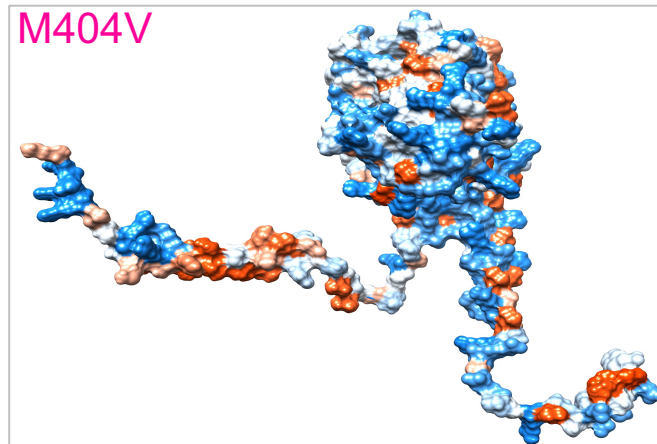
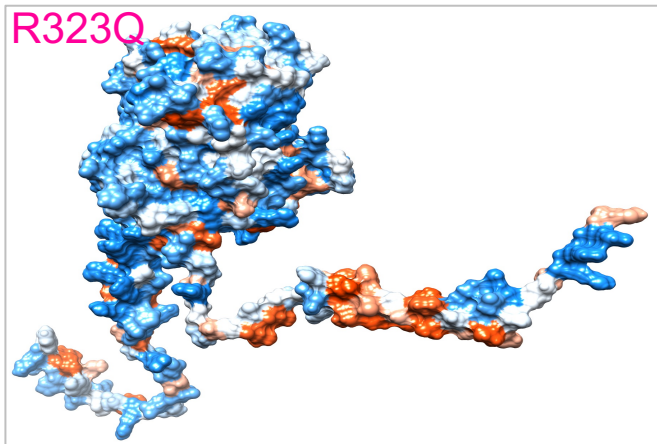
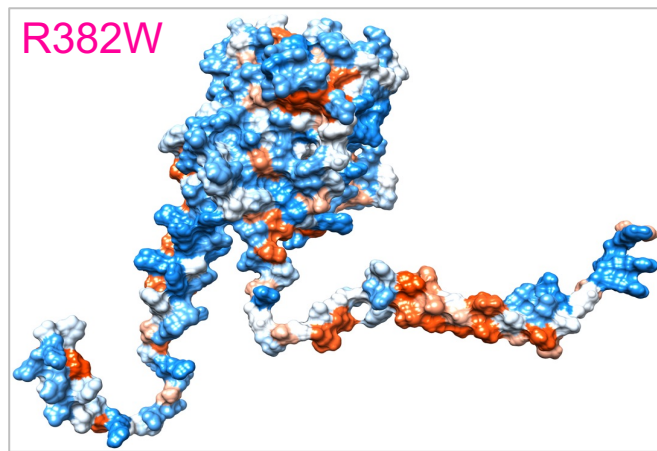
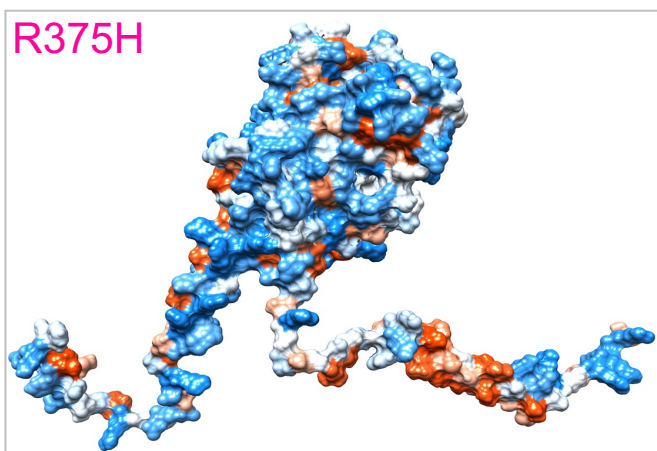
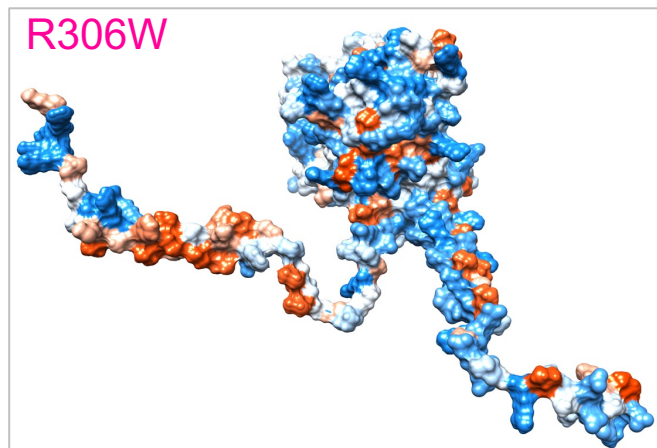
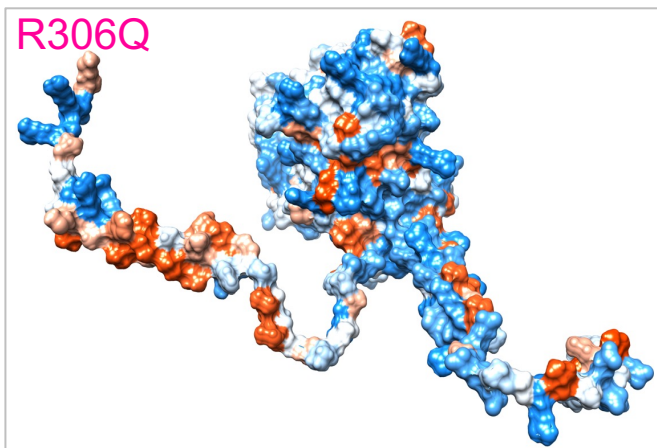
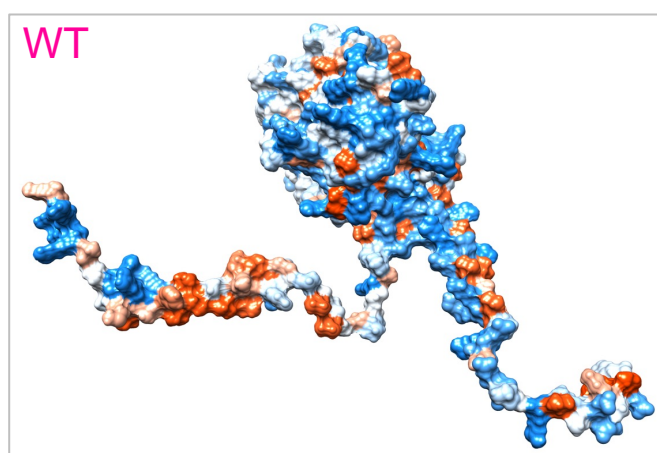
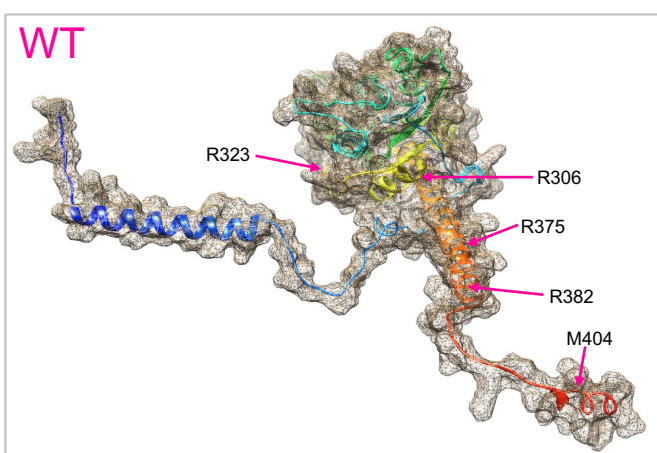
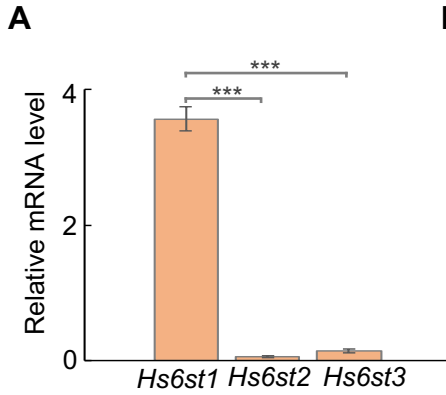


