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研究課題名（和文）多面的な研究アプローチによる遺伝性不整脈の発症機序の解明

研究課題名（英文）Multilateral Research on the Mechanisms of Inherited Arrhythmias

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研究成果の概要（和文）：遺伝性不整脈は近年明らかとされた疾患概念で、心臓の刺激・伝導・興奮・収縮などに関わる多種多様な蛋白をコードする遺伝子に起こる変異により、これらの蛋白の機能障害がおこり、主として心臓のリズム異常をきたす病気である。QT延長症候群、ブルガダ症候群、カテコラミン誘発性多形性心室頻拍、進行性伝導障害、QT短縮症候群などが対象である。我々は、コホート研究で集積した本疾患のゲノム解析をおこない、同定された遺伝子異常について従来の遺伝子組み替え、電気生理学的方法による機能解析、疾患特異的 iPS 細胞やコンピュータシミュレーション法を駆使して、多方面からの集学的アプローチによる病態解明をおこなった。

研究成果の概要（英文）：Variants of genes encoding a variety of ion channels or their associated proteins, determining the heart impulse conduction, excitation and contraction, were found to cause inherited arrhythmias, such as long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, progressive cardiac conduction defect, and short QT syndrome. This line of study offered a typical example that the scientific progress in genetics prompted the discovery of new genes responsible for human diseases and elucidated their specific molecular mechanisms of pathogenicity. By employing the multilateral approaches such as conventional patch-clamp and other physiological analyses in a heterologous expression system, patients-derived iPS-cardiomyocytes, and integrated computer simulation method, we investigated the pathological mechanisms underlying these inherited arrhythmias.

研究分野：　循環器内科学

キーワード：　遺伝性不整脈　循環器　高血圧　遺伝学　遺伝子　機能解析

１．研究開始当初の背景

我々は倫理委員会の承認を受け、1996 年（最初のＱＴ延長症候群関連遺伝子が報告された翌年）から、患者さんよりインフォームド・コンセントを得て、臨床像とゲノム DNA の集積を行ってきた。現在 5500 例をこえる症例を集積している。このコホートの大きさは海外の研究チームでの症例数と比べても極めて大きなもので、この日本人コホートを用いて、われわれに特有な循環器疾患の遺伝的背景さらにその発症メカニズムを、多面的に探求することが、本研究課題の目的である。

２．研究の目的

遺伝子異常の同定率は遺伝性 QT 延長症候群では６割弱、ブルガダ症候群では１割程度であるが、実は、発見されたすべての遺伝子異常が、病気の発症と結びついているわけではない。本研究課題では、多方面からの集学的アプローチによる機能解析、疾患特異的 iPS 細胞やコンピュータシミュレーション法を用いて、個々の遺伝子変異が果たして病態とどのように関連するかを明らかにする。

３．研究の方法

発見された多種多様な遺伝子異常(変異のみならず単一塩基多型（SNP)も含む)が招来する機能的な変化を検討するため、具体的には、(1)遺伝子組み換え法による変異株の作成、(2)転写機構に及ぼす影響を見るための分子遺伝学的アプローチ（minigene, RT-PCR など)、(3)チャネルあるいはその調節蛋白の細胞内輸送を見るためのイメージング法（GFP tagging や免疫染色法）(4)チャネルあるいはその調節蛋白の異常を起こす電気生理学的な変化を見るためのパッチクランプ法、(5)ヒト細胞モデルとしての疾患特異的iPS の作成、さらに(6)それらを統合的に解析するためのコンピュータシミュレーション法などを駆使する。

４．研究成果

平成 27～29 年度の 3 年間に、上記の方法論を用いた我々の論文発表等を５に記載する。Caチャネル遺伝子異常による QT 延長症候群、iPS 細胞を用いたカルモジュリン遺伝子異常による QT 延長の機序、リアノジン遺伝子異常に伴う一連の疾患群、2 次性 QT 延長症候群における遺伝的背景の解明、コンピュータシミュレーションによる疾患の説明等々多くの発信を行うことが出来た。

５．主な発表論文等

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