

Supplement 1. The gene ontology analysis of *MSX2*, *TFAP2A*, *SHH*, and *SMAD7* by Enrichr database.

Biological process			
Term	P-value	Adjusted P-value	Gene
Embryonic limb morphogenesis (GO:0030326)	1.89E-05	0.002847416	<i>TFAP2A</i> ; <i>SHH</i>
Kidney development (GO:0001822)	7.21E-05	0.005445242	<i>TFAP2A</i> ; <i>SHH</i>
Negative regulation of transcription by RNA polymerase II (GO:0000122)	1.55E-04	0.007814466	<i>TFAP2A</i> ; <i>SHH</i> ; <i>MSX2</i>
Regulation of cell differentiation (GO:0045595)	3.59E-04	0.009386243	<i>TFAP2A</i> ; <i>SHH</i>
Negative regulation of transcription, DNA-templated (GO:0045892)	4.10E-04	0.009386243	<i>TFAP2A</i> ; <i>SHH</i> ; <i>MSX2</i>
Molecular function			
Term	P-value	Adjusted P-value	Gene
Transcription regulatory region nucleic acid binding (GO:0001067)	6.62E-04	0.008396047	<i>TFAP2A</i> ; <i>MSX2</i>
Morphogen activity (GO:0016015)	0.001399341	0.008396047	<i>SHH</i>
Patched binding (GO:0005113)	0.001399341	0.008396047	<i>SHH</i>
Transcription cis-regulatory region binding (GO:0000976)	0.004350036	0.018614756	<i>TFAP2A</i> ; <i>MSX2</i>
Double-stranded DNA binding (GO:0003690)	0.00607616	0.018614756	<i>TFAP2A</i> ; <i>MSX2</i>
Sequence-specific DNA binding (GO:0043565)	0.007140115	0.018614756	<i>TFAP2A</i> ; <i>MSX2</i>
Cellular component			
Term	P-value	Adjusted P-value	Gene
Membrane raft (GO:0045121)	0.03220582	0.147732822	<i>SHH</i>
Endoplasmic reticulum lumen (GO:0005788)	0.055797007	0.147732822	<i>SHH</i>
Collagen-containing extracellular matrix (GO:0062023)	0.073866411	0.147732822	<i>SHH</i>
Intracellular organelle lumen (GO:0070013)	0.159125912	0.238688867	<i>SHH</i>
Nucleus (GO:0005634)	0.219003553	0.262804264	<i>TFAP2A</i> ; <i>MSX2</i>
Intracellular membrane-bounded organelle (GO:0043231)	0.278008067	0.278008067	<i>TFAP2A</i> ; <i>MSX2</i>

Supplement 2. The mRNA-miRNA interaction analysis of *SHH*, *TFAP2A*, and *MSX2* by miRWalk database.

