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FOXL2

Homo sapiens forkhead box L2

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FOXL2 is a member of the superfamily of Forkhead box transcription factors, whose mutations are responsible for the Blepharophimia/ptosis/epicanthus inversus syndrome in humans[1]. This rare genetic disorder is characterized by odd craniofacial defects, which can be isolated (BPES type I) or associated with premature ovarian failure (BPES type II). The genetic and molecular etiology of this relationship has been found between some BPES type I mutations, which have a mutant mutty suggests that mutations leading to BPES type I or II behave differentially in functional reporter assays[2]. The BPES phenotype is widely explained by the defects observed in the two different FoxL2 knock-out mouse models, through the mutations mention present a mainly unexplained high prematurity rate[3]. Although the mutations affecting the DNA binding domain of FOXL2 are thought to cause most of the ovarian genetic defects, with frequent exceptions, throughout female fertile life in Transgenic[4] a mouse transcriptomic study is a genuinine cell model has suggested the involvement of FOXL2 in the regulation of genes involved in cell proliferation, apoptosis, cell cycle, cell adhesion, extracellular matrix remodeling and differentiation and inflammation/vesicular processes[5]. FOXL2 involvement in the cellular response to oxidative stress has been confirmed and studied more in depth[6]. All of these processes are not mutually exclusive, and FOXL2 may well be involved in all of them, depending on its partners. FOXL2 is a highly post-translationally modified protein, modified by at least phosphorylation, sumoylation as well as SUMOylation, and its target gene specificity may be fine-tuned in response to various signals, depending on the post-translational modifications (PTMs) and interactions with other transcriptional modulators and co-factors[7]. Interestingly, the specific FOXL2 response element (FCREC) slightly divergent from other Forkhead, which is compatible with its unique role in gonad primordium development and maintenance. Although FOXL2 is thought to be a female-specific factor, it is also extremely characteristic. FOXL2 has also been involved in the organogenesis and function of the pituitary, where it is expressed mainly in thyrotrope and gonadotrope cells. Its described targets in the pituitary are the genes encoding the thyrotropin-releasing hormone receptor, the thyroid stimulating hormone β subunit and the α-glycoprotein hormone (human leptin-GRH)[8], of the beta subunit of FSH[9] and of follistatin[10]. To regulate GnRH and FoXL2 transcriptional activity, FOXL2 has been described to interact with the LIM-homeodomain protein LHX3 and the Pituitary homeobox 2 protein, which mode the regulation of the FSH beta-promoter activity[11]. Interestingly, recent studies have suggested a potential role for FOXL2 in the regulation of ovarian genesions cell tumorigenesis and growth[12]. Indeed, a somatic mutation has been found in 97% of adult granulosa cell tumors, and the second study identified a recurring somatic mutation in over 87% of the tumors[13].

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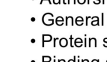
Binding sites

FOXL2 binds with high affinity the FOXL2 Response Element (FCREC), slightly divergent from the Forkhead consensus binding site (FCRE). FOXL2 also binds the Forkhead Response Element (FCRE) and FOXL2 binds to a high-affinity binding site consensus for FoXL2 was recently identified as AATTCTGAACGCCT. The FCREC has been shown to be enriched in the promoters of genes involved in cell cycle, cell adhesion, and extracellular matrix remodeling. Interestingly, changing from a the FCREC core sequence to a more conventional Forkhead binding site (FCRE) albeit with a lower affinity, indeed, a mutation of CG to TT greatly diminishes FOXL2 transcriptional activity on a reporter construct[14]. Finally, FOXL2 has been shown to antagonize the promoter of the DAX1 gene using the consensus FCRE (AACAACTA), located in the gonadotropin [ref Dax1 GEP], and the promoter of the P17 gene using the sequence 5-ATCAATGTA-3[15], which promote stimulation with both consensus. *Continued next page*



Binding profile from Pazar

Species	Homo sapiens
TF species	Homo sapiens
TF gene	FOXL2 (ENSG00000183054)
Evidence	Gel shift (ENSG00000183054)

