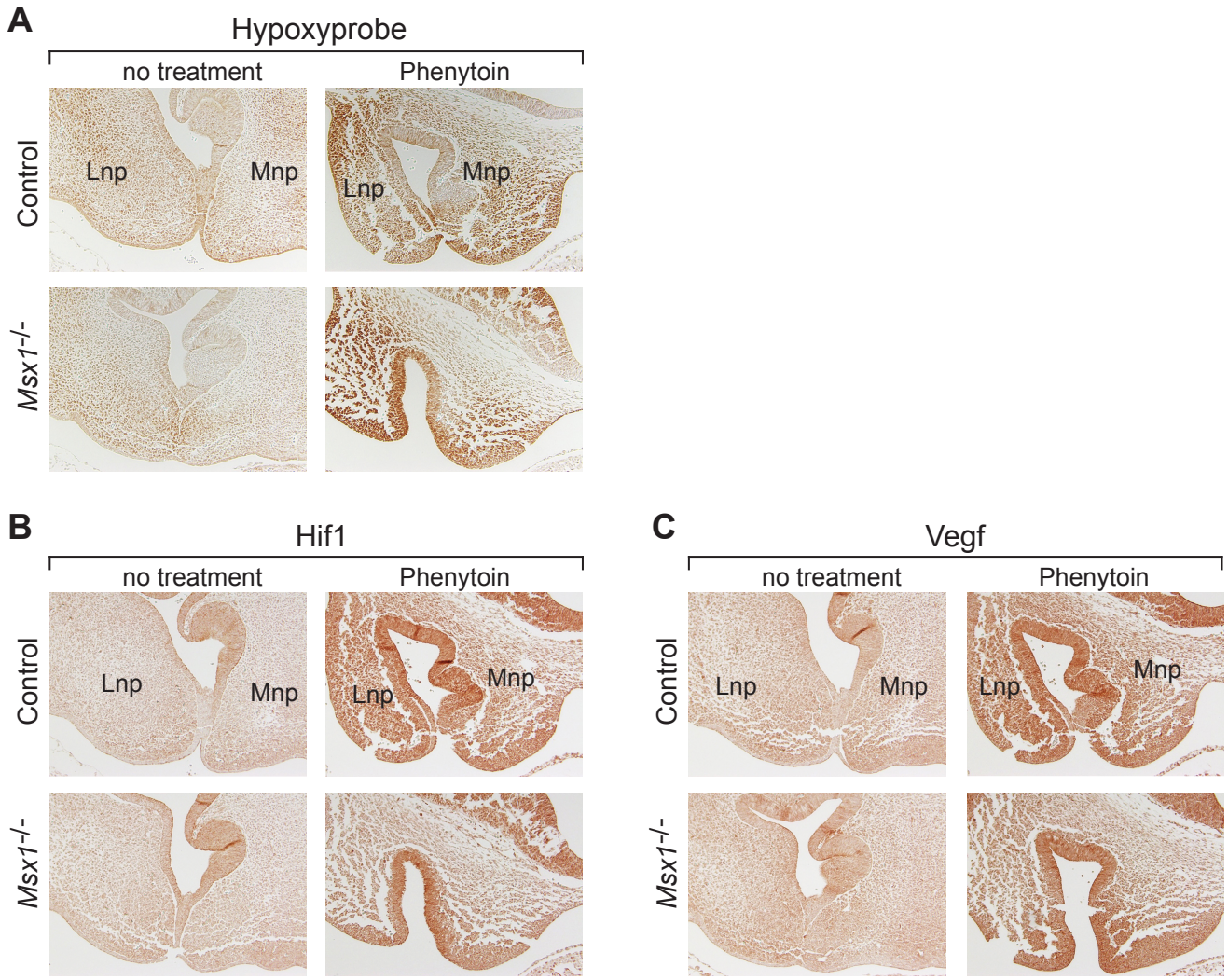

Fig. S1. Hypoxia and expression of Hif1 and Vegf in the lip-forming region at E11.0. In the experimental group, Phenytoin was injected at a concentration of 60mg/kg. (**A**) Hypoxic tissue is detectable in the medial nasal process (Mnp) and lateral nasal process (Lnp) of both control embryos and *Msx1*$^{-/-}$ mutants after Phenytoin injection. (**B**) Hif1 expression is induced in the experimental group but is weaker in *Msx1*$^{-/-}$ mutants when compared to that in controls. (**C**) Vegf is expressed after Phenytoin injection and appears stronger in the control embryo.

