（報告様式４）

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平成　29　年　5　月　30　日

平 成 28 年 度　委 託 研 究 開 発 成 果 報 告 書

I.　基本情報

事　　業　　名：（日本語）難治性疾患実用化研究事業
（英　語）Practical Research Project for Rare / Intractable Diseases

研究開発課題名：（日本語）遺伝性心血管疾患における集中的な遺伝子解析及び原因究明に関する研究
（英　語）Comprehensive Genome Analysis for Hereditary Cardiovascular diseases

研究開発担当者　（日本語）大学院医学系研究科　医化学講座　教授　高島　成二
所属 役職 氏名：（英　語）Osaka University Graduate School of Medicine,
Department of Cardiovascular Medicine, Professor,
Seiji Takashima

実　施　期　間：　平成　28　年　4　月　1　日　～　平成　29　年　3　月　31　日

分担研究開発課題名：
（日本語）ゲノム解析の実施、同定変異の基礎研究とその臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）
（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発分担者所属 役職 氏名：
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Shintaro Kinugawa

分担研究開発課題名：
（日本語）ゲノム解析の実施、同定変異の基礎研究とその臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）
（英　語）Genome analysis and applications for clinical use
(Collection of patients for the genome variant database)

研究開発分担者所属 役職 氏名：
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Tohoku University Graduate School of Medicine, Professor,
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分担研究開発課題名：
（日本語）遺伝性心血管疾患の症例集積と症例機能解析および
ゲノム情報解析システムの開発・普及推進
（英　語）Case collection, functional analysis of cardiovascular genetic diseases, and system development for genomic information

研究開発分担者所属 役職 氏名：
（日本語）東京医科歯科大学大学院医歯学総合研究科　循環制御内科学　教授 磯部　光章
（英　語）Department of Cardiovascular Medicine,
Tokyo Medical and Dental University, Professor,
Mitsuaki Isobe

分担研究開発課題名：
（日本語）ゲノム解析の実施、同定変異の基礎研究とその臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）
（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発分担者所属 役職 氏名：
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分担研究開発課題名：
（日本語）ゲノム解析の実施、同定変異の基礎研究とその臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）
（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発分担者所属 役職 氏名：
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分担研究開発課題名：

（日本語）ゲノム解析の実施、同定変異の基礎研究とその臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）

（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発分担者所属 役職 氏名：

（日本語）金沢大学医薬保健研究域医学系 大学院医薬保健学総合研究科
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（英　語）Department of Cardiovascular and Internal Medicine,
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分担研究開発課題名：

（日本語）不整脈疾患を中心とした遺伝性心血管疾患の症例集積と同定遺伝子の解析、および
ゲノム情報解析システムの開発

（英　語）Genome Analysis for hereditary arrhythmias and identifications of causal gene variants

研究開発分担者所属 役職 氏名：

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分担研究開発課題名：

（日本語）遺伝性心血管疾患における集中的な遺伝子解析及び原因究明に関する研究

（英　語）Genome Analysis for hereditary cardiovascular diseases and
identifications of causal gene variants

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分担研究開発課題名：

（日本語）遺伝性心筋症および不整脈疾患に対する症例の蓄積とゲノム解析の実施
ゲノム解析症例の収集と診療ガイドライン作成に向けた臨床情報のデータベース化

（英　語）Collection and genome analysis of patients with hereditary cardiomyopathy and arrhythmia
Collection of patients for the genome variant database

研究開発分担者所属 役職 氏名：

（日本語）奈良県立医科大学　第一内科　教授　斎藤　能彦

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分担研究開発課題名：

（日本語）ゲノム解析の実施、同定変異の基礎研究による臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）

（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発分担者所属 役職 氏名：

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分担研究開発課題名：

（日本語）ゲノム解析の実施、同定変異の基礎研究による臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）

（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発担当者所属 役職 氏名：

（日本語）大阪大学大学院医学系研究科　循環器内科学　教授　坂田　泰史

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分担研究開発課題名：

（日本語）ゲノム情報システムの開発統括と普及推進
・新規解析パイプラインと施設間共有システムの研究開発
・遺伝情報参照システムの研究開発
・全国ネットワーク受託解析システムの研究開発

（英　語）Development and dissemination of the genome-analysis system
・Development of genome-analysis pipelines
・Setting up of genome-analysis servers and development of the gene variant database
・Formulation of the genome-analysis research network

研究開発分担者所属 役職 氏名：

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分担研究開発課題名：

（日本語）ゲノム解析の基礎研究と臨床実用化
遺伝性心血管疾患における集中的な遺伝子解析および原因究明に関する研究

（英　語）Genome analysis and applications for clinical use
Investigation on gene analysis and mechanisms in the
hereditary cardiovascular disease

研究開発分担者所属 役職 氏名：

（日本語）九州大学大学院医学研究院　循環器内科　講師　井手　友美

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分担研究開発課題名：

（日本語）遺伝性心血管疾患の症例集積と症例機能解析およびゲノム情報解析システムの開発・普及推進

（英　語）Collection and clinical analysis of patients with hereditary cardiovascular diseases. Development and dissemination of the genome-analysis system.