Gene	miRNA	Binding	Energy	N*	Position	miRNA	Binding-P	Energy	N*	Position	
<i>MSX2</i>	hsa-miR-6775-5p	1	-40.4	23	3'UTR	hsa-miR-2467-5p	1	-32.2	18	3'UTR	
	hsa-miR-7110-5p	1	-35.7	18	3'UTR	hsa-miR-6798-5p	1	-31.9	19	3'UTR	
	hsa-miR-7110-5p	1	-35.7	18	3'UTR	hsa-miR-7109-5p	1	-31.8	16	3'UTR	
	hsa-miR-6803-5p	1	-34.9	17	3'UTR	hsa-miR-6727-5p	1	-31.8	18	3'UTR	
	hsa-miR-6729-5p	1	-34.5	20	3'UTR	hsa-miR-7109-5p	1	-31.8	16	3'UTR	
	hsa-miR-6724-5p	1	-33.9	20	3'UTR	hsa-miR-4739	1	-31.7	21	3'UTR	
	hsa-miR-6796-5p	1	-32.9	20	3'UTR	hsa-miR-1249-5p	1	-31.2	17	3'UTR	
	hsa-miR-6757-5p	1	-32.7	16	3'UTR	hsa-miR-1249-5p	1	-31.2	17	3'UTR	
	hsa-miR-7851-3p	1	-32.5	17	3'UTR	hsa-miR-1266-5p	1	-31.2	19	3'UTR	
	hsa-miR-2467-5p	1	-32.2	18	3'UTR	hsa-miR-6796-5p	1	-30.9	22	3'UTR	
	<i>SHH</i>	hsa-miR-149-3p	1	-31.5	16	3'UTR	hsa-miR-1303	1	-23.2	20	3'UTR
		hsa-miR-1207-5p	1	-28.4	19	3'UTR	hsa-miR-1207-3p	1	-23	13	3'UTR
		hsa-miR-1301-3p	1	-26.6	21	3'UTR	hsa-miR-1287-3p	1	-21.4	14	3'UTR
		hsa-miR-10398-3p	1	-26.5	16	3'UTR	hsa-miR-136-5p	1	-20.7	20	3'UTR
hsa-miR-128-1-5p		1	-26.1	19	3'UTR	hsa-miR-1236-5p	1	-20.6	17	3'UTR	
hsa-miR-125b-1-3p		1	-25.5	16	3'UTR	hsa-miR-135a-2-3p	1	-20.5	13	3'UTR	
hsa-miR-12130		1	-25.4	18	3'UTR	hsa-miR-148a-3p	1	-19.3	13	3'UTR	
hsa-miR-1291		1	-25.4	14	3'UTR	hsa-miR-1246	1	-19	17	3'UTR	
hsa-miR-134-5p		1	-24.5	17	3'UTR	hsa-miR-148b-3p	1	-18.6	13	3'UTR	
hsa-miR-135a-3p		1	-24.1	16	3'UTR	hsa-miR-1207-5p	1	-17.7	17	3'UTR	
<i>TFAP2A</i>		hsa-miR-432-5p	1	-26.9	19	3'UTR	hsa-miR-187-5p	1	-21.4	20	3'UTR
		hsa-miR-629-5p	1	-25.4	19	3'UTR	hsa-miR-134-5p	1	-21.2	21	3'UTR
		hsa-miR-29b-2-5p	1	-24.9	18	3'UTR	hsa-miR-668-5p	1	-21	16	3'UTR
		hsa-miR-503-5p	1	-24.8	18	3'UTR	hsa-miR-181a-2-3p	1	-20.9	13	3'UTR
	hsa-miR-202-3p	1	-24.1	16	3'UTR	hsa-miR-185-5p	1	-20.8	17	3'UTR	
	hsa-miR-597-3p	1	-24	18	3'UTR	hsa-miR-645	1	-20.6	15	3'UTR	
	hsa-miR-200c-3p	1	-23.7	20	3'UTR	hsa-miR-217-5p	1	-20.4	20	3'UTR	
	hsa-miR-670-5p	1	-23.4	19	3'UTR	hsa-miR-625-5p	1	-20.2	19	3'UTR	
	hsa-miR-1298-3p	1	-22.8	16	3'UTR	hsa-miR-936	1	-20.1	13	3'UTR	
	hsa-miR-526b-5p	1	-21.5	13	3'UTR	hsa-miR-150-5p	1	-19.5	12	3'UTR	

*N= Pairing

Supplement 3. List of SNPs detected in *MSX2*, *SMAD7*, *SHH* and *TFAP2A* genes by SIFT and PROVEAN online bioinformatics tools.