This data is sourced from Pazar, a public repository for transcription factor binding site sequence information. http://www.pazar.info/

http://www.clarep.lycos.com/frontiersrare/pfm48.html

Protein structure of FOXL2

Although the particular ID on picture of the Forkhead Domain (PDB ID 1VTN) is not available, the protein sequence homology and biochemical model results suggests the structure of its DNA binding domain is similar to the FOXO4 DNA binding domain (PDB ID 1 Nedrow-[16]). As the C-terminus of the FOXL2 protein, FOXL2 possesses two NLS sequences (one adjacent to the DNA binding domain and a second near the nuclear localization[17]) These proteins are more divergent outside of their DNA-binding domain, though a few motifs are conserved, such as a tryptophan and a sulphurous cysteine residue[18]. The molecular conformation of structure, if only, of these ancient regions is still widely unknown. Although the Forkhead domain of FOXL2 is a monomer in solution, and binds to DNA as a monomer, it is thought that it binds as a dimer to DNA sites and form[19]. The role and structure of FOXL2 outside of the Forkhead domain is still unknown (primary sequence, and secondary structure, and tertiary structure of FOXL2 response to BPES syndrome[20]. Phosphorylation of FOXL2 at Ser 33 by JNK kinase induces its ubiquitination and SUMOylation and increases cellular aggregation of the protein, as well as perturbation of protein activity in COS-1 cells[21].

Classification

Group	Winged-Helix / Fork-Head
Family	Forkhead Domain Family
Subfamily	FOXL2

Synonyms

Entrez Gene	668
Protein	NP_055560 (NM_014745)
Unigene	Hs.525704
Locus	3q23
Genbank	AF127936, AF230930, U41235
Symbols	FOXL2, FKHL, PFKH, JBSRF, JBSRF1

About

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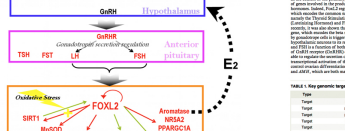

FIGURE 1: **FOXL2, a master regulator of the hypothalamus-pituitary-ovarian axis in females.** Red lanceolate indicate genes activated by FOXL2 (including itself). Green lanceolate indicate genes repressed by FOXL2. Black arrows or blunts (the green arrow from GRH to GRHR) indicate the hetero-regulatory loop that FOXL2 exerts on itself through activation of SIRT1. Black lanceolate indicate regulation of no regulation. The three circular compartment for reproduction females are shown in dotted. The hypothalamus, the anterior pituitary and the ovary. Hypothalamic secretion of GnRH (Gonadotropin Releasing Hormone) stimulates the secretion of LH and FSH by the anterior pituitary. Regulation of GnRH expression and secretion through 1 of an FFR-secretion, and the ovary, the female reproductive organ, which, in turn, regulates GnRH secretion and activity by the hypothalamus as well as the secretion of LH and FSH by the anterior pituitary. Regulation of the secretion of LH and FSH by the anterior pituitary, which, in turn, regulates the ovary. Ovarian secretion of steroid hormones (activating feedback loop) has been shown to enhance FOXL2 transcriptional capacity on stress response genes in granulosa ovarian cells. This scheme recapitulates FOXL2 key role in the hypothalamic-pituitary-ovarian axis. Abbreviations: Aromatase, Cytochrome P450 family 19 subfamily A polypeptide 1; CH25H, Cholesterol 25-hydroxylase; Chaperon, Steroidogenic Acute Regulatory Protein; DAX1, Dosage Sensitive Sex Reversal, Adrenal Hypoplasia Critical Region, on chromosome X, gene DAX1; GRH, Gonadotropin Releasing Hormone; GRHRS, Gonadotropin Releasing Hormone Receptor; IER3, Immediate Early Response 3; LH, Luteinizing Hormone; NR5A2, Nuclear Receptor Subfamily 5 Group A Member 2; PPARGC1A, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 Alpha; RnSOD, Mitochondrial Manganese Superoxide Dismutase; SOX9, Sex-determining Region Y-box 9; STAR, Steroidogenic Acute Regulatory Protein; TSH, Thyroid Stimulating Hormone; WNT2, Wnt/Wingless-type MMTV Integration Site Family Member 2.