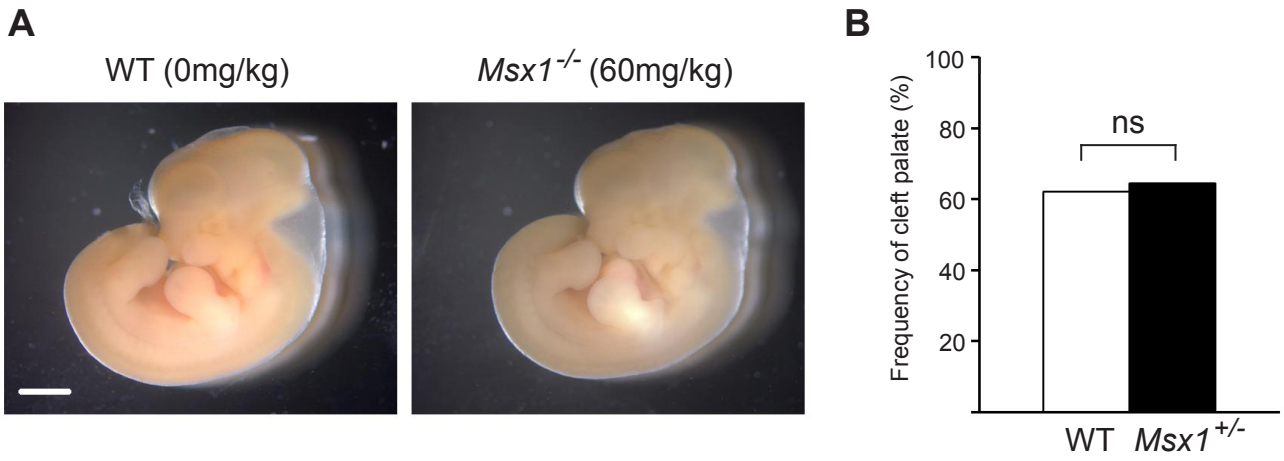

Fig. S2. Interaction between *Msx1* mutation and phenytoin-induced clefting is not influenced by the maternal genotype. (**A**) Lateral view of embryos (E11.5) exposed to phenytoin. Phenytoin injection does not affect general body development even in the complete absence of *Msx1*. (**B**) No significant difference of cleft palate frequencies is seen in phenytoin-exposed *Msx1*$^{+/-}$ embryos from wild-type (N=37) or *Msx1*$^{+/-}$ (N=45) mother, indicating that the genotype of the embryo but not that of the mother is the critical determinant of phenytoin-induced orofacial clefting. WT, wild type; ns, not significant. Scale bar: 1mm.