Gene	SNP	Ref/Alt	AAC	SIFT score	PROVEAN prediction	Prediction	Score	
<i>MSX2</i>	rs186769394	G/C	M129I	0.37	Tolerated			
	rs199732800	G/T	R199I	0	Deleterious	Deleterious	-7.514	
	rs199856192	G/A	M263I	0.014	Deleterious	Deleterious	-2.963	
	rs189666650	G/A	P145P	1	Tolerated			
	rs4242182	T/C	M129T	0.45	Tolerated			
	rs367614252	C/T	G85G	1	Tolerated			
	rs367614252	C/T	G85G	1	Tolerated			
	rs371794345	G/A	L10L	0.831	Tolerated			
	rs371794345	G/A	L10L	1	Tolerated			
	rs376630472	C/T	R39R	0.474	Tolerated			
	rs376630472	C/T	R39R	0.613	Tolerated			
	<i>SMAD7</i>	rs375674516	T/C	E203G	0.567	Tolerated		
		rs375674516	T/C	E203G	0.572	Tolerated		
		rs76172388	T/G	N209T	0.068	Tolerated		
rs76172388		T/G	N424T	0.087	Tolerated			
rs76172388		T/G	N423T	0.087	Tolerated			
rs200991750		T/G	T408P	0.003	Deleterious	Deleterious	-2.653	
rs200991750		T/G	T407P	0.003	Deleterious			
rs200991750		T/G	T193P	0.308	Tolerated			
rs267605193		C/T	G103D	0.032	Deleterious			
rs267605193		C/T	G318D	0.047	Deleterious	Deleterious	-6.046	
rs267605193		C/T	G317D	0.047	Deleterious			
rs267605193		C/T	G103D	0.058	Tolerated			
rs369444426		T/C	Q280R	0.325	Tolerated			
rs369444426		T/C	Q279R	0.326	Tolerated			
rs369444426		T/C	Q65R	0.342	Tolerated			
rs369444426		T/C	Q65R	0.357	Tolerated			
rs376228389		C/T	G41E	0.033	Deleterious			
rs376228389		C/T	G41E	0.162	Tolerated			
rs376228389		C/T	G255E	0.244	Tolerated			
rs376228389		C/T	G256E	0.247	Tolerated			
rs1052572		G/A	G404G	1	Tolerated			
rs1052572		G/A	G403G	1	Tolerated			
rs1052572		G/A	G189G	1	Tolerated			
rs3809922		G/A	L298L	1	Tolerated			
rs3809922		G/A	L83L	1	Tolerated			
rs3809922		G/A	L297L	1	Tolerated			
rs3809922		G/A	L83L	1	Tolerated			
rs3809923		G/C	G402G	1	Tolerated			
rs3809923		G/C	G401G	1	Tolerated			
rs3809923		G/C	G187G	1	Tolerated			
rs34151545		C/G	T391T	0.302	Tolerated			
rs34151545		C/G	T390T	0.308	Tolerated			
rs34151545		C/G	T176T	0.449	Tolerated			
<i>SHH</i>	rs28936675	C/T	G31R	0.001	Deleterious			
	rs199513347	G/T	R244S	0.064	Tolerated			
	rs368283830	C/G	E208Q	0.229	Tolerated			
	rs372353493	C/A	S195S	1	Tolerated			
	rs374095917	C/G	V215V	0.605	Tolerated			
	rs147587714	G/A	R155R	1	Tolerate			
	rs147587714	G/A	R68R	1	Tolerated			
	rs9333633	C/T	S190S	1	Tolerated			
	rs9333634	G/A	G210G	1	Tolerated			
	rs9333635	C/G	L299L	0.747	Tolerated			
	rs191903572	G/A	L360L	1	Tolerated			
	rs267607047	G/T	N115K	0	Deleterious	Deleterious	-5.269	
	rs267607047	G/T	N28K	0.002	Deleterious			
	rs200317108	C/T	E71E	1	Tolerated			
<i>TFAP2A</i>	rs143945720	C/T						
	rs1803116	G/A	A422V	0.116	Tolerated			
	rs1803116	G/A	A426V	0.118	Tolerated			
	rs1803116	G/A	A428V	0.118	Tolerated			
	rs1803116	G/A	A426V	0.118	Tolerated			

Supplement 3 (continued). List of SNPs detected in *MSX2*, *SMAD7*, *SHH* and *TFAP2A* genes by SIFT and PROVEAN online bioinformatics tools.

