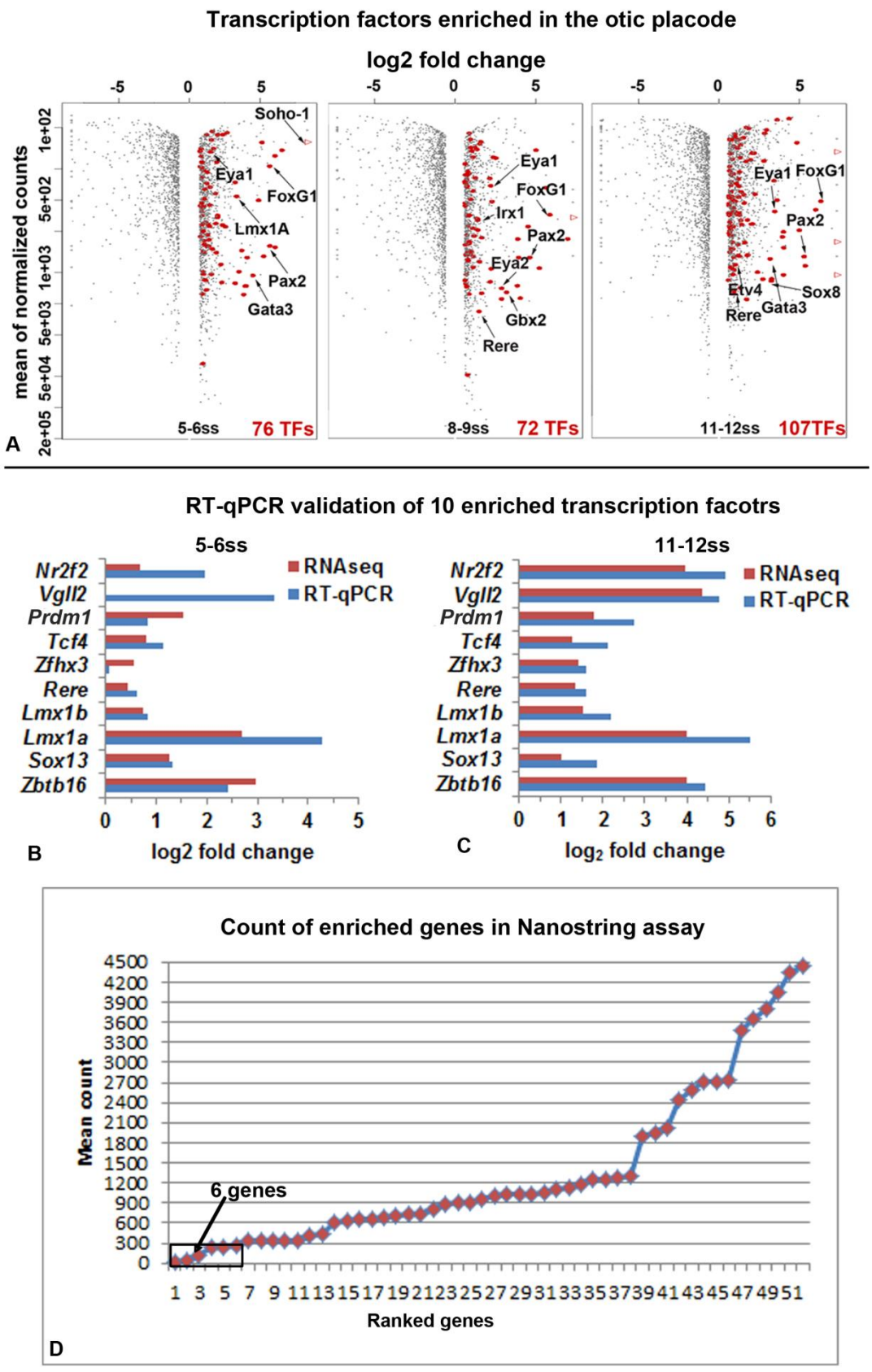

Fig. S1 Otic-enriched transcriptional regulators. A. Transcripts enriched in the otic placode were identified by comparison of the otic transcriptome to the whole embryo at ss3 and known and putative transcription factors were extracted. Numbers of otic enriched transcription factors (TF) at each stage are indicated in the lower right corner of each diagram. A few known otic regulators are labelled. **B, C.** Validation of enrichment of 10 otic transcription factors by RT-qPCR. At both 5-6ss (B) and 11-12ss (C), fold change was calculated relative to the expression in whole embryo at 3ss. Fold change from RNAseq is plotted alongside for comparison of consistency between two assays. **D.** Expression of 52 otic genes evaluated by NanoString. The genes are ranked based on their count. 46/52 otic enriched genes pass the count >300 threshold at 11-12ss.

