitutive activation of the receptor (Shore and Kaplan, 2011). This is of importance, since inhibition of aberrant ACVR1 signaling represents an attractive therapeutic approach for these patients. Kaplan et al. (2011) and Takahashi et al. (2012) were able to selectively suppress the effect of mutations of ACVR1 using an allele-specific RNA interference (ASP-RNAi) approach to target the mutated ACVR1 mRNA for degradation.

MicroRNAs (miRNAs) also play an essential role in regulating cell differentiation. Recently, it was reported that specific miRNAs are involved in modulating ACVR1/Alk-2 gene expression as suggested by binding sites prediction, reporter gene assays and mutational analysis at the miRNA binding sites. These studies have indicated that mir148b and mir365 were able to down-regulate ACVR1/Alk-2 expression, whereas mir26a showed a positive effect on its mRNA (Mura et al., 2012; Song et al., 2012). These findings suggest that miR-148a is an important mediator of ACVR1, thus offering a new potential target for the development of therapeutic agents against FOP.

Animal Model. Chakkalakal et al. (2012) developed a gene targeting strategy to obtain an Acvr1 knock-in model for FOP (Acvr1(R206H/+)). This unique knock-in mouse model provided novel insight into the genetic regulation of heterotopic ossification and established the first direct in vivo evidence that the R206H mutation of ACVR1 causes FOP. The authors demonstrated that the phenotype of Acvr1(R206H/) chimeric mice resemble the human disease: after radiographic analysis, it was observed that this mutation induced malformed first digits in the hind limbs and postnatal extraskeletal bone formation. Histological analysis of murine lesions showed inflammatory infiltration and apoptosis of skeletal muscle associated with formation of heterotopic bone through an endochondral pathway, as seen in FOP patients.

References

ten Dijke P, Ichijo H, Franzén P, Schulz P, Saras J, Toyoshima H, Heldin CH, Miyazono K. Activin receptor-like kinases: a novel subclass of cell-surface receptors with predicted serine/threonine kinase activity. Oncogene. 1993 Oct;8(10):2879-87

Attisano L, Wrana JL, Montalvo E, Massagué J. Activation of signalling by the activin receptor complex. Mol Cell Biol. 1996 Mar;16(3):1066-73

Liu X, Nagarajan RP, Vale W, Chen Y. Phosphorylation regulation of the interaction between Smad7 and activin type I receptor. FEBS Lett. 2002 May 22;519(1-3):93-8

Lin GT, Chang HW, Liu CS, Huang PJ, Wang HC, Cheng YM. De novo 617G-A nucleotide mutation in the ACVR1 gene in a Taiwanese patient with fibrodysplasia ossificans progressiva. J Hum Genet. 2006;51(12):1083-6

Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Cho TJ, Choi IH, Connor JM, Delai P, Glaser DL, LeMerrer M, Morhart R, Rogers JG, Smith R, Triffitt JT, Urtizberea JA, Zasloff M, Brown MA, Kaplan FS. A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet. 2006 May;38(5):525-7

Craft CS, Romero D, Vary CP, Bergan RC. Endoglin inhibits prostate cancer motility via activation of the ALK2-Smad1 pathway. Oncogene. 2007 Nov 8;26(51):7240-50

Jung BH, Beck SE, Cabral J, Chau E, Cabrera BL, Fiorino A, Smith EJ, Bocanegra M, Carethers JM. Activin type 2 receptor restoration in MSI-H colon cancer suppresses growth and enhances migration with activin. Gastroenterology. 2007 Feb;132(2):633-44

Nakajima M, Haga N, Takikawa K, Manabe N, Nishimura G, Ikegawa S. The ACVR1 617G>A mutation is also recurrent in three Japanese patients with fibrodysplasia ossificans progressiva. J Hum Genet. 2007;52(5):473-5

Fukuda T, Kanomata K, Nojima J, Kokabu S, Akita M, Ikebuchi K, Jimi E, Komori T, Maruki Y, Matsuoka M, Miyazono K, Nakayama K, Nanba A, Tomoda H, Okazaki Y, Ohtake A, Oda H, Owan I, Yoda T, Haga N, Furuya H, Katagiri T. A unique mutation of ALK2, G356D, found in a patient with fibrodysplasia ossificans progressiva is a moderately activated BMP type I receptor. Biochem Biophys Res Commun. 2008 Dec 19;377(3):905-9

Furuya H, Ikezoe K, Wang L, Ohyagi Y, Motomura K, Fujii N, Kira J, Fukumaki Y. A unique case of fibrodysplasia ossificans progressiva with an ACVR1 mutation, G356D, other than the common mutation (R206H). Am J Med Genet A. 2008 Feb 15;146A(4):459-63