Covalent modifications

FOXL2 is a phosphoprotein, as it contains a rich pattern of post-translational modifications (PTM) conserved both in human genomic-like KEN cells and in mice whole ovarian through 20 Western Blot experiments[22]. Indeed, in KEN cells, FOXL2 is mainly found as a 40 kDa band, but also as a 60 kDa band. Although FOXL2 PTM patterns are conserved in two distinct tests of modification, a basic poorly modified main and a more acidic hypermodified form, suggested by 2D electrophoresis, the exact nature of these modifications remains unknown. Some modification patterns are mutually exclusive, suggesting that co-existing PTM isoforms are likely to be functionally non-equivalent[23]. FOXL2 is known to be modified by phosphorylation, acetylation and SUMOylation[24]. SIRT1 activation induces deacetylation and ubiquitination of FOXL2 PTM and increases its cellular aggregation and activation of oxidative stress in KEN-transfected cells. The exact position of the residues actually modified in FOXL2 protein sequence have not yet been mapped this. Phosphorylation of FOXL2 at Ser 33 by JNK kinase induces its ubiquitination and induced PEP, one, after potentially modifiable residues[25]. *(continued on next)*

Targets

In the promoter of the pituitary, Foxl 2 has been shown to regulate the expression of genes involved in the production and the regulation of the pituitary hormones. Indeed, Foxl 2 regulates the transcription of the α(glycoh)[26] gene, which encodes the common subunit of all three pituitary hormones, namely the Thyroid Stimulating Hormone, TSH, and the gonadotropins LH and FSH, which are specific to the anterior pituitary. In the case of the α(glycoh) promoter, it was also shown that Foxl 2 can activate the transcription from the FST gene, which modulates the beta subunit of FSH[27]. The secretion of gonadotropins is regulated by the hypothalamic secretion of GnRH (Gonadotropin Releasing Hormone). Hypothalamic secretion is in response to gonadotropins, and the secretion of GnRH and FSH is a function of both the amounts of GnRH secreted and of the amount of GnRH receptors on the pituitary gonadotrope cells. Foxl 2 is also shown to be able to regulate the transcription of the GnRH receptor gene, through the transcriptional activation of the GnRH Gene[28]. In the ovary, Foxl 2 seems to regulate the expression of genes involved in steroidogenesis, such as the CYP19 and AMH, which are both under promoting factors[29]. *(continued on next)*

Interactions

Foxl 2 has been shown to be able to form heterodimers with the Ttx1 TOPDom family member[30]. Foxl 2 should remain to be found in forms, higher complexes with AP2 on a complex regulatory DNA, Ttx1, the GnRH Activating Sequence (GRAS), to promote transcription from the GnRH gene[31]. The Elongin subunit of Foxl 2 was proven to interact with Ttx1 in a yeast two-hybrid assay, and in a mammalian cell co-immunoprecipitation assay, it was also shown that Foxl 2 can activate the transcription from the Ttx1 gene, which models the beta subunit of FSH[32]. The secretion of gonadotropins is regulated by the hypothalamic secretion of GnRH (Gonadotropin Releasing Hormone). Hypothalamic secretion is in response to gonadotropins, and the secretion of GnRH and FSH is a function of both the amounts of GnRH secreted and of the amount of GnRH receptors on the pituitary gonadotrope cells. Foxl 2 is also shown to be able to regulate the transcription of the GnRH Gene[33]. In the ovary, Foxl 2 seems to regulate the expression of genes involved in steroidogenesis, such as the CYP19 and AMH, which are both under promoting factors[34]. *(continued on next)*

TABLE 1. Key genomic targets and regulators of FOXL2

Displaying the first 24 of 45 records. See more on site »