Gene Name	ss0-1				ss5-6					ss8-9					ss11-12							References
	aPPR	pPPR	NP	NNE	A	M	OEPD	NCC	NP	A	M	OEPD	NCC	NT	A	M	OP	EP	EPID	NCC	NT	
ARID3A																						S3 Fig
ARID3C												w										S3 Fig
ATN1																				w		S3 Fig
BACH2									w					w								mRNA-seq data (not shown)
PRDM1																						Fig 2
BMP4																						Streit and Stern, 1999; Bothe et al., 2011
cMYB							w					w										Betancur et al., 2011
CREBBP							w					w										S3 Fig
DACH2															OL		Rim					S3 Fig
DLX3																						Khudyakov and Bonner-Fraser, 2009
DLX5										OL												Streit, 2002
ETS1																						Geisha expression pattern; S3 Fig
ETS2																						mRNA-seq data (not shown)
ETV4															OL							Lunn et al., 2007
ETV5															OL							Lunn et al., 2007
EYA1	w	w																				Ishihara et al., 2008
EYA2																						McLarren et al., 2003; Ishihara et al., 2008
EYA4							w		w					w			Rim					S3 Fig
FOXD3																						Khudyakov and Bonner-Fraser, 2009
FOXG1																						Geisha expression pattern
FOXI2																						Khatri and Groves, 2013
FOXI3	w																					Khatri and Groves, 2013
FOXP1																						S3 Fig
FOXP4																	I					S3 Fig
FSTL4	w																					unpublished
GATA3																						Sheng and Stern, 1999; Bothe and Dietrich, 2003
GBX2																						Niss and Leutz, 1998; Shamim and Mason, 1998; Paxton et al., 2010
HMG1																						S3 Fig
HOMER2					OL					OL					OL							unpublished
HOXA2																						Paxton et al., 2010
HOXA3																						Paxton et al., 2011
IRX1																						Geisha expression pattern
IRX4																	Rim					Geisha expression pattern
IRX5																						S3 Fig
JAG1																						Paxton et al., 2010
KERATIN19																						McLarren et al., 2003; Geisha expression pattern
KLF7																						S3 Fig
KLF8																						S3 Fig
KREMEN1							w					w										Llears-Forero, 2013
KROX20																						Nonchev et al., 1996
LEF1							w															S3 Fig
LFNG																						Bothe and Dietrich, 2003
LMX1A																						Fig 2
LMX1B																	Rim					Adams et al., 2010
LZTS1																						Geisha expression pattern
MAFA																						Lecoin et al., 2004
MEIS1																						Sanchez-Guardado et al., 2011
MYB																						Betancur P et ak., 2011
MYCN																						Khudyakov and Bonner-Fraser, 2009
NFKB1																						unpublished
NKX5.1																	Rim					Herbrand et al., 1998
NOTCH1																						Groves and Bronner-Fraser, 2000
NR2F2																						Fig 2
OTX2									aNP													Plouhinec et al., 2005
PAX2																						Groves and Bronner-Fraser, 2000; Streit, 2002
PAX3																						Bothe et al., 2007; McCabe and Bronner-Fraser, 2008
PAX6									aNP													Bell et al., 2001; Bhattacharyya et al., 2004; Bhattacharyya and Bronner-Fraser, 2008
PHOX2A																						Begbie et al., 2002
PHOX2B																						Begbie et al., 2002
PNOC																						Lleras-Forero et al., 2013
PREP2																						S3 Fig
RERE																						Fig 2
SALL1																						Sweetman et al., 2005
SALL4																						Barembaum and Bronner-Fraser, 2007; Geisha expression pattern
SIP1																						Sheng et al., 2003
SIX1																						Streit, 2002
SIX4																						Esteve and Bovolenta, 1999
SNAIL1																						Geisha expression pattern
SNAIL2																						Nieto et al., 1994
SOHO1																						Kiernan et al., 1997
SOX1																						Uchikawa et al., 2011
SOX10																						Cheng et al., 2000; McKeown et al., 2005; Geisha expression pattern
SOX11																	Rim					S3 Fig
SOX13																						Fig 2
SOX2																						Dady A et al., 2012; Matsumata M et al., 2005
SOX3																						Rex et al., 1997; Abu-Elmagd et al., 2001; Mikawa et al., 2004; Streit and Stern, 1999
SOX8																						McKeown et al., 2005; Geisha expression pattern
SPRY1																						Geisha expression pattern
SPRY2																						Geisha expression pattern; Chambers and Mason, 2000
SSTR5																						Lleras-Forero et al., 2013
TBX10																						S3 Fig
TCF4																						Fig 2
TCF7L1																						Schmidt et al., 2004
TEAD3																						S3 Fig
TFAP2C																						Qiao et al., 2012
TFAP2E																						S3 Fig
VGLL2																						Fig 2
ZBTB16																						Fig 2
ZFHX3																						Fig 2
ZNF384																						S3 Fig
ZNF385C	w	w																				mRNA-seq data (not shown)
ZNF521																						mRNA-seq data (not shown)

