New BRAF knock-in mice provide a pathogenetic mechanism of developmental defects and a therapeutic approach in cardio-facio-cutaneous syndrome

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Dr. Yoko Aoki's research group has been studying the molecular mechanisms for RASopathies, a group of phenotypically overlapping syndromes caused by germline mutations that encode components of the RAS-MAPK pathway. They, in collaboration with Prof. Ogura's group (Institute of Development, Aging and Cancer, Tohoku University), generated and analyzed knock-in mice expressing the Braf Q241R mutation, which corresponds to the most frequent mutation in cardio-facio-cutaneous (CFC) syndrome, Q257R. BrafQ241R/+;Cre mice manifested embryonic/neonatal lethality, showing liver necrosis, edema, craniofacial abnormalities, thickened cardiac valves, ventricular noncompaction and ventricular septal defects, which recapitulate the major phenotypes of CFC syndrome. Prenatal treatment with a MEK inhibitor, PD0325901, rescued the embryonic lethality with amelioration of craniofacial abnormalities and edema in BrafQ241R/+;Cre embryos. Combination treatment with PD0325901 and a histone 3 demethylase inhibitor (GSK-J4) further increased the rescue from embryonic lethality, ameliorating enlarged cardiac valves. These results suggest that the new BRAF knock-in mice recapitulate major features of RASopathies and that epigenetic modulation as well as the inhibition of the ERK pathway will be a potential therapeutic strategy for the treatment of RASopathies.

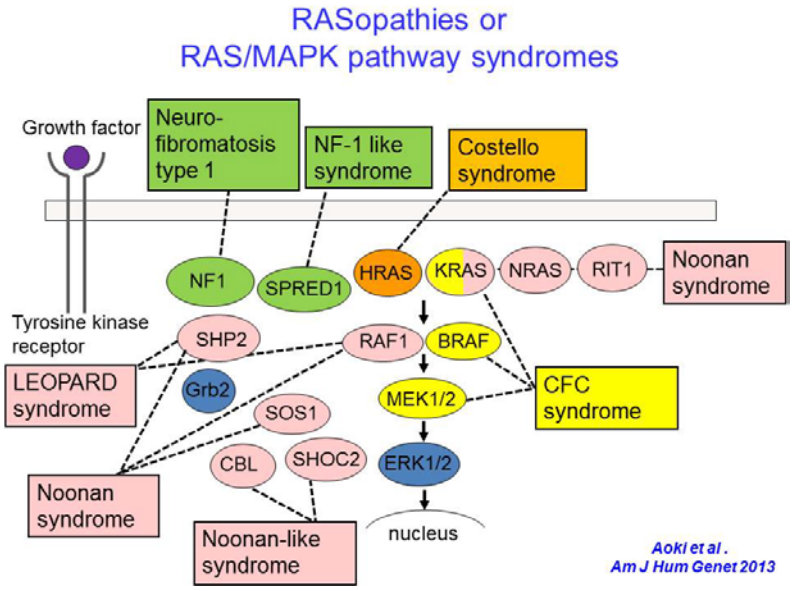

Figure 1. RASopathies. *BRAF*, *MAP2K1/2* or *KRAS* mutations have been identified in individuals with CFC syndrome.

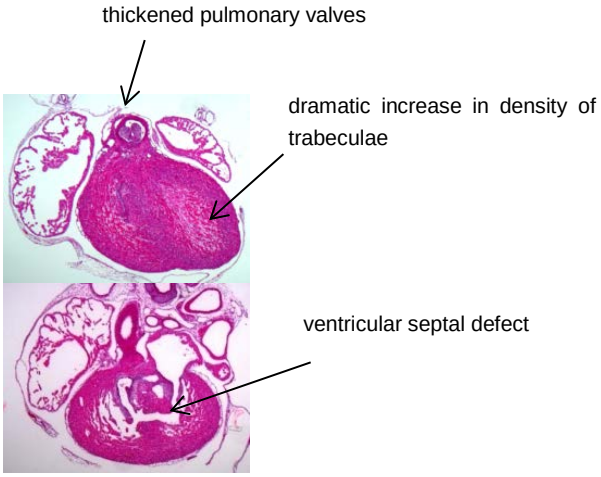

Figure 2. Heart defects observed in *Braf*$^{Q241R/+}$; *Cre* embryos at E16.5.

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