Takahashi M, Otsuka F, Miyoshi T, Otani H, Goto J, Yamashita M, Ogura T, Makino H, Doihara H. Bone morphogenetic protein 6 (BMP6) and BMP7 inhibit estrogen-induced proliferation of breast cancer cells by suppressing p38 mitogen-activated protein kinase activation. J Endocrinol. 2008 Dec;199(3):445-55

Bocciardi R, Bordo D, Di Duca M, Di Rocco M, Ravazzolo R. Mutational analysis of the ACVR1 gene in Italian patients affected with fibrodysplasia ossificans progressiva: confirmations and advancements. Eur J Hum Genet. 2009 Mar;17(3):311-8

Herrera B, van Dinther M, Ten Dijke P, Inman GJ. Autocrine bone morphogenetic protein-9 signals through activin receptor-like kinase-2/Smad1/Smad4 to promote ovarian cancer cell proliferation. Cancer Res. 2009 Dec 15;69(24):9254-62

Kaplan FS, Xu M, Seemann P, Connor JM, Glaser DL, Carroll L, Delai P, Fastnacht-Urban E, Forman SJ, Gillessen-Kaesbach G, Hoover-Fong J, Köster B, Pauli RM, Reardon W, Zaidi SA, Zasloff M, Morhart R, Mundlos S, Groppe J, Shore EM. Classic and atypical fibrodysplasia ossificans progressiva (FOP) phenotypes are caused by mutations in the bone morphogenetic protein (BMP) type I receptor ACVR1. Hum Mutat. 2009 Mar;30(3):379-90

Kevenaar ME, Themmen AP, van Kerkwijk AJ, Valkenburg O, Uitterlinden AG, de Jong FH, Laven JS, Visser JA. Variants in the ACVR1 gene are associated with AMH levels in women with polycystic ovary syndrome. Hum Reprod. 2009 Jan;24(1):241-9

Jung B, Gomez J, Chau E, Cabral J, Lee JK, Anselm A, Slowik P, Ream-Robinson D, Messer K, Sporn J, Shin SK, Boland CR, Goel A, Carethers JM. Activin signaling in microsatellite stable colon cancers is disrupted by a combination of genetic and epigenetic mechanisms. PLoS One. 2009 Dec 14;4(12):e8308

Lee DY, Cho TJ, Lee HR, Park MS, Yoo WJ, Chung CY, Choi IH. ACVR1 gene mutation in sporadic Korean patients with fibrodysplasia ossificans progressiva. J Korean Med Sci. 2009 Jun;24(3):433-7

Petrie KA, Lee WH, Bullock AN, Pointon JJ, Smith R, Russell RG, Brown MA, Wordsworth BP, Triffitt JT. Novel mutations in ACVR1 result in atypical features in two fibrodysplasia ossificans progressiva patients. PLoS One. 2009;4(3):e5005

Sun Y, Xia W, Jiang Y, Xing X, Li M, Wang O, Zhang H, Hu Y, Liu H, Meng X, Zhou X. A recurrent mutation c.617G>A in the ACVR1 gene causes fibrodysplasia ossificans progressiva in two Chinese patients. Calcif Tissue Int. 2009 May;84(5):361-5

Carvalho DR, Navarro MM, Martins BJ, Coelho KE, Mello WD, Takata RI, Speck-Martins CE. Mutational screening of ACVR1 gene in Brazilian fibrodysplasia ossificans progressiva patients. Clin Genet. 2010 Feb;77(2):171-6

Du J, Huang LL, Tan YQ, Cheng DH, Li SF, Li LY, Lu GX. Mutation Analysis and Prenatal Exclusion of Fibrodysplasia Ossificans Progressiva in a Chinese Fetus. Genet Test Mol Biomarkers. 2010 Jan 10;

Guo H, Peng D, Xu M, Xue J, Lu L, Xu X, Liu Y, Xiong Z, Pan Q, Hu Z, Xia K. Report of two FOP cases with 617G>A mutation in the ACVR1 gene from Chinese population. Clin Dysmorphol. 2010 Oct;19(4):206-8

Ratbi I, Borcciadi R, Regragui A, Ravazzolo R, Sefiani A. Rarely occurring mutation of ACVR1 gene in Moroccan patient with fibrodysplasia ossificans progressiva. Clin Rheumatol. 2010 Jan;29(1):119-21

Romero D, Terzic A, Conley BA, Craft CS, Jovanovic B, Bergan RC, Vary CP. Endoglin phosphorylation by ALK2 contributes to the regulation of prostate cancer cell migration. Carcinogenesis. 2010 Mar;31(3):359-66