Key	
Expression	
No expression	
Not checked	
w = weak expression	w
Anterior/Lens	A
Medial/Trigeminal	M
Anterior Neural Plate	aNP
Posterior/OEPD	OEPD
Otic Placode	OP
Epibranchial Placode	EP
Epidermis	EPID
Anterior Neural Ridge	ANR
Neural Plate/Crest	NCC
Neural Fold/Tube	NT
Olfactory Placode	OL

Fig. S2 Summary of the expression patterns of 95 otic genes. This table was assembled using data from the literature and our own new data. References are provided in the table.

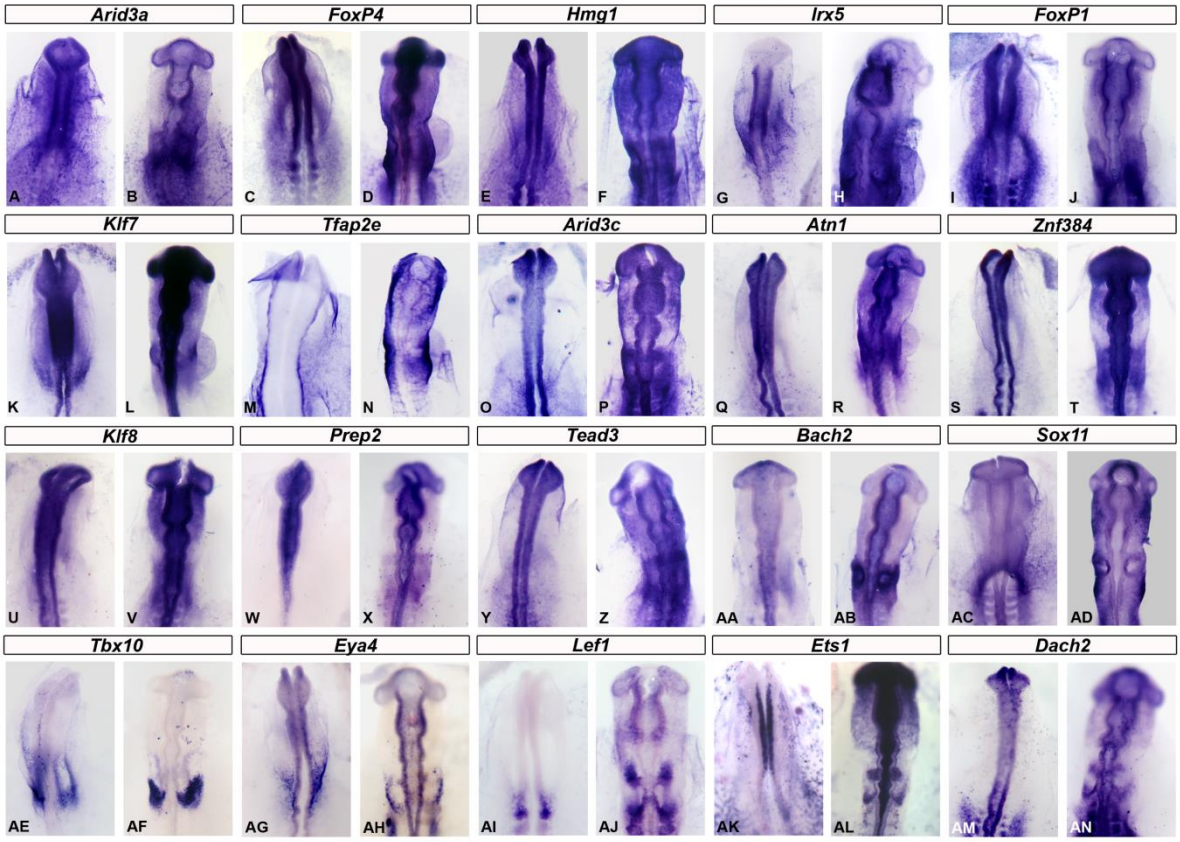

Fig. S3 Expression patterns of new otic and epibranchial transcription factors. *Arid3a* (**A, B**), *FoxP4* (**C, D**), *Hmg1* (**E, F**), *Irx5* (**G, H**) and *FoxP1* (**I, J**) are expressed from OEP stages and remain widely expressed in the otic and epibranchial territories, except for *FoxP4* which becomes confined to the epibranchial region (**D**). *Klf7* (**K, L**) is already expressed at 6ss and becomes restricted to the epibranchial domain at 12ss (**L**). *Tfap2e* (**M, N**) is expressed in neural crest cells and later in the epibranchial placodes. Late onset genes (after 11-12ss) include *Arid3c* (**O, P**), *Atn1* (**Q, R**), *Znf384* (**S, T**) *Klf8* (**U, V**), *Prep2* (**W, X**), *Tead3* (**Y, Z**), *Bach2* (**AA, AB**). *Sox11* (**AC, AD**), *Tbx10* (**AE, AF**), *Eya4* (**AG, AH**), *Lef1* (**AI, AJ**), *Ets1* (**AK, AL**) and *Dach2* (**AM, AN**) are localized at the ridge the otic cup and/or in neural crest cells (*Lef1*, *Ets2*). Most factors are also expressed in other domains like the neural tube and underlying mesoderm.

