SnapShot: Forkhead Transcription Factors I

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Human Gene Symbol (Localization)	Potentially Regulated by	Potentially Regulates	Cellular and Developmental Roles	Mutant Mouse Phenotype	Role in Cancer/ Human Disease
FOXA1 (14q21.1)	FOXA2, FOXA3, RXRA, PMA, MSA, Ie86, INS1, NR0B2, DHT, POU5F1, FOXD3, GR, PRKACA, LRP5, ER	GCG, TCF1, TFF1, INS1, PRDM15, XBP1, PISD, COL18A1, NRIP1, ATP5J, DSCAM, NDUFV3, SOD1, LIN52, PFKFB1	Epithelial cell differentiation; branching morphogenesis; development of lung, liver, prostate, and pancreas.	Severe growth retardation, hypoglycemia, electrolyte imbalance. Die soon after birth.	Expressed in luminal type A breast cancer; expressed in human prostate carcinomas.
FOXA2 (20p11.21)	SHH, GLI1, FOXA2, LPS, PMA, NR1H4, IL13, RNF111, IFT88, NR4A3, DYNC2LI1, GATA6, SFTPC, INS1, 1-alpha, vitamin D3	FOXA1, FOXA2, Pepck, ABCB4, ALDOB, TCF1, SHH, HNF4A, SLC10A1, INS1, WNT7B, PDX1, DLK1, PCK1, FOXA3	Epithelial cell differentiation; branching morphogenesis; development of forebrain, lung, liver, prostate, and pancreas.	Node and notochord missing. Foregut morphogenesis defective. Embryos die by E10. Conditional β cell knockout causes hypoglycemia.	Expressed in neuroendocrine small cell carcinomas.
FOXA3 (19q13.32)	TCF1, FOXA2, TCF2, PMA, Ie86, AGN194204, fenofibrate, pirinixic acid, CLOCK, NR0B2, GR, PRKACA	Pepck, FOXA1, FOXA2, TF, TAT, CYP2C8, CYP2C9, CYP2C19, CYP3A4, SLC2A2, TCF1, NR3C1	Cell glucose homeostasis and response to starvation.	Expression of several liver-specific genes is reduced.	
FOXB1 (15q22.2)	CTNNB1		Development of neural tube, mammillary body nerve process.	Variable phenotype with neural tube defects, growth retardation, and reduced lactation in surviving females.	
FOXC1 (6p25.3)	ER, valproic acid, trichostatin A, LY294002, camptothecin, tert-butyl-hydroquinone, TGFB1, Erk, EGF, FLNA	LFNG, EFNB2, DLL1, MESP1, NOTCH1, HES5, MESP2, TCF15, luciferase reporter gene, TBX1, glycosaminoglycan	Germ cell migration; mesenchymal cell differentiation; development of kidney, skeleton, brain, ureter, heart, lacrimal gland, ovarian follicle, and tooth.	Hydrocephalus, ocular, skeletal, renal, and cardiovascular abnormalities. Die shortly after birth. Abnormalities in anterior segment in heterozygotes.	Functions as tumor suppressor. Associated with Axenfeld-Rieger syndrome and glaucoma iris hypoplasia.
FOXC2 (16q24.1)	LY294002, TNF, CITED2, Ins, IKBKG, IGF2, INSR, CHUK, NFKBIA, PD98059, wortmannin, SHH, ER, PDGF-BB, PMA	FABP4, CEBPA, PRKAR1A, PLIN, ADIPOQ, LFNG, UCP1, PPARGC1A, EFNB2, DLL1, MESP1, PPARA, NOTCH1, SLC2A4, HES5	Cell proliferation; development of kidney, heart, ureter, and skeleton.	Craniofacial and vertebral column defects. Most die perinatally or before. Lymph node hyperplasia and distichiasis in heterozygotes.	Associated with aggressive basal-like breast cancers and Lymphoedema-Distichiasis.
FOXD1 (5q12-q13)	ETS1, TERT, Small/Large T-antigen, HRAS, HOXA11, HOXD11, SHH, SMO, SMAD6	PGF, EPHB1, FOXJ1, CSNK1A1, ZIC2, ISL1, PRKAR1A, Nfat	Axon guidance; kidney development.	Kidney defects. Die within 1 day after birth.	
FOXD2 (1p33)	SMO	PRKAR1A	Modulates cAMP sensitivity; kidney development.	40% have kidney hypoplasia and hydroureter.	
