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Familial congenital heart disease induced by heterozygous missense mutation in *Nkx2-5*: Genetic and beyond genetic effects?

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Introduction: Heterozygous missense mutations in the homeodomain of human *NKX2-5* lead to a high penetrance of diverse cardiac anomalies, including Tetralogy of Fallot, along with near complete penetrance of Atrioventricular (AV) conduction defects, compared with mutations outside the homeodomain. We recently replicated a disease-causing missense mutation in the homeodomain in a knockin mouse model, *Nkx2-5^{+R52G}*, which demonstrate a high incidence of cardiac malformations and AV conduction defects. Although these mutant mice were backcrossed over 8 generations and expected to have almost the same genetic codes, these mice demonstrate pleiotropic cardiac anomalies, suggesting the presence of non-genetic effects.

Hypothesis: Since maternal health conditions are critical for normal embryonic development, we hypothesize that cardiac defect in the mutant mother's affects embryonic cardiac development.

Methods: Heterozygous mutant and wild-type mice were mated in two different groups: (Group 1) female mutant *Nkx2-5^{+R52G}* and male normal mice; (Group 2) female normal mice and male mutant *Nkx2-5^{+R52G}* mice. The offspring were analyzed postnatal day 7 (P7) by which the mutant mice with severe cardiac anomalies are expected to die.

Results: The genotype of the offspring from Group 2 follows the Mendelian's law (51% wild-type and 49% mutant, n=115). However the ratio of the genotype from Group 2 was 65% wild-type and 35% mutant (n=89), suggesting that half of the mutant mice died before postnatal day 7.

Conclusion: Our results indicate that when the mothers have heterozygous *Nkx2-5* mutation, less number of mutant mice survive until P7, and lead to near 50% of loss of mutant offspring by P7.

Biography

Hideko Kasahara completed her MD and PhD from Nagoya University and National Institute of Physiological Sciences in Japan, and postdoctoral studies from University of Michigan and Beth Israel Deaconess Medical Center/Harvard University. She is currently Associate Professor, University of Florida College of Medicine. She has published 48 papers, half of which are related to *Nkx2-5* in reputed journals, and has been serving as an editorial board member of Laboratory Investigation.

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