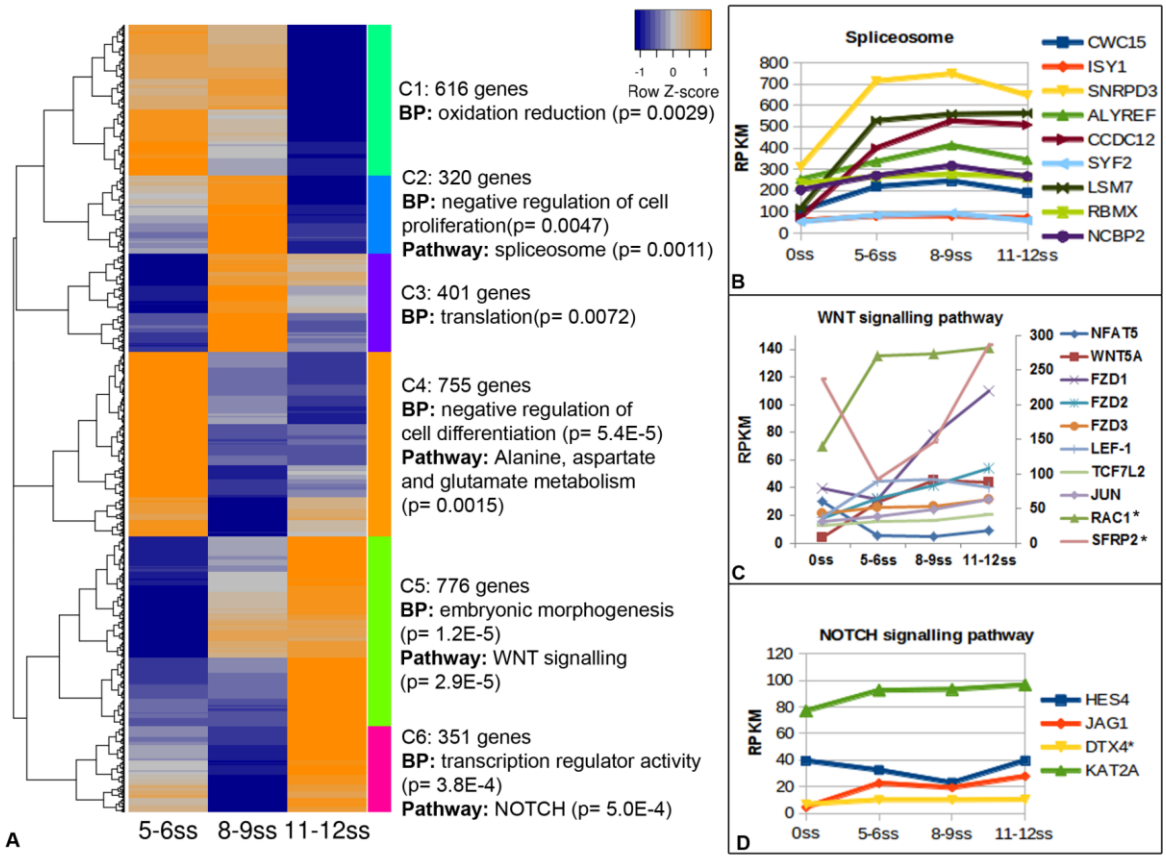

Fig. S4 Otic genes are partitioned into different clusters. A. 6 clusters are revealed by hierarchical clustering (C1-6). The top enriched biological process and signalling pathway are indicated for each cluster. **B-D** expression profiles of signalling pathway components in cluster C2 (**B**), C5 (**C**) and C6 (**D**). * in C indicates genes whose expression is plotted against the second axis on the right hand side, while * in D indicates that Log2(RPKM) is used to plot DTX4 expression.

Source	Interaction	Target	System	Evidence
Interactions within the posterior PPR				
Dlx5/6 (Dlx3b/4b), Six1/Eya2	Promote	Foxi3 (Foxi1)	Chick, *Xenopus*, Zebrafish	(Hans et al., 2007; Hans et al., 2004; Khatri et al., 2014; Nissen, 2003; Phillips et al., 2004; Pieper et al., 2012; Solomon, 2003)
FGF	Promotes	Etv4	Chick, Zebrafish	(Lunn et al., 2007; Raible and Brand, 2001; Roehl and Nusslein-Volhard, 2001)
Gbx2	Represses	Otx1/2/5	*Xenopus*	(Steventon et al., 2012)
Dlx5/6 (Dlx3b/4b), Foxi3 (Foxi1), Irx1, Six1/Eya2	Promote	Six1	Chick, *Xenopus*, Zebrafish	(Ahrens and Schlosser, 2005; Glavic et al., 2004; Khatri et al., 2014; Pieper et al., 2012; Woda, 2003)
Dlx5/6 (Dlx3b/4b), Foxi3 (Foxi1), Six1/Eya2	Promote	Eya1/2	Chick, medaka Zebrafish	(Christophorou et al., 2009; Esterberg and Fritz, 2009; Khatri et al., 2014; Kwon et al., 2010; Leger and Brand, 2002; Litsiou et al., 2005; Pieper et al., 2012)