Gene	SNP	Ref/Alt	AAC	SIFT score	PROVEAN prediction	Prediction	Score
<i>TFAP2A</i>	rs1803116	G/A	A420V	0.12	Tolerated		
	rs9350373	G/C	R352G	0.004	Deleterious		
	rs9350373	G/C	R356G	0.004	Deleterious	Deleterious	-5.999
	rs9350373	G/C	R350G	0.004	Deleterious		
	rs9350373	G/C	R358G	0.004	Deleterious		
	rs9350373	G/C	R356G	0.004	Deleterious		
	rs9350373	G/C	T308T				
	rs144275164	T/G	E307A	0.036	Deleterious		
	rs144275164	T/G	E311A	0.036	Deleterious	Deleterious	-5.534
	rs144275164	T/G	E305A	0.036	Deleterious		
	rs144275164	T/G	E313A	0.036	Deleterious		
	rs144275164	T/G	E311A	0.036	Deleterious		
	rs372468982	C/G	Q144H	0.019	Deleterious		
	rs372468982	C/G	Q99H	0.023	Deleterious		
	rs372468982	C/G	Q95H	0.04	Deleterious		
	rs372468982	C/G	Q101H	0.046	Deleterious		
	rs372468982	C/G	Q99H	0.047	Deleterious		
	rs372468982	C/G	Q93H	0.047	Deleterious		
	rs372468982	C/G	Q99H	0.047	Deleterious		
	rs372468982	C/G	Q3H	0.177	Tolerated		
	rs377114324	C/T	V303M	0.002	Deleterious		
	rs377114324	C/T	V307M	0.003	Deleterious		
	rs377114324	C/T	V301M	0.003	Deleterious		
	rs377114324	C/T	V309M	0.003	Deleterious		
	rs377114324	C/T	V307M	0.003	Deleterious		
	rs3734391	G/A	N415N	1	Tolerated		
	rs3734391	G/A	N419N	1	Tolerated		
	rs3734391	G/A	N413N	1	Tolerated		
	rs3734391	G/A	N421N	1	Tolerated		
	rs3734391	G/A	N419N	1	Tolerated		
	rs2230116	C/A	T392T	1	Tolerated		
	rs2230116	C/A	T396T	1	Tolerated		
	rs2230116	C/A	T390T	1	Tolerated		
	rs2230116	C/A	T398T	1	Tolerated		
	rs2230116	C/A	T396T	1	Tolerated		
	rs141711078	G/A	Y302Y	1	Tolerated		
	rs141711078	G/A	Y306Y	1	Tolerated		
	rs141711078	G/A	Y300Y	1	Tolerated		
	rs141711078	G/A	Y308Y	1	Tolerated		
	rs141711078	G/A	Y306Y	1	Tolerated		
	rs201494266	G/A	T399T	1	Tolerated		
	rs201494266	G/A	T403T	1	Tolerated		
	rs201494266	G/A	T397T	1	Tolerated		
	rs201494266	G/A	T405T	1	Tolerated		
	rs201494266	G/A	T403T	1	Tolerated		
	rs369051842	G/A	L136L	1	Tolerated		
	rs369051842	G/A	L140L	1	Tolerated		
	rs369051842	G/A	L134L	1	Tolerated		
	rs369051842	G/A	L142L	1	Tolerated		
	rs369051842	G/A	L140L	1	Tolerated		
	rs369051842	G/A	L44L	1	Tolerated		
	rs369051842	G/A	L140L	1	Tolerated		
	rs1803117	G/A	L317L	1	Tolerated		
	rs1803117	G/A	L321L	1	Tolerated		
	rs1803117	G/A	L315L	1	Tolerated		
	rs1803117	G/A	L323L	1	Tolerated		
	rs1803117	G/A	L321L	1	Tolerated		
	rs140377026	G/A	P302L				
	rs140377026	G/A	T345T	1	Tolerated		
	rs140377026	G/A	T349T	1	Tolerated		
	rs140377026	G/A	T343T	1	Tolerated		
	rs140377026	G/A	T351T	1	Tolerated		
	rs140377026	G/A	T349T	1	Tolerated		

Supplement 3 (continued). List of SNPs detected in *MSX2*, *SMAD7*, *SHH* and *TFAP2A* genes by SIFT and PROVEAN online bioinformatics tools.

