



AB003. S1-2. Genetic and environmental risk factors for cholangiocarcinoma (CCA)

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Abstract: CCA contains two subtypes based on the location: intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC). Various epidemiological risk factors for this tumor type are reported. Intrahepatic cholelithiasis and primary sclerosing cholangitis is the well-known predisposing factor for ICC. In South East Asia, the endemic liver flukes are major epidemiological factors. In addition, hepatitis viral infection, alcohol intake and obesity are reported to be risk factors. International collaborative study for CCA identified 10 mutational signatures [COSMIC signatures 1, 5, 8, 16, and 17, APOBEC

signatures, mismatch-repair deficiency-associated signatures (COSMIC signatures 6 and 20), and Aristolochic Acid (AA)-exposure signature 22]. Fluke-positive cholangiocarcinoma were enriched for APOBEC signatures. Recently an outbreak of CCA among workers in an offset color proof-printing company was reported in Japan. All patients had been exposed to high concentrations of chemical compounds, including 1,2-dichloropropane (1,2-DCP) and/or dichloromethane (DCM). Whole exome sequencing of four CCA cases of the printer workers demonstrated unique and predominant mutational spectra, that are distinct from known COSMIC mutational signatures. We performed whole exome sequencing of more than 250 Japanese CCA cases and identified somatic mutations in genes that have been reported to associate with familial CCA cases, which suggests potentially germline contribution to CCA. Collectively, large-scale and comprehensive genetic analyses have revealed diverse and unique contribution of both environmental and germline for CCA carcinogenesis.

Keywords: Mutational signature; aristolochic acid; APOBEC; dichloropropane (DCP)

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