Dlx5/6 (Dlx3b/4b), Foxi3 (Foxi1), Six1/Eya2	Promote	Six4	Chick, *Xenopus*, Zebrafish	(Altmann et al., 1997; Christophorou et al., 2009; Esterberg and Fritz, 2009; Kwon et al., 2010; Leger and Brand, 2002; McLarren et al., 2003)
Interactions from PPR to OEPs				
FGF	Through	MAPK	Chick	(Yang et al., 2013)
Dlx5/6 (Dlx3b/4b), Gbx2, Foxi3 (Foxi1), FGF, Six1/Eya1/2	Promote	Pax2	Chick, mouse, *Xenopus*, zebrafish	(Bricaud and Collazo, 2006; Christophorou et al., 2009; Freter et al., 2008; Hans et al., 2007; Hans et al., 2004; Khatri et al., 2014; Ladher et al., 2000; Ladher et al., 2005; Leger and Brand, 2002; Mackereth et al., 2005; Maroon et al., 2002; Martin and Groves, 2006; Padanad et al., 2012; Padanad and Riley, 2011; Phillips et al., 2004; Solomon and Fritz, 2002; Solomon et al., 2004; Steventon et al., 2012; Sun et al., 2007; Wright and Mansour, 2003)
Pax2	Represses	Pax3	Chick	(Dude et al., 2009)
FGF	Represses	Pax6	Chick	(Bailey et al., 2006)
Pax2	Promotes	Six1	Zebrafish	(Bricaud and Collazo, 2006)
FGF	Promotes	Sox8	Chick	(Yang et al., 2013)
FGF, Foxi3 (Foxi1)	Promotes	Foxg1	Chick, mouse	(Freter et al., 2012; Khatri et al., 2014; Urness et al., 2010; Yang et al., 2013)
Pax2*, Etv4*	Promote	Sall4	Chick	(Barembaum and Bronner-Fraser, 2010)
Interaction between mesoderm and neural plate				
FGF	Promotes	Wnt	Chick,	(Ladher et al., 2000; Phillips et al., 2004; Rogers et al., 2011)

Fig. S5 Known interactions from the literature.