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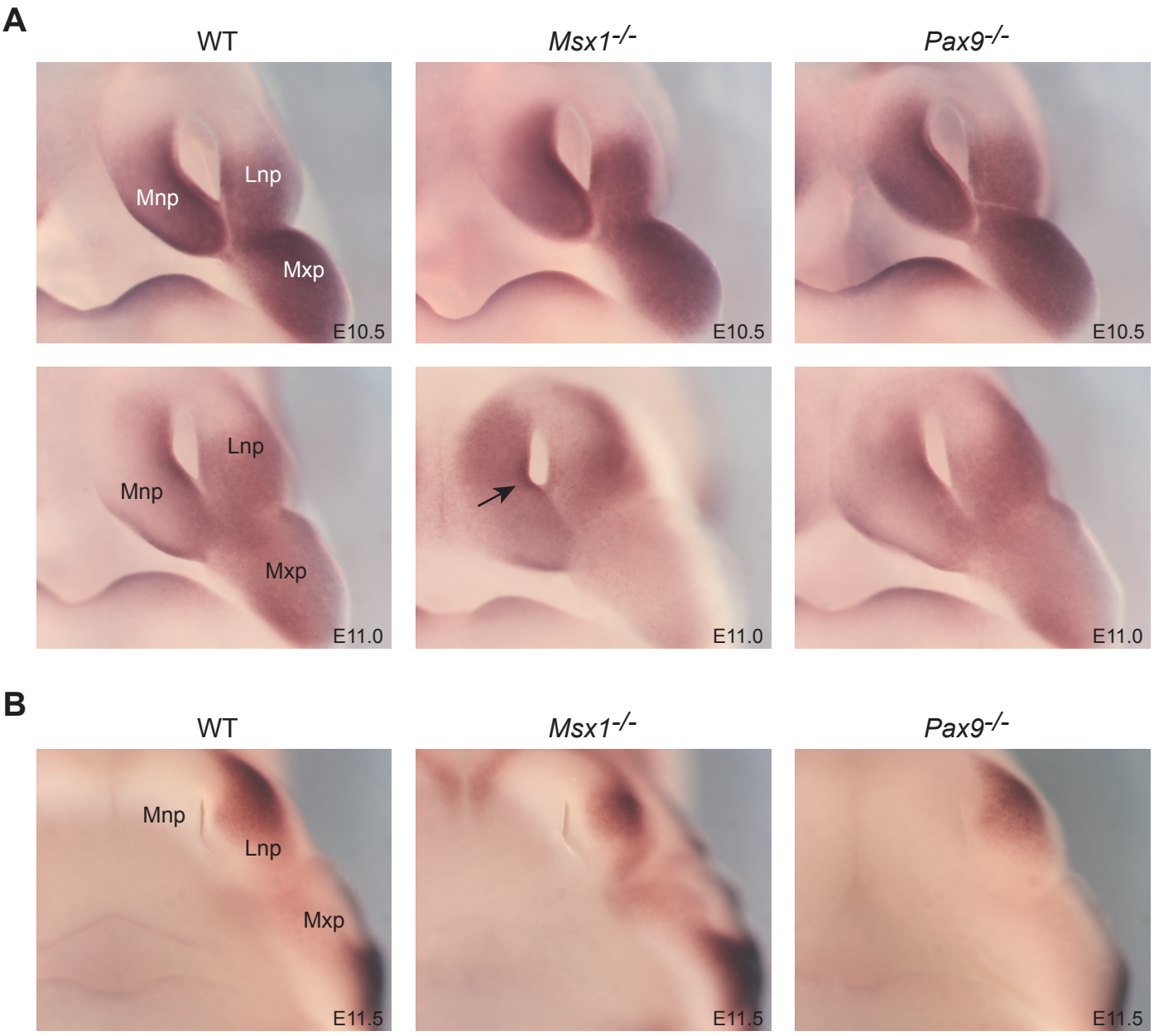

Fig. S3. Whole-mount in situ hybridization of genes paralog to *Msx1* and *Pax9*. The expression patterns of *Msx2* (**A**) and *Pax1* (**B**) are not changed among wild-type (WT), *Msx1*$^{-/-}$ and *Pax9*$^{-/-}$ embryos, respectively. Note the kink on the nasal aspect of the Mnp in the *Msx1*$^{-/-}$ embryo at E11.0 (arrow).

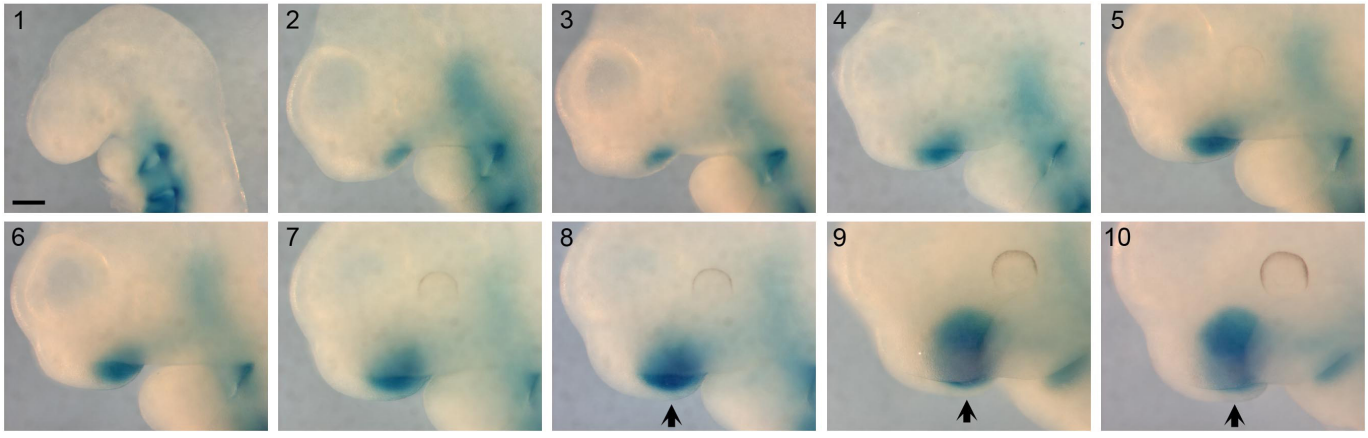

Fig. S4. Pax9 expression is gradually down-regulated in the distal region of the developing Mnp. Lateral view of X-gal stained *Pax9*$^{+/-}$ embryos between E10.0 to E10.75 (arranged in a chronological order and labelled 1-10). Note that at earlier stages *Pax9* is initially expressed at the tip of the Mnp, after which the expression becomes restricted to more proximal regions as development proceeds(arrows). Scale bar: 250 µm.