研究開発分担者所属 役職 氏名：

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分担研究開発課題名：

（日本語）ゲノム解析の実施、同定変異の基礎研究による臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）

（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

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分担研究開発課題名：

（日本語）ゲノム解析の実施、同定変異の基礎研究による臨床実用化
（ゲノム解析症例の収集と臨床情報のデータベース化）

（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

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分担研究開発課題名：

（日本語）ゲノム解析の実施、同定変異の基礎研究による臨床実用化
全国普及を目指すゲノム情報システムの開発と普及推進

（英　語）Genome analysis and applications for clinical use
Collection of patients for the genome variant database

研究開発担当者所属 役職 氏名：

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Yoshihiro Asano

II. 成果の概要（総括研究報告）

研究代表による報告（和文）

＜１．報告概要＞

遺伝性心血管疾患は一つの臨床病型に数多くの候補遺伝子が含まれており、循環器難病の原因同定に際して症例間比較が困難であることが多く、循環器分野独特の解析戦略が必要である。循環器疾患の特性を考慮しつつ遺伝難病のゲノム解析拠点形成のため、既知遺伝子の臨床診断応用、未診断疾患に対する新規原因遺伝子同定の両者に重点を置き、大家系に対する遺伝子同定および少数症例解析にも対応した情報解析システムを開発し、創薬研究への展開も視野に事業を実施した。

全国の大学病院等から循環器疾患 10 領域（①拡張型心筋症，②肥大型心筋症，③拘束型心筋症，④不整脈原性右室心筋症，⑤ 左室緻密化障害，⑥ 遺伝性不整脈疾患（QT 延長・徐脈等），⑦ 代謝性疾患（Fabry 病等），⑧ 脂質異常症（虚血性疾患），⑨ 先天性心疾患，⑩ 自己免疫疾患・血管疾患（肺高血圧（Sarcoidosis，大動脈炎，肺高血圧））の遺伝学的解析依頼（学内を含む）のターゲット遺伝子パネル解析および、全エクソーム解析を実施した。遺伝学的解析結果およびその機能解析を行った研究から、新規の責任遺伝子を 2 件、変異を 5 件発見し、約 120 件の論文が受理された。また、本研究の遺伝学的解析により 3 年間で約 38%が責任遺伝子変異として同定でき循環器領域の遺伝子解析の臨床応用に向けた基盤整備に大きく貢献した。

＜２．本研究事業における実施項目＞

１．循環器症例の蓄積
２．家系解析の実施
３．蓄積された疾患バリアント情報
４．メンデル遺伝病の候補バリアントの同定と機能解析
５．循環器ゲノム解析研究者の情報ネットワークの構築、研究情報共有、共同研究の実施

＜３．基盤的成果および次年度以降も継続維持が必要な事項＞

１．循環器疾患ゲノム変異情報データベースの構築と疾患関連形質情報の付与（国内症例変異に準拠）
２．標準化フォーマットとして統一化された全エクソーム解析のシーケンスおよび情報解析運用手順
３．標準化フォーマットとして統一化された疾患パネル解析のシーケンスおよび情報解析運用手順
４．同定変異分子に対する、創薬を見据えた迅速生体機能解析系の確立
５．創薬化合物スクリーニング系の開発（国内発の創薬開発）
６．医師主導型臨床試験へむけたブリッジ的研究基盤の構築

＜４．各項目における成果＞

１．共通プロトコールによるゲノム解析体制の構築：

同意取得、ゲノム抽出、既知遺伝子解析、情報解析、未知変異に対する全エクソーム解析まで症例エントリーから共通パイプラインを用いて、その結果を施設間で共有できるよう解析体制を構築した。

２．独自新規解析パイプラインの開発と施設間共有：

ゲノム解析研究者、ウェットラボ研究者、情報解析者、臨床医が分野を超えて協力し解析パイプラインの開発を行った。受付サーバーに加えて実際の計算処理を行うクラスタ型解析サーバー（2 計算ノード