The table summarizes the interactions described in the otic gene regulatory network (Fig.7) including the appropriate references. Gene names are colour-coded as in the networks and use chick nomenclature; names used in other species are shown in brackets. * Experimentally verified direct interactions. References are listed in the final section of supplementary information.

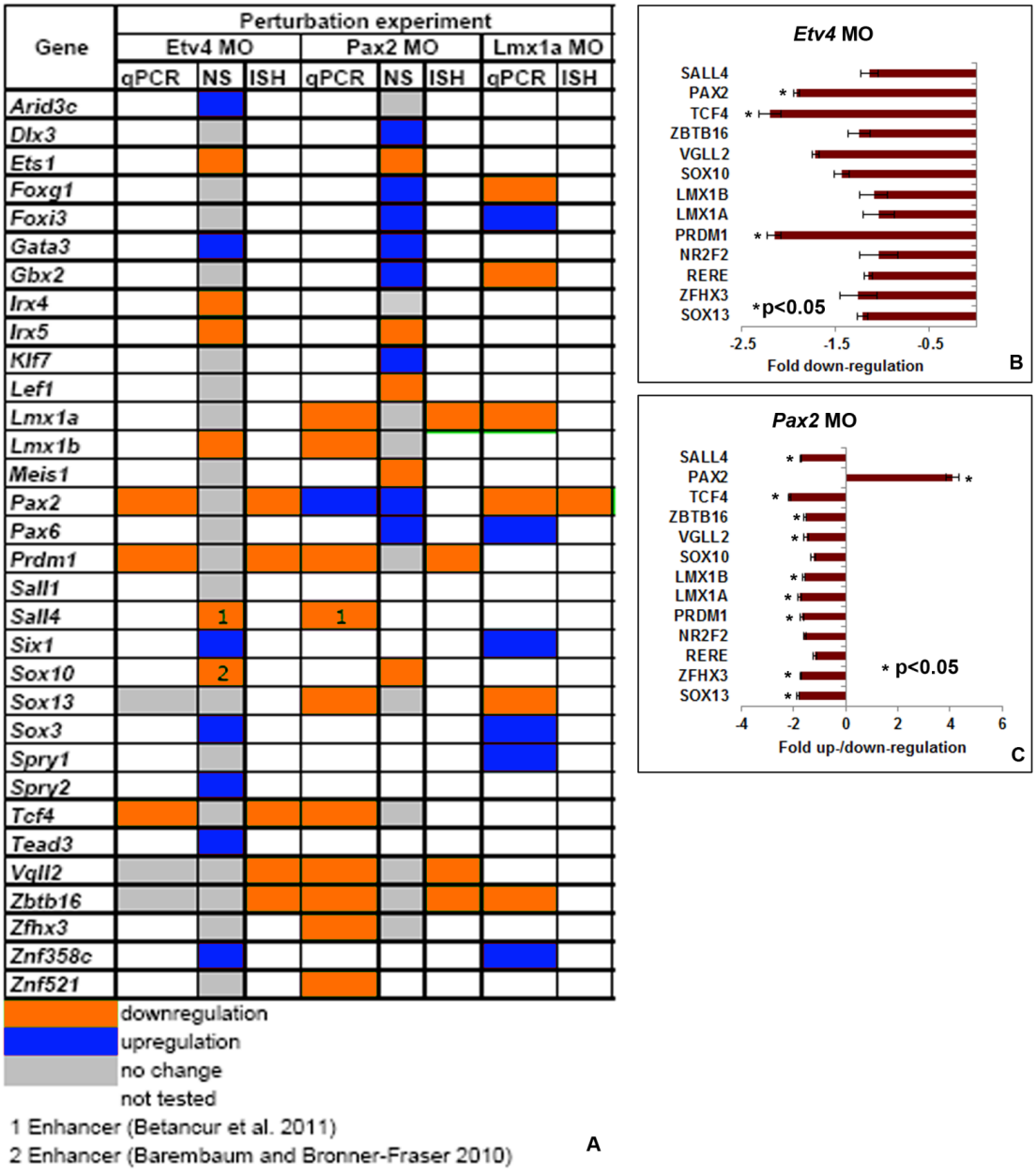

Fig. S6 Summary of perturbation experiments. A. Summary of Etv4, Pax2 and Lmx1a morpholino knockdown experiments evaluated with qPCR, NanoString (NS) and *in situ* hybridization (ISH). **B, C**. Evaluation of Pax2 and Etv4 knockdown by qPCR. * significantly affected genes (p-value<0.05).