		α1		α2	
Human	MRRRRAGGR	MVERASKFVLVVAGS	VCFMLILYQYAGPGLSLGAPGGR	APPDDLDFPTDP	PHYEKKYYFPVREL 75
Mouse	MRRRRAGGR	MVERASKFVLVVAGS	ACFMLILYQYAGPGLSLGAPGGR	VPPDDLDFPTDP	PHYEKKYYFPVREL 75
		β1	α3		
Human	ERSLRFD	MKGGDDVIVFLHIQKTGGTTFGRHLVQNVRL	EVPCDCRPGQKKCTCYRPNRRETWLF	SRFSTGW	SCGLH 150
Mouse	ERSLRFD	MKGGDDVIVFLHIQKTGGTTFGRHLVQNVRL	EVPCDCRPGQKKCTCYRPNRRETWLF	SRFSTGW	SCGLH 150
	α4		β2	α5	
Human	ADWTELTNCVPGVLD	RRRSAAALRTPRKFFYYITLLRDPVSRYLSEWRHVQ	RGATWKTS	SLHMCDGRTPTPEELPPCY 225	
Mouse	ADWTELTNCVPGVLD	RRRSPAGLRSPRKFFYYITLLRDPVSRYLSEWRHVQ	RGATWKTS	SLHMCDGRTPTPEELPPCY 225	
	α6	α7	α8	β3	α9
Human	EGTDWSGCTLQEFMDCPYNLANNRQVRMLADLSLVGCYNLSF	IPEGKRAQLLLES	SAKKNLRGMAFFGLTEFQ	RKT 300	
Mouse	EGTDWSGCTLQEFMDCPYNLANNRQVRMLADLSLVGCYNLSF	IPESKRAQLLLES	SAKKNLRGMAFFGLTEFQ	RKT 300	
		α10	α11		
Human	QYLFERTFNLKFIRPFMQYNSTRAGGVEVDEDTIR	RIEELNDLDMQLDYAKDLFQORYQYKRQLERREQRL	RSR 375		
Mouse	QYLFERTFNLKFIRPFMQYNSTRAGGVEVDEDTIR	HIEELNDLDMQLDYAKDLFQORYQYKRQLERREQRL	RNR 375		
Human	EERLLHRAKEALPRED	ADEPGRVPTEDYMSHIIEKW 411			
Mouse	EERLLHRSKEALPRED	PEEPGRVPTEDYMSHIIEKW 411			