約 40 計算コア）と冗長化ストレージ（約 100TB）によって構成した。これらの構成要素は in-house ネットワークによって互いに接続されており、このネットワークを介して一連のデータ処理が自動的に行われるように構築されている。これらの上にシーケンサーによる配列データを含む検体情報を受付サーバーから解析パイプラインに投入できるシステムを構築した。心血管疾患の解析に適する循環器専用のスクリプトも組み込んだ解析プログラムを構築し、遺伝性心血管疾患の原因遺伝子同定のみならず、同定された分子に対する未知作用機序解析および創薬基礎研究開発も視野に統合的な標的シーズ探索システムを構築した。次世代解析拠点施設と連携し、in-house variant data の蓄積にも協力しながら、本研究に適した独自スクリプトを構築した。本研究はこれらの情報解析システムを各研究班の情報解析に共有共通化して用いることであり、今年度の症例についても順次適用し解析が始まっている。さらに小家系または単症例の遺伝性疾患を対象に、原因遺伝子を同定するアルゴリズムを開発した。

３．共通ゲノム解析パイプラインに基づく解析と循環器疾患ゲノム変異 DB の構築：
研究班全体で検出したバリアント情報も共有しつつ、公共データベースにおける変異情報、疾患注釈情報を参照可能にし、かつ検索機能の付いた、本邦初の循環器疾患ゲノム変異データベースが完成する。

４．既知遺伝子解析および新しい循環器疾患の分類法の確立：
臨床における疾患既知遺伝子変異を検出する迅速な臨床ゲノム診断を将来提供するためのシステムを構築する取り組みを行った。Agilent 社 Haloplex または Illumina 社の TruSeq custom amplicon kit を基本にした心筋症既知遺伝子パネルスクリーニングおよび不整脈既知遺伝子パネルスクリーニングを標準的に用いることができる体制を整えた。心疾患既知遺伝子スクリーニング解析によって、発症原因と考えられる既知遺伝子変異やフレームシフト・ストップコドン・スプライシング変異は、拡張型心筋症の 37%、肥大型心筋症の 43%、不整脈原性右室心筋症の 33%、Marfan 症候群の 25%、ブルガダ症候群、QT 延長症候群、およびファブリー病において 100%で同定でき、我々は非常に強力なスクリーニング系を構築していると考えられる。既知遺伝子の臨床診断応用にむけた臨床情報の付与された変異データベース化を行った。

５．未知遺伝子迅速機能解析による同定された原因変異の生体機能解析と創薬への応用：
ゲノム解析対象症例の蓄積は計画通り進み、遺伝性疾患を疑う家系としては心筋症・不整脈合わせて約 450 症例のサンプルを収集し、全エクソーム解析およびパネルシーケンス解析を実施した。未知遺伝子変異に対して分子機能解析を開始し責任遺伝子変異としての検証を行っている。一部遺伝子については創薬開発に際して必要な迅速生理機能解析系、化合物スクリーニング系の開発を行い、創薬候補としての化合物探索、さらに同定済みの化合物については治療に向けた製剤化開発に進めることができた。

＜４．今後の展望＞
以上の成果および情報解析システム、パイプラインおよび変異データベースを中心とした基盤的技術は基礎的検証から創薬開発にまで至る一貫したシステムであり、国内でも世界基準に照らして先進的であるとともに、循環器疾患を専門に扱う中で大変貴重な財産となった。循環器領域の難病克服に向けた大変重要な知見と診断治療方法の開発に資するものであり、さらなる発展と本技術の継続維持が望まれる。

（英文）

A. System refining of gene analysis.

1. Genome analysis research using nationwide uniform protocol

The facilities that conduct all the exosome analysis, the panel analysis, and the information analysis were added as a joint research facility to the plan, and the system was constructed so that common analysis can be implemented uniformly at each facility. At Osaka University, genome analysis by the Human Genome Ethics Plan common to each department was realized, and an analysis system capable of using other genomic information as a disease control was prepared.

2. Analysis based on unified genome analysis pipeline and construction of genomic mutation DB of cardiovascular disease

For information analysis, update work is done to the basic pipeline in each fiscal year, and analyzes are always conducted using the latest common pipeline. Mutation detection analysis using a server can be carried out naturally, but in order to identify many disease causes, it is necessary to have a database enabling shared search between cases of detected mutations. Therefore, a genome database of cardiovascular diseases was constructed. By constructing this system, it is possible to refer mutation information and disease annotation information in the public database while sharing the variant information detected by the research team as a whole, and it becomes the first Japanese cardiovascular disease genome mutation database with search function.