Ambrosio EP, Drigo SA, Bérgamo NA et al.. Recurrent copy number gains of ACVR1 and corresponding transcript overexpression are associated with survival in head and neck squamous cell carcinomas. Histopathology. 2011 Jul;59(1):81-9

Barnett CP, Dugar M, Haan EA. Late-onset variant fibrodysplasia ossificans progressiva leading to misdiagnosis of ankylosing spondylitis. Am J Med Genet A. 2011 Jun;155A(6):1492-5

Gregson CL, Hollingworth P, Williams M, Petrie KA, Bullock AN, Brown MA, Tobias JH, Triffitt JT. A novel ACVR1 mutation in the glycine/serine-rich domain found in the most benign case of a fibrodysplasia ossificans progressiva variant reported to date. Bone. 2011 Mar 1;48(3):654-8

Ohte S, Shin M, Sasanuma H, Yoneyama K, Akita M, Ikebuchi K, Jimi E, Maruki Y, Matsuoka M, Namba A, Tomoda H, Okazaki Y, Ohtake A, Oda H, Owan I, Yoda T, Furuya H, Kamizono J, Kitoh H, Nakashima Y, Susami T, Haga N, Komori T, Katagiri T. A novel mutation of ALK2, L196P, found in the most benign case of fibrodysplasia ossificans progressiva activates BMP-specific intracellular signaling equivalent to a typical mutation, R206H. Biochem Biophys Res Commun. 2011 Apr 1;407(1):213-8

Shore EM, Kaplan FS. Role of altered signal transduction in heterotopic ossification and fibrodysplasia ossificans progressiva. Curr Osteoporos Rep. 2011 Jun;9(2):83-8

Chakkalakal SA, Zhang D, Culbert AL, Convente MR, Caron RJ, Wright AC, Maidment AD, Kaplan FS, Shore EM. An Acvr1 R206H knock-in mouse has fibrodysplasia ossificans progressiva. J Bone Miner Res. 2012 Aug;27(8):1746-56

Dandara C, Scott C, Urban M, Fieggen K, Arendse R, Beighton P. Confirmation of the recurrent ACVR1 617G>A mutation in South Africans with fibrodysplasia ossificans progressiva. S Afr Med J. 2012 May 8;102(7):631-3

Kaplan J, Kaplan FS, Shore EM. Restoration of normal BMP signaling levels and osteogenic differentiation in FOP mesenchymal progenitor cells by mutant allele-specific targeting. Gene Ther. 2012 Jul;19(7):786-90

Morales-Piga A, Bachiller-Corral J, Trujillo-Tiebas MJ, Villaverde-Hueso A, Gamir-Gamir ML, Alonso-Ferreira V, Vázquez-Díaz M, Posada de la Paz M, Ayuso-García C. Fibrodysplasia ossificans progressiva in Spain: epidemiological, clinical, and genetic aspects. Bone. 2012 Oct;51(4):748-55

Mura M, Cappato S, Giacopelli F, Ravazzolo R, Bocciardi R. The role of the 3'UTR region in the regulation of the ACVR1/Alk-2 gene expression. PLoS One. 2012;7(12):e50958

Song H, Wang Q, Wen J, Liu S, Gao X, Cheng J, Zhang D. ACVR1, a Therapeutic Target of Fibrodysplasia Ossificans Progressiva, Is Negatively Regulated by miR-148a. Int J Mol Sci. 2012;13(2):2063-77

Takahashi M, Katagiri T, Furuya H, Hohjoh H. Disease-causing allele-specific silencing against the ALK2 mutants, R206H and G356D, in fibrodysplasia ossificans progressiva. Gene Ther. 2012 Jul;19(7):781-5

Whyte MP, Wenkert D, Demertzis JL, DiCarlo EF, Westenberg E, Mumm S. Fibrodysplasia ossificans progressiva: middle-age onset of heterotopic ossification from a unique missense

mutation (c.974G>C, p.G325A) in ACVR1. J Bone Miner Res. 2012 Mar;27(3):729-37

Eresen Yazıcıoğlu C, Karatosun V, Kızıldağ S, Ozsoylu D, Kavukçu S. ACVR1 gene mutations in four Turkish patients diagnosed as fibrodysplasia ossificans progressiva. Gene. 2013 Feb 25;515(2):444-6

Slattery ML, John EM, Torres-Mejia G, Herrick JS, Giuliano AR, Baumgartner KB, Hines LM, Wolff RK. Genetic variation in bone morphogenetic proteins and breast cancer risk in hispanic and non-hispanic white women: The breast cancer health disparities study. Int J Cancer. 2013 Jun 15;132(12):2928-39

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