（報告様式４）

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I.　基本情報

事　　業　　名：（日本語）オーダーメイド医療の実現プログラム
（英　語）Tailor-Made Medical Treatment with the BioBank Japan Project (BBJ)

研究開発課題名：（日本語）疾患関連遺伝子等の探索を効率化するための遺伝子多型情報の高度化
（英　語）High-quality genetic research to identify susceptibility genes of common diseases

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分担研究　（日本語）
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II.　成果の概要（総括研究報告）

本課題は、バイオバンク等に収集された DNA サンプル等を用いたゲノム解析を実施し、疾患関連遺伝子研究及び薬剤関連遺伝子研究のための基盤情報を提供する事を目的としている。平成 28 年度は、バイオバンク・ジャパン等で収集された DNA サンプルを用いた新たなゲノム解析は実施せず、平成 27 度までに得られたゲノムデータを用いて疾患関連遺伝子研究を実施し、研究基盤を維持した。また平成 27 年度調整費で実施した全ゲノムシークエンスデータの検証の準備を行った。

以前に本課題で得られた、バイオバンク・ジャパンの疾患検体の SNP データと 3 つのゲノムコホート(J-MICC, JPHC, 東北 MM) から得られたコントロールの SNP データを用いて、種々のゲノムワイド関連解析を実施した。このうち、心房細動に関しては、東京医科歯科大学との共同研究として進め、最終的には 11,300 人の心房細動患者と 153,676 人の対照者からなるゲノムワイド関連解析

を行って 6 箇所の新たな心房細動感受性ゲノム領域を同定した。さらに遺伝子セットエンリッチメント解析を行うことで神経堤細胞の分化経路が発症に関わることを示し、またハーバード大学が主導する国際共同研究 AFGen とも協調して足並みをそろえて解析を進め、論文化した（平成 29 年 4 月、Nature genetics 誌にオンライン掲載)。脳梗塞については、岩手医科大学と共同で Stroke 誌に論文を報告した（平成 29 年 2 月)。その他にも、理化学研究所はバイオバンク・ジャパンサンプルのゲノムワイド関連解析結果を用いて、脂質、テロメア長、肺がんなど多数の国際的なゲノム解析共同研究に参加している。これは、国際的なゲノム解析研究成果のほとんどに日本人の結果が含まれることを意味しており、将来の我が国におけるゲノム医療において非常に重要な貢献である。

さらに、様々な臨床情報を用いたゲノムワイド量的形質座（QTL）解析を実施している。このうち、米国ミシガン大学が主導する赤血球数の国際共同研究の成果について、平成 28 年 10 月に American Journal of Human Genetics 誌に掲載された。

平成 27 年度に作成した 1,037 例の全ゲノムシークエンスデータを用いて、バイオバンク・ジャパン全サンプルと 3 つのゲノムコホート(JMICC, JPHC, 東北 MMB)の SNP アレイデータのインピュテーション解析を行った。並行して、構造変異（Structural variant, SV）の解析を進めている。
薬剤関連遺伝子研究では、抗結核薬による肝障害、婦人科がんにおける治療関連遺伝子、抗血小板薬クロピドグレルの関連遺伝子を同定した。

The aim of this project is to perform various genomic researches using DNA samples collected at BioBank Japan and provide basic information for susceptibility genes on disease and drug responses. In FY2016, we did not start new genomic research, but maintained research infrastructure and conducted various genomic research using data obtained until FY2015.

We set up the system for the validation of variant call of whole genome sequencing data obtained last year. We performed genome-wide association studies (GWAS) of various diseases using the data of BioBank Japan samples and 3 population-based cohorts (J-MICC, JPHC, Tohoku MM), which was obtained in this project previously. Among them, GWAS for atrial fibrillation was conducted as a collaborative research with Tokyo Medical and Dental University, and identified 6 new susceptibility loci by using 11,300 cases and 153,676 controls. Furthermore, by gene set enrichment analysis, we clarified that the differentiation pathway of neural crest cells is involved in the onset of atrial fibrillation. This GWAS was performed in parallel with the international collaborative research, AFGen, and the results were published in Nature Genetics (AOP April, 2017). As for cerebral infarction, we published the results to Stroke (2017;48(2):253-258.) in collaboration with Iwate Medical University. In addition, RIKEN Center for Integrative Medical Sciences is participating in numerous international GWAS consortium using the results of BioBank Japan data. This will be a very important contribution for the implementation of genome medicine in the future.

Furthermore, we have been conducting genome-wide quantitative trait locus (QTL) analysis for various phenotypes using the same GWAS dataset. Among them, the results of

the international collaborative research on the erythrocytes trait was published in the American Journal of Human Genetics (2017;100(1):51-63).

Using 1,037 whole genome sequencing data created in FY2015, we performed whole genome imputation analysis to the GWAS data of Biobank Japan and 3 population-based cohorts. Analysis to detect structural variation (SV) is also ongoing.

For pharmacogenomics research, we identified susceptibility genes for anti-tuberculous drugs induced liver damage, therapeutic-related genes in gynecological cancer, and related genes of antiplatelet drug clopidogrel.

III. 成果の外部への発表

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（4）特許出願

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