2012 年度　Translational Research 振興事業　総括報告書

１．研究テーマ

不整脈疾患における先制医療としての遺伝子診断と機能解析の開発

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４．３年間の主な進捗状況と活動報告（年次計画予定における研究成果）

１）次世代シークエンサーを活用した遺伝性不整脈の遺伝子診断

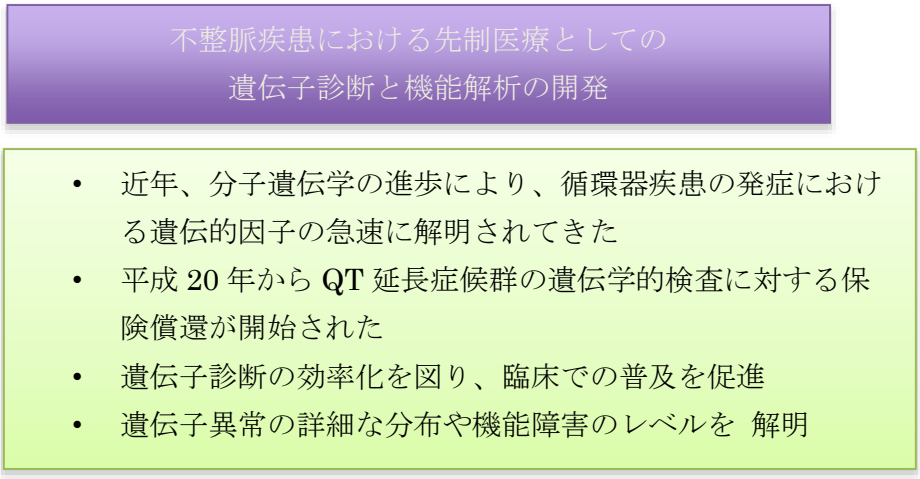
Translational Research 振興事業の研究助成をいただき、大きく２つのテーマについて、上の班構成で研究をすすめた。不整脈疾患のなかでも、とくに先天性 QT 延長症候群（LQTS）をはじめとする遺伝性不整脈の分野においては、遺伝子診断技術の進歩とともに、新規原因遺伝子が続々と同定されてきている。ただ新規原因遺伝子における遺伝子変異同定率は低く、従来の Sanger 法での解析は時間・費用対効果が悪く、全患者に対して複数の遺伝子を対象としたスクリーニングを行うことは非現実的であった。ところが、次世代シークエンサー(Next Generation Sequencing:　以下 NGS)の登場により、複数の遺伝子を短時間でスクリーニングすることが可能となった。

このように遺伝子診断法の cost-performance は劇的に改善してきており、従来の Sanger 法による最終的な genetic variant の同定のまえに、NGS によるスクリーニングが可能となってきた。本研究班では、遺伝性不整脈を対象に、より迅速かつ正確に genetic variant を発見する方法を模索した。

すなわち遺伝性不整脈の原因として報告されている約 50 個の遺伝子パネルをデザインし、これまで変異が同定されていない 355 人の遺伝性不整脈患者に対し、次世代シークエ

ンサーを用いた解析を実施した。その結果、次のような結果が得られた。
・臨床的に LQTS と診断されていた患者 90 名中、カテコラミン感受性多型性心室頻拍（CPVT）の原因遺伝子である RYR2 変異を 13 名に同定した。これらの患者について臨床診断を再検討したところ、CPVT の確定診断に至った。
・これまで頻度が少なく、遺伝子が大きいためスクリーニング対象遺伝子から除外していた LQTS4 型及び LQTS11 型の原因遺伝子である ANK2 及び AKAP9 に変異を同定し、LQTS の原因が明らかになった。
・壮年期男性に突然死を来す Brugada 症候群と催不整脈性右室心筋症（ARVC）の Overlap が報告されているが、我々のコホートでも Brugada 症候群症例に ARVC の原因遺伝子であるデスモゾーム変異を同定した。

このように、遺伝性不整脈と診断されながら原因となる遺伝子変異が同定されていなかった患者について、疾患の原因と考えられる多くの変異を同定することが可能になった。また疾患の原因遺伝子を同定できることにより、新たな疾患概念を確立することが可能になり、今後の更なる研究発展が期待される。



（図） 本研究開始時のコンセプト

２）iPS 由来心筋細胞（iPS-CM）を用いた遺伝性不整脈の原因解明

本研究班のもうひとつの大きなテーマは、遺伝性不整脈症例で発見された genetic variant に関する機能解析法の解明である。2006 年の iPS 細胞確立の報告以来、各疾患における iPS 由来細胞を用いた疾患原因解明が続けられている。我々も iPS 由来心筋細胞(iPS-CM) を用いた疾患解明を進めている。iPS-CM は成人の心筋と比較し幼弱なため、まずは電子顕微鏡を用いて経時的な形態学的変化を観察した。iPS 細胞から心筋に分化させた後、1 年間の培養を行ったが、1 年後でも M band の形成は不十分であり、心筋の成熟度は低いことが明らかになった。

引き続き、CPVT 患者由来の iPS-CM の解析を実施した。その結果、運動負荷と同様の影響を与えるイソプロテレノール負荷を行うことで、心室頻拍を再現することができ、RyR2 安定効果のある薬剤 S107 が、その心室頻拍を抑制することを示した。

5. 3 年間の研究班から発信できた業績のまとめ

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