Gene	SNP	Ref/Alt	AAC	SIFT Score	PROVEAN Prediction	Prediction	Score
<i>TFAP2A</i>	rs145673154	G/T	R120R	1	Tolerated		
	rs145673154	G/T	R124R	1	Tolerated		
	rs145673154	G/T	R118R	1	Tolerated		
	rs145673154	G/T	R126R	1	Tolerated		
	rs145673154	G/T	R169R	1	Tolerated		
	rs145673154	G/T	R124R	1	Tolerated		
	rs145673154	G/T	R28R	1	Tolerated		
	rs145673154	G/T	R124R	1	Tolerated		
	rs181105841	G/C	A389A	1	Tolerated		
	rs181105841	G/C	A393A	1	Tolerated		
	rs181105841	G/C	A387A	1	Tolerated		
	rs181105841	G/C	A395A	1	Tolerated		
	rs181105841	G/C	A393A	1	Tolerated		
	rs200847258	G/C	L398L	1	Tolerated		
	rs200847258	G/C	L402L	1	Tolerated		
	rs200847258	G/C	L396L	1	Tolerated		
	rs200847258	G/C	L404L	1	Tolerated		
	rs200847258	G/C	L402L	1	Tolerated		
	rs140905560	G/C	P237P	1	Tolerated		
	rs140905560	G/C	P241P	1	Tolerated		
	rs140905560	G/C	P235P	1	Tolerated		
	rs140905560	G/C	P243P	1	Tolerated		
	rs140905560	G/C	P15P	1	Tolerated		
	rs140905560	G/C	P241P	1	Tolerated		
	rs140905560	G/C	P145P	1	Tolerated		
	rs140905560	G/C	P241P	1	Tolerated		
	rs140905560	G/C	P98P	1	Tolerated		
	rs140905560	G/T	P237P	1	Tolerated		
	rs140905560	G/T	P241P	1	Tolerated		
	rs140905560	G/T	P235P	1	Tolerated		
	rs140905560	G/T	P243P	1	Tolerated		
	rs140905560	G/T	P15P	1	Tolerated		
	rs140905560	G/T	P241P	1	Tolerated		
	rs140905560	G/T	P145P	1	Tolerated		
	rs140905560	G/T	P241P	1	Tolerated		
	rs140905560	G/T	P98P	1	Tolerated		
	rs143363077	G/A	S95S	0.919	Tolerated		
	rs143363077	G/A	S187S	1	Tolerated		
	rs143363077	G/A	S191S	1	Tolerated		
	rs143363077	G/A	S185S	1	Tolerated		
	rs143363077	G/A	S193S	1	Tolerated		
	rs143363077	G/A	S191S	1	Tolerated		
	rs143363077	G/A	S191S	1	Tolerated		
	rs143363077	G/A	S48S	1	Tolerated		
	rs142511319	G/C	L249L	1	Tolerated		
	rs142511319	G/C	L253L	1	Tolerated		
	rs142511319	G/C	L247L	1	Tolerated		
	rs142511319	G/C	L255L	1	Tolerated		
	rs142511319	G/C	L27L	1	Tolerated		
	rs142511319	G/C	L253L	1	Tolerated		
	rs142511319	G/C	L157L	1	Tolerated		
	rs142511319	G/C	L253L	1	Tolerated		
rs142511319	G/C	L110L	1	Tolerated			
rs143258135	C/A	G20V	0.029	Deleterious	Deleterious	-3.859	
rs143258135	C/A	G22V	0.034	Deleterious			
rs143258135	C/A	G20V	0.035	Deleterious			
rs143258135	C/A	G20V	0.035	Deleterious			
rs143258135	C/A	G14V	0.039	Deleterious			
rs143258135	C/A	G16V	0.044	Deleterious			
rs143258135	C/A	G65V	0.052	Tolerated			