3. Genome information analysis focusing on clinical sequence, construction of mutational interpretation system

Osaka University Graduate School of Medicine established the Bioinfoinformatics Initiative Committee which created a clinical information input template, gathered data there, and developed a system that cooperates with the hospital medical information system including blood sampling. The input information is accumulated in the clinical research database installed in the university through the secure network. The subject ID is automatically issued and the correspondence table between the patient ID and the subject ID is managed by the system. Clinical data collected from other facilities is also stored Clinical research DB. It becomes a system to manage with subject ID.

B. Functional analysis of causative genes

1. Known gene mutation analysis

In this study, we completed the screening of known genes in 354 cases (266 onset cases, 88 cases without onset). We detected point mutation, frame shift, nonsense mutation, and splicing mutation in known genes considered to be the cause of onset among patients; 45% of dilated cardiomyopathy, 55% of hypertrophic cardiomyopathy, 50% of arrhythmogenic right ventricular cardiomyopathy, 25% of Marfan syndrome, 100% in Brugada syndrome, extended QT syndrome, and Fabry disease. We were able to construct a high quality and sensitive screening system.

2. New (unknown) gene mutation analysis

In this study, about 450 cases of all exome analysis were completed and their genome database of disease was constructed. Differential narrowing analysis is performed on the families that did not correspond to known genes, and the following new mutations are identified and developed into drug discovery research for molecular targeted drug development. In addition, we analyzed multifaceted cases of familial cases which cannot be identified by simple differential narrowing analysis in all exosome analyzes using whole genome analysis and array structure analysis.

(1) Identification of novel mutations in genetic bradycardia disease family

We identified novel genes assumed to be involved in arrhythmia episodes from families with an autosomal dominant genetic form. The disease showed a very high penetrance rate, and another non-synonymous mutation in the same gene could be identified from another family that allowed familial onset. Co-segregation and exclusion of Japanese common variant can also be confirmed, confirming that this gene is the causative gene of this arrhythmia. By developing specific inhibitors, development as a first in class remedy for this disease is expected.

(2) Identification of novel sarcomeric gene MYLK3 mutation in genetic cardiomyopathy family.

A new causative gene of cardiomyopathy was identified. Since it is suggested that the MYLK3 activator will be a therapeutic agent for heart failure, further screening of small compound activators will be carried out in the future.

3. Identification of disease-related molecules and drug discovery screening

As a gene analysis center close to the patient, we can identify the gene mutation first. Therefore not only identification of the etiological genes but also identification of appropriate drug discovery targets leading to the development of therapeutic drugs is important. We set up our own large-scale screening system based on the function of pathogenesis genes, screened compounds and succeeded in identifying the lead compounds shown below.

(1) Establishment of assay system for inhibition of target protein degradation and compound screening

(2) Establishment of assay system to quantify redox reaction and large scale screening

Since this assay system is also extremely applicable, it is applied to the development of activity enhancers or inhibitors of disease candidate genes to be identified in the future.

C. Technology development for improving diagnostic rate

Entire analysis of all processes from genome extraction, library construction and sequence analysis using the same facility enables gene contract analysis under low cost. We also worked on a cardiomyopathy disease panel with 100 genes and an arrhythmia disorder panel carrying 50 genes and created a disease mutation detection algorithm combined with candidate gene information specific to cardiovascular disease and all exome analysis data. Also by making judgment as pathogenic

mutation according to guidelines for mutational interpretation of ACMG, it became possible to confirm the reliability of mutation data detected.

We developed a method to analyze mutation data by analysis pipeline. An algorithm (HDR method) that narrows down causative genes for genetic diseases of small family or single cases was developed as software with GUI. In addition, by introducing knowledge processing technology based on machine learning (AI: artificial intelligence), we advanced research and development to realize extraction and accumulation of knowledge difficult to find by manual analysis and its effective visualization. We examined a method for constructing an evaluation formula that characterizes disease - related traits by mutation information.

D. Sharing genetic analysis data to other research groups

We have made efforts to construct a system to provide rapid clinical genomic diagnosis to detect genetic mutations in clinical disease. We shared our data with the results of Agilent Haloplex developed by University of Tokyo Advanced Science and Technology Research Center and TruSeq custom amplicon kit by Illumina developed by Shiga University of Medicine. Construction of a genome database of cardiovascular diseases is ongoing.

E. Future prospects

The above results and basic technologies centering on information analysis systems, pipelines and mutation databases are a consistent system enables us to lead the basic verification of causative genes and drug discovery, It became a valuable asset in dealing specialized treatment of cardiovascular diseases. It contributes to the development of very important findings and diagnostic and therapeutic methods for overcoming intractable diseases in the cardiovascular field. Further development and continuous maintenance of this technology are desired.