Type	Key genomic target	Gene ID	TF complex	Reference	Source
Target	Human AMH [1]	EG 268	(not provided)	17738616	Author (UK)
Target	Human AR [2]	EG 367	(not provided)	17738641	Author (UK)
Target	Human CYP19 [3]	EG 1588	(not provided)	18081931	Author (UK)
Target	Mouse Amh [4]	EG 11766	(not provided)	15721305	Author (UK)
Target	Mouse Amh [5]	EG 11766	(not provided)	18081931	Author (UK)
Target	Human BCL2A1 [6]	EG 597	(not provided)	17738641	Author (UK)
Target	Human BCL2A1 [7]	EG 597	(not provided)	17738641	Author (UK)
Target	Human CGA [8]	EG 1081	(not provided)	17738641	Author (UK)
Target	Human CGB [9]	EG 1084	(not provided)	17738641	Author (UK)
Target	Human CXCL12 [10]	EG 6345	(not provided)	17738641	Author (UK)
Target	Human CYP19 [11]	EG 1588	(not provided)	17738641	Author (UK)
Target	Human CYP19 [12]	EG 1588	(not provided)	17738641	Author (UK)
Target	Human EGR3 [13]	EG 1959	(not provided)	17738641	Author (UK)
Target	Human EGR3 [14]	EG 1959	(not provided)	17738641	Author (UK)
Target	Human EYP1A1 [15]	EG 1543	(not provided)	18081931	Author (UK)
Target	Human FSHB [16]	EG 2673	(not provided)	17738641	Author (UK)
Target	Mouse Fst [17]	EG 14313	(not provided)	18081931	Author (UK)
Target	Rat Steroi [18]	EG 114508	(not provided)	18064703	Author (UK)
Target	Human FSHB [19]	EG 2673	(not provided)	18182839	Author (UK)
Target	Human FSHB [20]	EG 2673	(not provided)	18182839	Author (UK)
Target	Human FSHB [21]	EG 2673	(not provided)	18324958	Author (UK)
Target	Human FSHB [22]	EG 2673	(not provided)	18324958	Author (UK)

TABLE 2. Interactors of FOXL2

Interactor	Nature of interaction (from author)	Experimental validations	References	Source
Mouse Dax1	Not specified	Two hybrid	18102501	Author (EMBL)
Human FOXL2	Unknown	Co-purification	20081665	Author (EMBL)
Mouse Aph	Physical with another TF complex binds DNA	Two hybrid	12642860	Author (EMBL)
Human LATS1	Physical: enzyme modification: phosphorylation	Co-purification	20403531	Author (EMBL)
Human LHX3	Unknown	Two hybrid	15180847	Author (EMBL)
Human PIAS3	Physical with another TF	17183647	Author (EMBL)
Human PIAS1	Physical: enzyme modification: sumoylation	Co-purification	20081665	Author (EMBL)
Human PIAS4	Physical: enzyme modification: sumoylation	Co-purification	20081665	Author (EMBL)
Human SUMO1	Physical: enzyme modification: sumoylation	Co-purification	18182501	Author (EMBL)
Human SUMO3	Physical with another TF complex binds DNA	Co-purification	18182501	Author (EMBL)
Human UBE2I	Physical with another TF complex binds DNA	Two hybrid	12642860	Author (EMBL)
Human UBE2I	Physical: enzyme modification: sumoylation	Co-purification	20081665	Author (EMBL)

Genetics

Mutations are responsible for the Blepharophimia/ Ptosis/ Epicanthus Inversus Syndrome (BPES; MIM 110100). This genetic disorder is characterized by the fact that 1.9000 female is characterized by eyelid malformations, including small palpebral fissures, epicanthus inversus, eyelids ptosis and a flat nasal bridge. Malformations can be associated with premature ovarian failure (POF). Although the mutations affecting the DNA binding domain of FOXL2 are thought to cause most genetic defects[35], BPES may be complicated in ovarian disorders. Indeed, in a case of extreme BPES in a large consanguineous Indian family has been reported, the mutation affecting the DNA binding domain of FOXL2 is associated with premature ovarian failure[36]. Although FOXL2 mutations include expansions of polyalanine domain (20% of cases), nonsense mutations (mostly in the forkhead domain) and missense mutations, the genotype-phenotype correlation remains very obscure (diagnosis problem). No clear genotype-phenotype correlation can be established to explain how mutations can lead to BPES type I or II. Although the mutations affecting the DNA binding domain of FOXL2 are thought to cause most genetic defects, exceptions are frequent. Indeed, a study focused on reporter systems in comparison to FOXL2 mutations, in a phenotypic-genotype manner[37]. *(continued on next)*