Table. S1 Otic-enriched genes. Genes enriched in the otic placode at 5-6ss, 8-9ss and 11-12ss using fold change > 1.5 and a padj<0.1. Genes labelled "NA" are removed because their RPKM is <4 or count number <300.

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Table. S2 Otic-enriched genes. Genes enriched in the otic placode at 5-6ss, 8-9ss and 11-12ss using fold change >1.5 as cut-off. Genes labelled "NA" are removed because their RPKM is <4 or count number <300.

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Table. S3 Time course of differentially expressed genes. Genes labelled "NA" are removed because RPKM is <4 or count number <300.

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Table. S4 Otic transcription factors used for cluster analysis. The data sheet contains transcription factors enriched in otic territory (see Fig 1) and differentially expressed from time-course analysis (see Fig 3) except those downregulated at 5-6ss relative to HH6. The fold change was calculated with DEseq relative to HH6 and the normalized RPKM was acquired from Cuffdiff2.

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Table. S5 Genes affected by Etv4 and Pax2 knockdown. NanoString nCounter data showing changes in gene expression after Etv4 and Pax2 knockdown. Genes with a mean expression count of less than 300 in either condition are excluded from any analysis.

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Table S6. Plasmids used for RNA probe synthesis

Probes obtained from ESTs		
Gene name	**EST number**	**Polymerase**
Arid3c	ChEST974l21	T3
Atn1	ChEST996j15	T3
Bach2	ChEST403d9	T3
Dach2	ChEST739i13	T3
Eya1	ChEST668d18	T3
Eya4	ChEST645d12	T3
FoxP1	ChEST899l18	T3
FoxP4	ChEST899n10	T3
Hmg1	ChEST69e14	T3
Klf8	ChEST376o15	T3
Lmx1a	ChEST609m14	T3
Nr2f2	ChEST848j5	T3
Prep2	ChEST190g11	T3
Rere	ChEST764l24	T3
Sox13	ChEST437d11	T3
Tead3	ChEST772a17	T3
Tfap2e	ChEST104e8	T3
Vgll2	ChEST976p9	T3
Zbtb16	ChEST1038b13	T3
Zfhx3	ChEST472l4	T3
Znf384	ChEST537d14	T3

Probes obtained from cloned sequences			
Gene name	**Vector**	**Primers**	**Polymerase**
Arid3a	TOPO pCR2.1	F 5' GGCGAGAGATCACCAAGG 3' R 5' CCAGTGCCATCTTCTTCTCC 3'	T7
Blimp1	TOPO pCR2.1	F 5' AGGCTTCCTTGCCAAGGA 3' R 5' TGTGAAGCCTTTATTGCAAGTCT 3'	T7
Ets1	TOPO pCR2.1	F 5' CATCCAGGAAGTTCCCACTG 3' R 5' GGGTCACGAAGGATGACTGA 3'	T7
Irx5	TOPO pCR2.1	F 5' GGTTACAACTCGCACCTCCA 3' R 5' GAGCCGTAGTTCGTGTAGCC 3'	T7
Klf7	TOPO pCR2.1	F 5' TGAGGACTTGGACTGCTTCC 3' R 5' TCACCTGTGTGAGTCCTCTGG 3'	T7
Tbx10	TOPO pCR2.1	F 5' CAGGCAGGAGGATGTTCC 3' R 5' TTCAACTGGGTGATCCGG 3'	T7

Probes obtained from different sources				
Gene name	**Vector**	**Polymerase**	**Source**	**Reference**
Lef1	Slax	T7	C. D. Stern	Skromne & Stern, 2001
Pax2	pBluescript KS II	T3	C. D. Stern	Streit, 2002
Sox11	pBluescript KS II	T3	P. Scotting	Uwanogho et al, 1995
Soho-1	pBluescript KS II	T3	D. Fekete	Kiernan et al., 1997
Tcf4	pGEM-T-Easy	SP6	C. Kiecker	Quinlan et al., 2009

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