A ZEBRAFISH (DANIO RERIO) MODEL IDENTIFIES NOVEL GENETIC MECHANISMS FOR NICOTINE REINFORCEMENT AND HUMAN SMOKING BEHAVIOR.

Date: August 2nd (Tue) 16:00-17:00, 2016　　平成 28 年 8 月 2 日（火）16:00～
Place: Center for AIDS Research, 2F, Seminar Room　　ｴｲｽﾞ学研究ｾﾝﾀｰ 2 階ｾﾐﾅｰ室

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Abstract

There is substantial genetic variability in smoking behaviour, but the molecular mechanisms underlying this habit remain largely unknown. We performed a population-based behavioural genetic screen of N-ethyl-N-nitrosourea (ENU)-mutagenized zebrafish to establish heritability of nicotine conditioned place preference and identify relevant genes. We then examined the gene effects on human smoking in three study groups: chronic obstructive pulmonary disease (COPD) (n=272); asthma (n = 293); residents and carers in sheltered accommodation; (n=298). Change in place preference (Cp) for nicotine was normally distributed in the first generation. The second generation had a mean Cp of 0.08 for low response families (P = 0.0002) and 0.07 for high responders (P = 0.001). The third generation had mean Cp of 0.21 for high and 0.01 for low responders. 14 gene breaking mutations were present in the high responder line of which only one in SLIT3 segregated with Cp. Analysis of gene expression in nicotinergic and dopaminergic signaling pathways in wild type and SLIT3 mutant (2, 3 and 5 day) zebrafish larvae showed increased expression of CHRNA5. In human studies two loci in SLIT3, were associated with number of cigarettes smoked each day (-4.24, [95% CI -6.80, -1.68, p=0.00125], -3.99, [-6.534, -1.44, p=0.00227]). Nicotine preference is heritable in fish as in humans and loss of function mutations in SLIT3 which affect axonal guidance lead to increased nicotine preference. This work establishes a new animal model for nicotine addiction and identifies a novel mechanism underlying nicotine dependence in humans.

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