Supplemental Figure S1. Protein structure of the human HS6ST1 predicted by the AlphaFold. α , α -helix. β , β -strand.

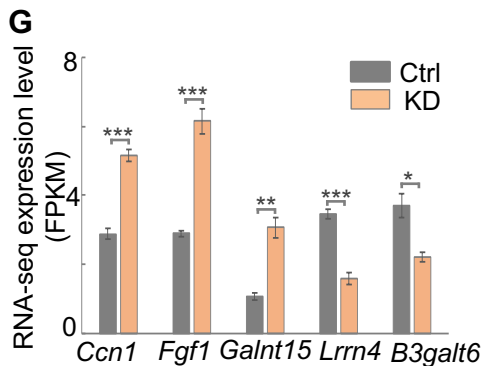
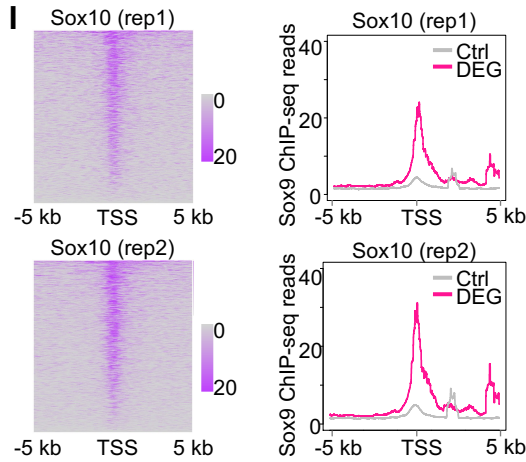
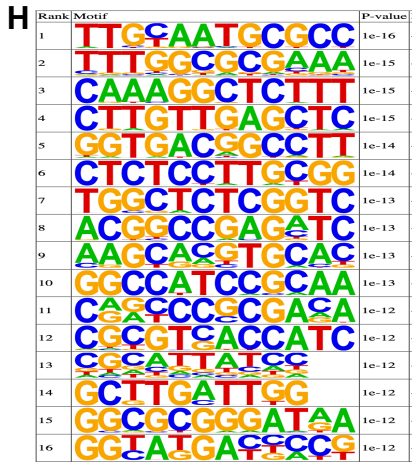
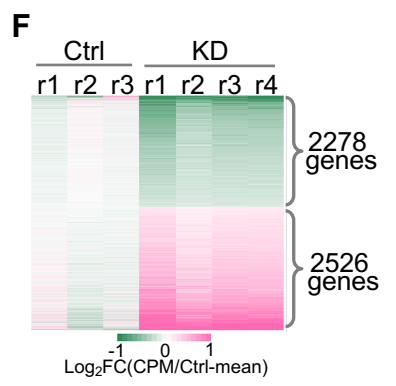
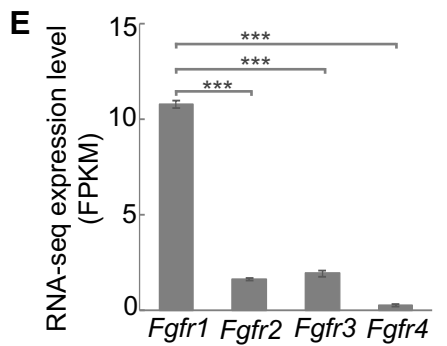
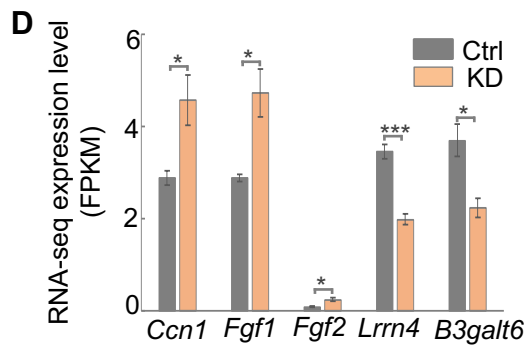
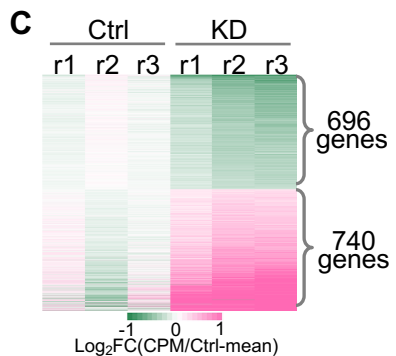


