NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

BIOLOGY COLLOQUIUM

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Hosted by A/P Ge Ruowen

Next-Generation Sequencing Approaches to Study the Genetic Susceptibility to Nasopharyngeal Carcinoma



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Nasopharyngeal carcinoma (NPC) is a cancer, which is rare in most parts of the world. Because of its high incidence in regions of Southern China, including Hong Kong, it is dubbed the "Guangdong tumor". Around 10% of NPC patients have a familial history of NPC, with an increased relative risk for getting NPC, as compared to the general population. There are other NPC patients, who develop this cancer at an especially early age (younger than 20). Little is known about these early-age onset (EAO) cases. The aim of our studies was to elucidate the molecular genetic basis for why NPC patients with a family history of the disease or those that develop the cancer early in life are more susceptible to NPC than others in Hong Kong. Therefore, we used the state-of-the-art sequencing and powerful bioinformatics tools to screen the genomes of NPC patients having an inherited genetic susceptibility and compared them to control individuals, who do not develop this cancer. In the discovery stage, we sequenced 56 independent family history positive (FH+) and 39 EAO patients, who were diagnosed with NPC at or younger than 20 years of age, and 59 sporadic NPC patients using the whole-exome sequencing (WES) approach. The WES data of 895 non-cancer controls mainly from Hong Kong and 415 non-cancer controls from Sichuan, China were used for comparison. Using a mixed model association test, we identified a novel 3'UTR variant at a G protein-coupled receptor associated with increased risk of NPC. This finding was confirmed in independent patient and control cohorts. Using a systematic filtering strategy and the gene-level burden tests, we found multiple rare deleterious variants at a macrophage-stimulating protein receptor mapped to the chromosome 3p21.3 region in the EAO and FH+ cases. Furthermore, we sequenced 322 FH+ families, 220 sporadic cases, and 317 healthy individuals independent from the discovery cohort using targeted gene sequencing of over one thousand selected genes mainly relevant to cell differentiation, chromosome organization, cell cycle, cell adhesion, DNA repair, telomere maintenance, and immune response in the validation stage. Details of the study will be presented. Functional characterization of the validated variants and the candidate genes associated with genetic susceptibility is underway. Our ultimate goal is to identify useful biomarkers to identify individuals at high risk for NPC. Early detection of NPC would improve treatment outcomes and improve the quality of life of NPC patients and their families.

Artwork by Ann Nee, DBS, NUS