Figure S1: Spatial loss of EZH2 function in the CM is comparable between the E8.5-CM^{Ezh2} and E9.5-CM^{Ezh2} mutants. (A) *PdgfrαCreER/+;Ezh2$^{fl/fl}$* Rosa 26 Reporter lineage-marked CM in E13.5 coronal sections of frontal (plane I) and parietal (plane II) bone primordia of E9.5-CM^{Ezh2} mutants. (B) Schematic of coronal sections at the frontal (plane I) and parietal (plane II) bone primordia. (C) H3K27me3 immunofluorescence in coronal sections in the frontal bone primordia and parietal bone primordia showing comparable depletion of H3K27me3 in the CM of E8.5-CM^{Ezh2} and E9.5-CM^{Ezh2} mutants (scale bar = 200μm).

Figure S2: Whole mount analysis of E13.5 and E17.5 of E8.5-CM^{Ezh2} mutants. (A) Gross phenotype of E8.5-CM^{Ezh2} mutant embryos at E13.5. The shortened snout and limbs are apparent (B) *PdgfrαCreER/+;Ezh2$^{fl/fl}$* Rosa 26 Reporter lineage-marked CM in coronal sections at E13.5 in the frontal (plane I) and parietal (plane II) bone primordia. (C) At E17.5, E8.5-CM^{Ezh2} mutants also exhibit truncated limbs (I), defects in vasculature (II), and omphalocele (III). Vasculature defects are apparent by hemorrhaging blood vessels.

Figure S3: Quantification of the mandible and snout in e8.5-CM^{Ezh2} mutants. (A) Quantification of the length and volume from the microCT 3D images of the mandible. (B) Quantification of the length and volume of the pre-maxilla, maxilla, and nasal bones from the microCT 3D images. (C) Representative microCT 3D images of the interparietal bone. Definition of

landmarks: (1) Posterior point of the condylar process (2) Most anterior point of the mandible (3) Posterior-medial point of the palatine process of the maxilla (4) Most anterior-superior point of the premaxilla.

Figure S4: The cell survival and proliferation index is comparable between the CM of controls and E8.5-CM^{Ezh2} mutants. (A) Schematic of E10.5 mouse embryo and plane of interest in the coronal plane. Plane I refers to future frontal bone and plane II refers to the future parietal bone. Blue region on the coronal representations indicates the area of cell counts. (B) Immunofluorescence for cell death by activated Caspase-3 on E10.5 coronal sections in plane I and plane II in controls and E8.5-CM^{Ezh2} mutants (scale bar = 100µm). (C) Fluorescent staining of EdU on E10.5 coronal sections in plane I and plane II in controls and E8.5-CM^{Ezh2} mutants (scale bar = 100µm). (D,E) Quantification of activated Caspase-3 immunoflourescence, total number of DAPI positive cells, and EdU staining in controls and E8.5-CM^{Ezh2} mutants in the CM (D) and frontonasal process (E). (F) Quantification of activated Caspase-3 in controls and E9.5-CM^{Ezh2} mutants.

Figure S5: Comparable expression of bone initiation program markers in controls and E9.5-CM^{Ezh2} mutants. (A) Alkaline phosphatase staining in plane I and plane II in E13.5 coronal sections. (B) Immunofluorescence on E13.5 coronal sections for OSX in E9.5-CM^{Ezh2} mutants. Scale bars = 200µm.

Figure S6: The effects of RA signaling activation in the CM. (A) Skeletal preparations examining the effect on skull bones following administration of exogenous 100µg/gm body weight at-RA at E10.0. Alcian blue marks cartilage and alizarin red marks bone (scale bars = 2mm). (B) RT-qPCR for the three RARs in E13.5 manually enriched CM. (C) RT-qPCR for *Crabp2* in E8.5-CM^{Ezh2} and E8.5-CM^{Ezh2} + BMS-453 mutants from E13.5 manually enriched CM. (D) Gross phenotypes of the different doses of BMS-453. (2mm).

Figure S7: E8.5-CM^{Ezh2} mutants exhibit ectopic expression of the *Hox* genes. (A) Schematic of manual enrichment of the CM at E13.5. (B) RT-qPCR for relative mRNA quantity of target genes for signaling pathways known to play a role in skull bone formation in enriched CM. (C) RT-qPCR for the RA-sensitive gene, *Stra6*. (D) RT-qPCR for a subset of *Hox* genes.

Table S1. Expression level changes between the controls and E8.5-CM^{Ezh2} mutants. Heat map comparing difference in fold change between the control and E8.5-CM^{Ezh2} mutant in E13.5 manually enriched CM. The average fold change of the control was subtracted from the average fold change of the mutant and the values were mapped.