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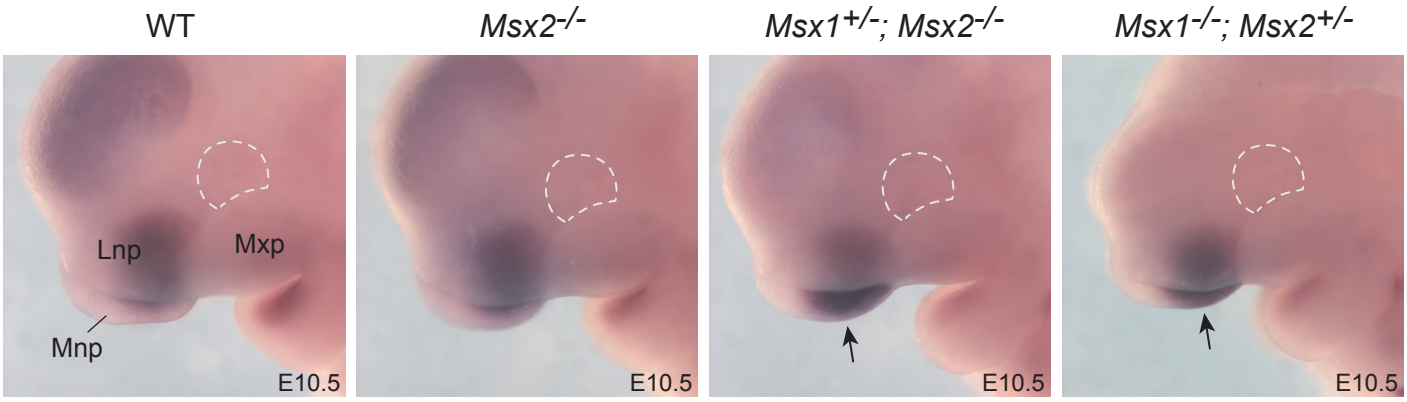

Fig. S5. *Pax9* expression at E10.5 is expanded in the medial nasal process (Mnp) of *Msx1*/*Msx2* compound mutants. Images show lateral views; the visible part of the eye is outlined to aid orientation. Note the distally expanded expression of *Pax9* in the Mnp of *Msx1*$^{+/-}$*; Msx2*$^{-/-}$ and *Msx1*$^{-/-}$*; Msx2*$^{+/-}$ embryos (arrows).

