Supplemental Results

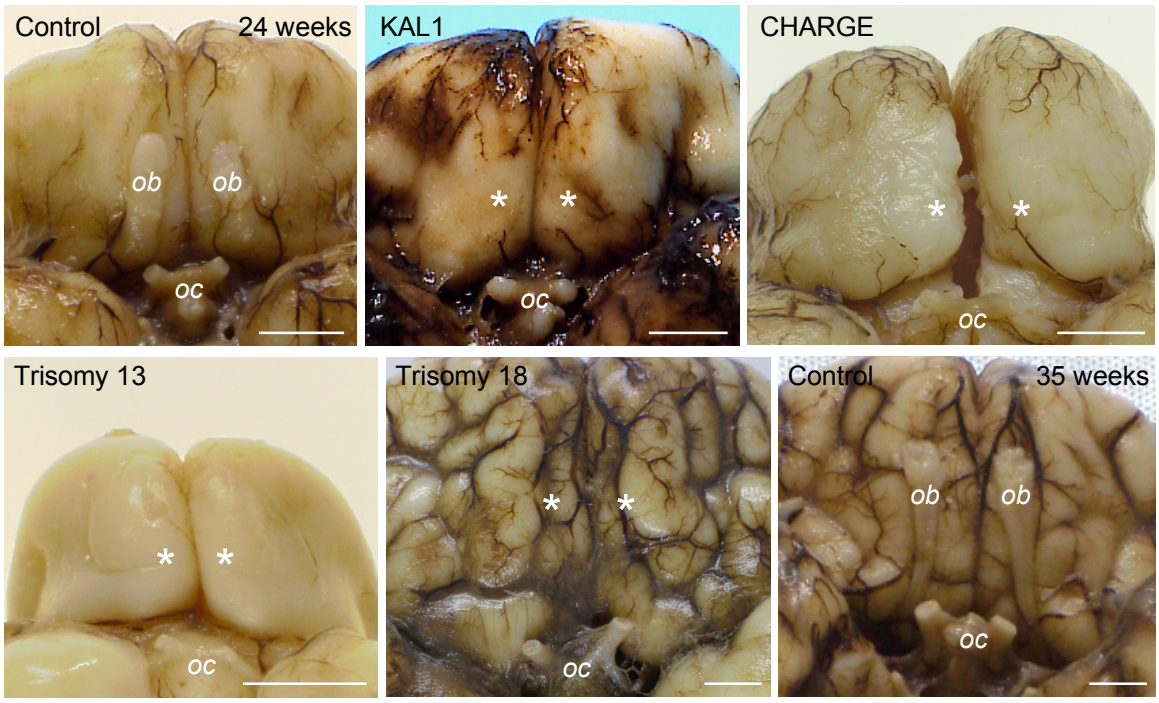
Fetopathological and genetic analyses of the Kallmann syndrome 1 (KAL1), CHARGE syndrome, trisomy 13, and trisomy 18 fetuses.

KAL1 fetus. Severe oligohydramnios and bilateral renal agenesis were detected by ultrasonography at 22 weeks gestation. A maternal uncle had been diagnosed with X chromosome-linked Kallmann syndrome, so the disease, which can include unilateral or bilateral renal agenesis, was also suspected in the fetus. Termination of pregnancy was carried out at 25 weeks of gestation. Fetopathological examination displayed an arhinencephalic male fetus. Bilateral renal and ureteral agenesis was associated with lung hypoplasia (Potter malformative sequence). Genetic analysis confirmed that the fetus had the same c.769C>T (p.R257X) nonsense mutation in *KAL1* as its uncle.

CHARGE syndrome fetus. Cardiac malformation was detected by ultrasonography at 21 weeks gestation, and termination of pregnancy was carried out at 23 weeks. CHARGE syndrome was suspected from the association of arhinencephaly, asymmetrical misshaped pinnas, and heart defect (Ebstein anomaly of the tricuspid valve) on fetopathological examination, combined with a normal 46, XY karyotype. In addition, omphalocele and thymus atrophy were noted. Close examination also showed the abnormal presence of bilateral spherical structures, approximately 1 mm in diameter, on the dorsal aspect of the ethmoid bone cribriform plate (see Figure 2*D*). Aplasia of the three semicircular canals was visualized on X-ray examination of the skull. Genetic analysis revealed a c.7231delG (p.A2411fsX32) frame-shifting mutation in *CHD7*.

Trisomy 13 fetus. Cleft lip and palate, omphalocele, and liver calcifications were detected by ultrasonography at 15 weeks gestation. Cytogenetic analysis of amniotic fluid cells showed a 47, XX+13 karyotype. Termination of pregnancy was carried out at 18 weeks. Fetopathological examination showed an arhinencephalic female fetus with dilated cerebral ventricles. In addition, aortic bicuspidia, tricuspid malformation, and ectopic thymus were noted.

Trisomy 18 fetus. Retarded growth, agenesis of the corpus callosum, and cardiac malformation were detected by ultrasonography at 31 weeks gestation. Cytogenetic analysis of amniotic fluid cells showed a 47, XY+18 karyotype. Termination of pregnancy was carried out at 35 weeks. Fetopathological examination displayed an arhinencephalic male fetus with a micropenis. In addition, corpus callosum agenesis, dextroposition of the aorta, aortic and tricuspid bicuspidia, lung hypoplasia, and right hand arthrogryposis were noted.



Supplemental Figure 1. Absence of the olfactory bulbs in the KAL1, CHARGE, trisomy 13, and trisomy 18 fetuses.

The rostral forebrains (ventral aspect) of the four arhinencephalic fetuses and two control fetuses aged 24 and 35 weeks are shown. Asterisks denote the position of the absent olfactory bulbs in the KAL1, CHARGE, trisomy 13, and trisomy 18 fetuses. Abbreviations: *ob*, olfactory bulb; *oc*, optic chiasma. Scale bars: 1 cm