III. 成果の外部への発表

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奈良県立医科　斎藤

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（3）「国民との科学・技術対話社会」に対する取り組み

阪大　高島

1. **心臓～その働きものの正体を探る，高島　成二，夢ナビライブ 2015 福岡会場，2015/10/17 国内**

阪大　朝野

1. **「実臨床、臨床、基礎をつなぐ疾患ゲノム解析　～候補遺伝子絞り込みにおける基礎的パイプラインの構築と次なる戦略～」，朝野　仁裕，アメリエフ勉強会，2014/9/22 国内**
2. 大阪大学国際シンポジウム～次世代医学アカデミア・データセンター情報基盤構築を目指して～,「ゲノム疫学研究」，朝野　仁裕，大阪大学，2015　国内

阪大　坂田

1. 「拡張不全の発症メカニズム」，坂田泰史，第 49 回ヒューマンサイエンス総合研究セミナー，砂防会館別館，2017/3/2，国内

日本医科大　清水

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2. 「きょうの健康」『忍び寄る！心臓突然死を防ぐ』口頭, 清水　涉, NHK Eテレ出演

2017年 4/3(月)～4/6(木)　8:30～8:45PM　4夜連続放送

① 突然死はなぜ起こる？ (VF/VT 虚血性心疾患)

② 若年・中年を襲う突然死　(LQTS、Brugada、CPVT)

③ 心筋症による突然死　(HCM、DCM、ARVC)

④ 突然死を防げ ＝AEDなどの実演あり＝

（4）特許出願

出願　2014-212799

2014.10.17『ゲノム解析装置、ゲノム解析方法及びゲノム解析プログラム』国立大学法人大阪大学

（報告様式４）

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平成　　年　　月　　日

平 成 ２ ８ 年 度　委 託 研 究 開 発 成 果 報 告 書

I. 基本情報

事　業　名：（日本語）**難治性疾患実用化研究事業**
（英　語）Practical Research Project for Rare / Intractable Diseases

研究開発課題名：（日本語）**遺伝性心血管疾患における集中的な遺伝子解析及び原因究明に関する研究**
（英　語）Comprehensive Genome Analysis for Hereditary Cardiovascular diseases

研究開発担当者　（日本語）**大学院医学系研究科　医化学講座　教授**　高島　成二
所属 役職 氏名：（英　語）Osaka University Graduate School of Medicine,
Department of Cardiovascular Medicine, Lecturer,
Seiji Takashima

実 施 期 間：平成 28 年 4 月 1 日 ～ 平成 29 年 3 月 31 日

分担研究開発課題名(実施内容)

日本語：

①ゲノム解析の実施、同定変異の基礎研究とその臨床実用化

・既知遺伝子解析技術の開発

・新規原因遺伝子同定と迅速機能解析による創薬シーズ応用開発

②日本語：全国普及を目指すゲノム情報システムの開発と普及推進

・全国ネットワーク受託解析システムの研究開発

英　語：

①Genome analysis and applications for clinical use

1) Technology development for efficient mutation detection of known causative genes

2) Identification of novel cardiomyopathy-related genes and functional analysis of its mutations

②Development and dissemination of the genome-analysis system

研究開発分担者（AMED 直接契約）

所属 役職 氏名：

（日本語）東京大学先端科学技術研究センター　教授　油谷　浩幸

（英　語）Hiroyuki Aburatani Professor,

Research Center for Advanced Science and Technology,

The University of Tokyo

分担研究開発課題名(実施内容)

日本語：

ゲノム解析の実施、同定変異の基礎研究とその臨床実用化

1)　既知遺伝子解析技術の開発

2)　新規原因遺伝子同定と迅速機能解析による創薬シーズ応用開発

3)　ゲノム解析症例の収集と診療ガイドライン作成に向けた臨床情報のデータベース化

英　語：

Genome analysis and applications for clinical use

1) Development of the technology to efficiently detect mutations of known genes

2) Identification of novel cardiomyopathy-related genes and functional analysis of its mutations

3) Construction of database for integration of genomic and clinical information

研究開発分担者　　（日本語）東京大学大学院・医学系研究科・講師　森田　啓行

所属 役職 氏名：(英　語)Graduate School of Medicine, the University of Tokyo・Lecturer　Hiroyuki Morita

II. 成果の概要（総括研究報告）

・ 研究開発分担者による報告の場合

研究開発代表者：　大学院医学系研究科　医化学講座　教授　高島　成二　　総括研究報告を参照。

III. 成果の外部への発表

（1）学会誌・雑誌等における論文一覧（国内誌　2　件、国際誌　7　件）

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（３）「国民との科学・技術対話社会」に対する取り組み

該当なし

（４）特許出願

該当なし