Ontologies

Displaying 23 of 246 key TF-to-MeSH associations. Numbers indicate Fisher's exact test p-value. See more on site »

Blepharophimia 0.0 × 10^-10 Eye Abnormalities 1.1 × 10^-10 Eyelid Diseases 1.1 × 10^-10 Blepharoptosis 1.1 × 10^-10
Congenital Abnormalities 1.1 × 10^-10 Eye Manifestations, Ocular 1.1 × 10^-10 Eye Diseases 1.1 × 10^-10 Syndrome 1.1 × 10^-10
Diseases 1.1 × 10^-10 Congenital, Hereditary, and Neonatal Diseases and Abnormalities 1.1 × 10^-10
Ovarian Diseases 1.1 × 10^-10 Adnexal Diseases 1.1 × 10^-10 Gonadal Disorders 1.1 × 10^-10 Genital Diseases, Female 1.1 × 10^-10
Endocrine System Diseases 1.1 × 10^-10 Female Urogenital Diseases 1.1 × 10^-10 Pathologic Processes 1.1 × 10^-10
Female Urogenital Diseases and Pregnancy Complications 1.1 × 10^-10 Neoplasms 1.1 × 10^-10 Neoplasms, Germ Cell and Embryonal 1.1 × 10^-10
Granulosa Cell Tumor 1.1 × 10^-10 Adenomas, Multiple 4.4 × 10^-7 Sex Cord-Gonadal Stromal Tumors 1.1 × 10^-10 Neoplasms, Gonadal Tissue 1.0 × 10^-10