FOXD3 (1p31.3)	retinoic acid, IL3, PAX3	FOXA1, FOXA2	Trophectodermal cell differentiation; placental development.	Epiblast size is reduced and primitive streak does not form.	
FOXD4 (9p24.3)					
FOXD5 (2q13)					
FOXD6 (9q21.11)					
FOXE1 (9q22.33)	TSH, TNF, IFNG, forskolin, IGF1, TG, A23187, Insulin, PMA, CREB1, decitabine, DHT	TPO, SLC5A5, thyroid hormone	Development of thyroid gland and palate.	Cleft palate, partially developed or absent thyroid gland. Die within 2 days after birth.	Associated with thyroid agenesis, cleft palate, choanal atresia, polyhydramnios, and spiky hair.
FOXE2 (22q13-qter)					
FOXE3 (1p33)	BMP7, Fgfr, MAB21L1	CDKN1C, DNASE2B, PROX1, PDGFRA	Epithelial cell proliferation; eye development.	Lens, iris, and corneal epithelium are connected. Lens size is reduced.	Associated with ocular anterior segment anomalies and cataracts.
FOXF1 (16q24.1)	BMP4, 5-fluorouracil, FOXM1, FGF10, SMO, FGF7, PTCH1, NFkB, TNF, etoposide, SHH	VCAM1, ITGA5, HGF, Collagen Type IV, PDGFRA	Epithelial cell proliferation; development of colon, gall bladder, lung, mesenchyme, and smooth muscle.	Defects in mesodermal differentiation, yolk sac vasculogenesis, chorioallantoic fusion, and amnion expansion. Die around E9. Heterozygotes have alveolarization defects.	Liver metastasis of colorectal cancer associated with low FOXF1 mRNA in stromal fibroblasts.
FOXF2 (6p25.3)	IKBKB, IKBKG, CHUK, TITF1, NFKBIA, TNF, SMO	WNT5A, Col I, Collagen Type IV, CTNNB1	Epithelial cell proliferation; colon development.	Cleft palate, abnormal tongue. Mice die shortly after birth.	Liver metastasis of colorectal cancer associated with low FOXF2 mRNA in stromal fibroblasts.
FOXG1 (14q12)	SH2B1, Insulin, Fsh, NGFB, oleic acid, AKT1, glutamic acid, INS, IGF1, OTX1, OTX2, GBX2, CHRD, NOG, LPS	BCL2L11, CDKN1A, CDKN1B, FASLG, CDKN2B, Cdkn2b, SERPINE1, FOXH1, SMAD2, RB	Neuronal differentiation; cell cycle progression; forebrain development.	Cerebral hemispheres are reduced in size. Die shortly after birth.	Overexpressed in hepatoblastoma.
FOXH1 (8q24.3)	SMAD4, FOXG1B, DHT, TGFB1, SIM1, ARNT2	AR, Mix.2, FOXA2	Development of axial and prechordal mesoderm, definitive and visceral endoderm, notochord, and primitive streak.	Variable pattern defects: either axial defects, no anterior structures, or no structures from embryo proper.	FoxH1 corepresses androgen receptor, which plays a role in prostate cancer.
FOXI1 (5q35.1)		SLC26A4, SLC4A9, SLC4A1, ATP6V1B1, SLC12A3	Inner ear development.	Defects in vestibulum and cochlea. Deaf with impared balance. Overt acidosis. 50% die perinatally.	

See online version for legend and references.
Forkhead Transcription Factors II will appear in the October 5 issue of *Cell*.

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Forkhead transcription factors were first discovered more than 10 years ago in *Drosophila* and are characterized by a shared 100 amino acid DNA-binding motif, termed the "winged helix" or "forkhead" domain. Conserved forkhead domains have been identified in eukaryotic organisms from yeast to humans. The human genome contains more than 40 *FOX* genes. The forkhead transcription factors have been shown to play diverse roles in development, metabolism, immunology, cancer, and cell-cycle control.

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