Supplemental Figure S2. Protein structures of the WT and mutant human HS6ST1 predicted by the AlphaFold.



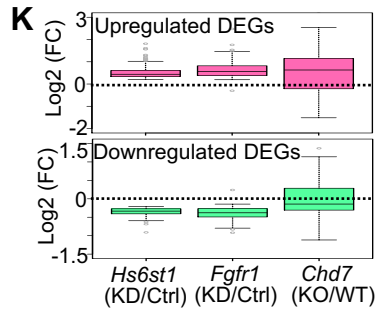
B

	Total read pairs	Uniquely mapped read pairs
Ctrl replicate 1	88,036,346	76,381,000 (86.76%)
Ctrl replicate 2	54,384,194	46,598,448 (85.68%)
Ctrl replicate 3	40,630,458	34,720,575 (85.45%)
siHs6st1 replicate 1	22,058,825	19,032,190 (86.28%)
siHs6st1 replicate 2	30,229,727	26,121,458 (86.41%)
siHs6st1 replicate 3	23,244,310	20,113,225 (86.53%)
siFgfr1 replicate 1	26,938,712	23,214,144 (86.17%)
siFgfr1 replicate 2	20,623,653	18,224,942 (88.37%)
siFgfr1 replicate 3	39,069,745	33,166,410 (84.89%)
siFgfr1 replicate 4	156,060,365	135,088,193 (86.56%)



J

ANOS1	HS6ST1	FGFR1	SOX10
CHD7	FGF8	FGF17	OL14RD
HESX1	FEZF1	PROK2	GNRHR
SOX3	SEMA3A	PROKR2	AXL
SEMA7A	WDR11	NSMF	LHX4
GNRH1	GLI2	SEMA3E	PLXNA1
IL17RD	DUSP6	SPRY4	FLRT3
KLB	DCC	NTN1	IGSF10
TUBB3	CCDC141		



Supplemental Figure S3. siRNA knockdown (KD) of Hs6st1 (siHs6st1) and Fgfr1 (siFgfr1) in Neuro 2a cells followed by RNA sequencing (RNA-seq). **A**, qPCR results of the expression levels of the three *Hs6st* genes in Neuro 2a cells. **B**, Statistics of the sequencing and mapping of the RNA-seq data. **C**, Heatmap of the fold changes of the differentially expressed genes upon *Hs6st1* knockdown (KD). r1, biological replicate 1. **D**, RNA-seq expression levels of five genes in the control (Ctrl) and *Hs6st1* knockdown (KD). **E**, RNA-seq expression levels of the four *Fgfr* genes in Neuro 2a cells. **F**, Heatmap of the fold changes of the differentially expressed genes upon *Fgfr1* knockdown (KD). **G**, RNA-seq expression levels of five genes in the control (Ctrl) and *Fgfr1* knockdown (KD). **H**, The identified *de novo* motifs by Homer. **I**, Heatmaps and line plots showing the Sox10 ChIP-seq signals at the promoter regions. **J**, The thirty-four Kallmann syndrome-linked genes. *, *P*-value < 0.05; **, *P*-value < 0.01; ***, *P*-value < 0.001; one-tailed t-test. **K**, The expression changes (log₂FC) of overlapping DEGs in *Hs6st1* KD, *Fgf1* KD, and *Chd7* knockout (KO).