References

1 Prud'Ah' [1] et al. The positive forkhead transcription factor FOXL2 is involved in steroidogenesis/aromatase expression in human granulosa cells. Biochem Biophys Res Commun
2 Benayoun, J et al. The blepharophimia/ptosis/epicanthus inversus syndrome FOXL2 mutations are dominant negative and affect cell proliferation. Am J Hum Genet
3 Uhlenhaut, H et al. Female ovarian dysgenesis and oocyte depletion in mice lacking the forkhead transcription factor Foxl2 in granulosa cells. Mol Endocrinol
4 Kuroki, S et al. The mouse forkhead transcription factor Foxl2 is required for granulosa cell proliferation and suppresses ectopic nanog and Sox2 expression in adult ovaries. Biol Reprod
5 Ruiz-Llorente, J et al. Evolution and expression of FOXL2. J Mol Evol
6 Ellsworth, B et al. Transcriptome profiling of FOXL2-regulated genes in fetal mouse ovaries and functional analysis of a conserved intergenic region. Endocrinology
7 Benayoun, B et al. Functional polymorphism in the regulatory domain of FOXL2 leads to post-translational modification and protein aggregation and impairs. Hum Mol Genet 19(2)
8 Ellsworth, B et al. Differential aggregation and functional impairment of polyalanine expansion mutations of human FOXL2 transcription factor identified in. Hum Mol Genet 17(1)
9 Ellsworth, B et al. Loss of function and gain of function in frontonasal dysplasia mutations of the FOXL2 polyalanine tract. Pediatrics 118(1)
10 Pisarska, M et al. Forkhead box L2 is a repressor of the proximal promoter of the human follistatin gene. Biochem Biophys Res Commun
11 Ellsworth, B et al. The gonadotropin releasing hormone receptor 1 promoter is regulated by the LIM-homeodomain protein LHX3 and the forkhead box L2 protein. Mol Cell Endocrinol
12 Pisarska, M et al. FOXL2 is a repressor of the human gonadotropin-releasing hormone receptor 1 promoter. Biol Reprod
13 Shelley, D et al. Transcriptional control of human follicle stimulating hormone-beta gene expression. Endocr Rev
14 Pisarska, M et al. Forkhead transcriptional factors: control and function in ovarian granulosa cell tumors. Int J Gynecol Pathol
15 Pisarska, M et al. Forkhead box L2 binding sites and FOXL2-mediated transcriptional activity of the human DAX1 promoter. Endocrinology
16 Pisarska, M et al. Forkhead transcriptional factors: FOXL2 and FOXO1 regulation of the human P17 promoter. Biochim Biophys Acta
17 Cocquet, J et al. Gene structure and transcriptional orthology of mouse Foxl2 and human FOXL2 genes. Biochim Biophys Acta (Gene Struct Expr)
18 Crisponi, L et al. Female-specific expression of a conserved cis-acting element in the FOXL2 gene suggests the sex-specific hormonal milieu of ovarian cell lineages. Hum Mol Genet 10(1)
19 Cocquet, J et al. Transcriptional factor FOXL2 interacts with DFFRX and induces apoptosis. Biochem Biophys Res Commun
20 Cocquet, J et al. Expression of a novel paralogous mammalian FOXL2 (the first evidence for a conserved form of the forkhead domain). Genomics
21 Rayner, J et al. FoxL2 modulates cell growth and survival in response to oxidative stress. Cell Cycle
22 Garcia, E et al. Sex-specific DNA deletion in the FOXL2 gene in a patient with premature ovarian failure and blepharophimia-ptosis-epicanthus inversus syndrome. Clin Genet
23 Leroux, F et al. Functional evidence implicating FOXL2 in human ovarian cancer and identification of an FOXL2 allele in a case of BPES. J Med Genet
24 Pailhoux, E et al. A 1.1-kb deletion triggers transcriptionally silencing of the FOXL2 gene in cattle. Biol Reprod
25 Bruno, J et al. Novel mutations in the forkhead transcription factor FOXL2 in blepharophimia syndrome and ovarian dysgenesis. J Med Genet 43(6)
26 Crisponi, L et al. Genetic and functional dissection of the bipedal enhancer of the human alpha-glycoprotein hormone gene. Genes Dev 15(5)
27 Ellsworth, B et al. Transcriptional control of follicle-stimulating hormone-beta: cooperative interaction between the homeodomain protein Pitx2 and the forkhead protein Foxl2. Mol Cell Endocrinol 179(1-2)
28 Ellsworth, B et al. Transcriptional control of the gonadotropin-releasing hormone receptor 1 promoter. Endocrinology
29 Ellsworth, B et al. Transcriptional control of the human follicle-stimulating hormone-beta gene. Endocr Rev
30 Ellsworth, B et al. Transcriptional control of the human follicle-stimulating hormone-beta gene. Endocr Rev
31 Ellsworth, B et al. Transcriptional control of the gonadotropin-releasing hormone receptor 1 promoter. Endocrinology
32 Ellsworth, B et al. Transcriptional control of the human follicle-stimulating hormone-beta gene. Endocr Rev
33 Ellsworth, B et al. Transcriptional control of the gonadotropin-releasing hormone receptor 1 promoter. Endocrinology
34 Pisarska, M et al. Forkhead box L2 binding sites and FOXL2-mediated transcriptional activity of the human DAX1 promoter. Endocrinology
35 Pisarska, M et al. Forkhead transcriptional factors: FOXL2 and FOXO1 regulation of the human P17 promoter. Biochim Biophys Acta
36 Cocquet, J et al. Gene structure and transcriptional orthology of mouse Foxl2 and human FOXL2 genes. Biochim Biophys Acta (Gene Struct Expr)
37 Crisponi, L et al. Genetic and functional dissection of the bipedal enhancer of the human alpha-glycoprotein hormone gene. Genes Dev 15(5)

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