| 京都大学 | 博士 （ ゲノム医学 ） | 氏　名 | Tomoko Nakanishi |
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| 論文題目 | Genetic determinants of respiratory diseases and their clinical implications（ゲノミクスで拓く呼吸器疾患病態解明とその臨床的意義の検討） | | |

（論文内容の要旨）

Despite the successful prosecution of large-scale genetic association studies to identify thousands of genetic determinants for respiratory diseases, the way to translate these insights into clinical fields has remained unrefined. This doctoral thesis presented potential avenues to translate such genetic findings into the clinical management of respiratory diseases, encompassing alpha-1 antitrypsin deficiency (AATD), idiopathic pulmonary fibrosis (IPF) and coronavirus disease 2019 (COVID-19).

First, AATD is a rare monogenic disorder caused by mutations in the SERPINA1 gene. This thesis demonstrated that in the UK Biobank, among 140 European-ancestry participants with the PI*ZZ genotype of SERPINA1, the most common AATD-associated genotype, only nine were diagnosed with AATD. Nonetheless, those with PI*ZZ had a substantially increased burden of multiple symptoms and diseases, including COPD and cirrhosis. The thesis concluded that genetic testing would help identify those at risk and contribute to early intervention, such as smoking cessation counselling.

Second, IPF is a progressive, fatal fibrotic form of interstitial lung disease leading to decreased lung compliance and resulting in respiratory failure. The current thesis used a Mendelian Randomization (MR) approach, a causal inference technique, to efficiently scan hundreds of plasma proteins to identify potential disease-influencing proteins for IPF. The thesis identified that circulating FUT3 was associated with a reduced risk of IPF (odds ratio [OR]: 0.81 per 1 SD increase in FUT3), and concluded that FUT3 could be further investigated as drug targets for treatment, as well as noninvasive biomarkers of disease risk.

Lastly, the thesis applied the same approach to study the novel COVID-19 pandemic. It evaluated the major common genetic risk for severe COVID-19 on chromosome 3, which was tagged by the rs10490770 C allele. Risk allele carriers age ≤60 years had higher odds of death or severe respiratory failure (OR: 2.7) compared with those >60 years (OR: 1.5). This risk variant improved the prediction of severe disease similarly to most clinical risk factors. Thus, it implicates the use of this genetic risk to realize genetics-guided clinical management. Similarly, the thesis also used MR to identify potential disease-influencing proteins for COVID-19 severity and susceptibility. It identified that an SD increase in OAS1 levels was associated with reduced COVID-19 death or ventilation needs (OR: 0.54), hospitalization (OR: 0.61), and susceptibility (OR: 0.78). The thesis concluded that known pharmacological agents that increase OAS1 levels could be explored for their effect on COVID-19 outcomes.

In summary, this doctoral thesis provided a novel contribution to the field of genetics in respiratory medicine, by demonstrating potential opportunity to realize clinical benefits of emerging worldwide genomic efforts and by identifying potentially druggable disease-influencing plasma proteins.

(Summary of Dissertation Examination Results)

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From the very convincing answers of the candidate to the numerous questions of the defense committee members, it is clear that she has a deep understanding of a wide range of topics related to human genetics. As a result of the oral defense of her thesis held on-line on April 5th, 2022, we certify that the candidate has passed the oral examination.