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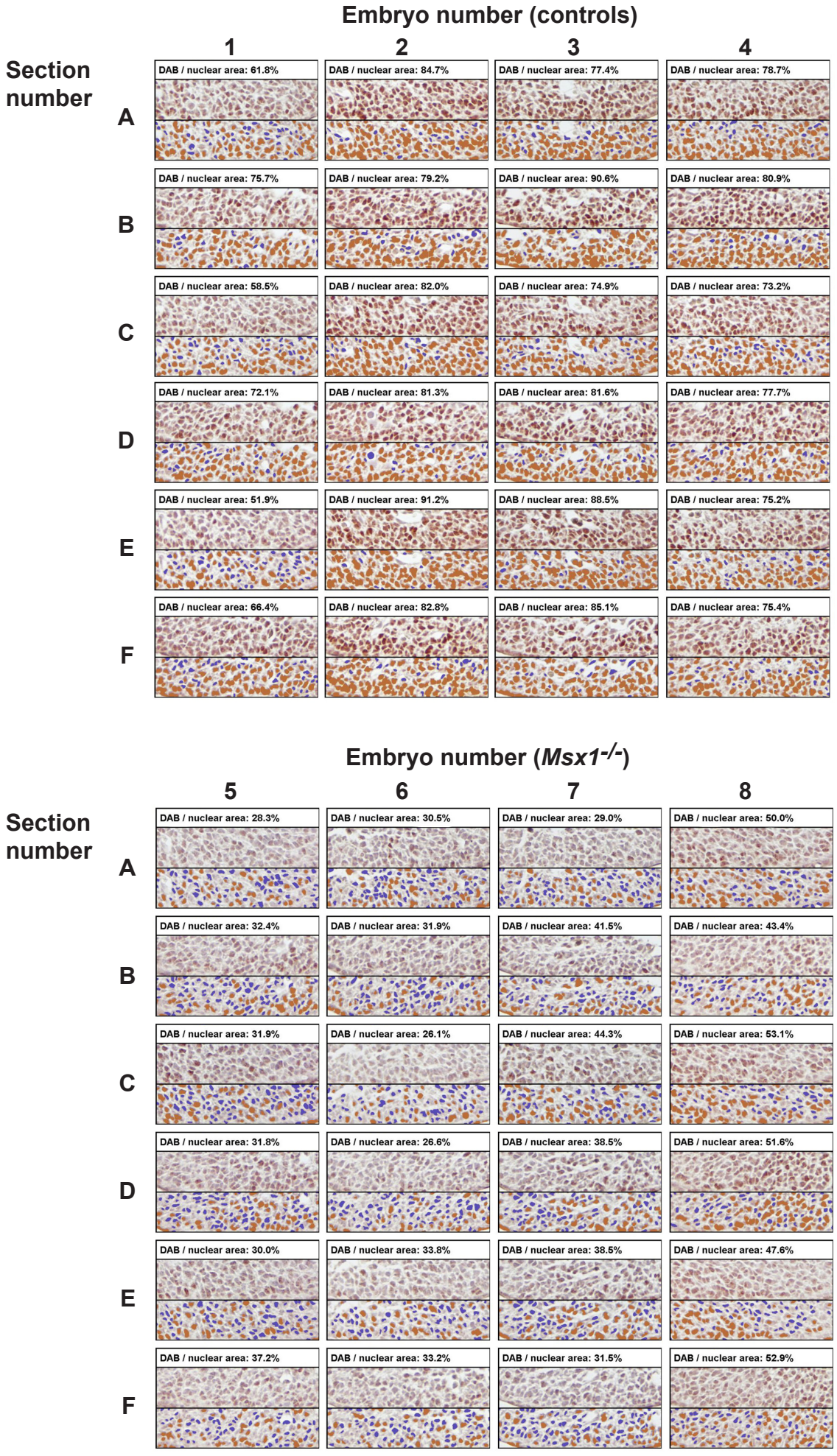

Fig. S6. Quantification of pSMAD-positive nuclei in the Mnp of controls and *Msx1*$^{-/-}$ embryos. Each panel is subdivided and shows DAB staining (top) and software-aided (ImmunoRatio) identification of pSMAD-positive cells (bottom). See Table S2 for statistical computation.

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Table S1. Raw data of sample numbers of phenytoin-induced cleft lip and cleft secondary palate. Upper rows indicate phenytoin dosage in mg/kg body weight of the pregnant mother. Note that total numbers of cleft lip (CL) are subdivided into unilateral (U) and bilateral (B) CL, while hypoplastic (H) upper lips were not counted as CL and thus were not considered in the statistical analysis. Numbers of cleft secondary palate (CP) are subdivided into partial (P) and complete (C) clefts and were all considered in the statistical analysis. N = number of embryos analysed; ns = not significant; / = no informative result or sample number to low for statistical analysis.

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Table S2. Statistical evaluation of pSMAD-positive nuclei in the Mnp of control and *Msx1* $^{-/-}$ embryos. In both groups four samples with 6 sections each were analysed using ImmunoRatio (Fig.S6) to determine the percentage of stained nuclei.

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Table S3. A total of 1073 human genes are annotated in GO:0009887 (animal organ morphogenesis; column A, list retrieved in January 2020). GWAS data analysed by VEGAS Pathway Analysis was available for 632 genes, of which 557 genes could be directly matched to GO:0009887 (shown in grey). 166 out of 557 genes (29,8%) have previously been shown to be involved in human or mouse lip, palate or facial development.

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Table S4. 75 genes were identified by VEGAS Pathway analysis that are not included in the most recent GO:0009887 (list retrieved in January 2020). 18 out of 75 genes (24%) have previously been shown to be associated with defects in human or mouse lip, palate or facial development.

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Table S5. Of 112 loci recently identified to be associated with variations in facial morphology 32 genes could be matched to genes listed in GO:0009887 ("organ morphogenesis") that were present in our Vegas Pathway Analysis

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