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研究課題名（和文） 生物学的製剤に対する薬剤反応性遺伝子の同定

研究課題名（英文） A study on genes that associated with response to biologic agents.

研究代表者

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研究成果の概要（和文）：

既知の疾患感受性遺伝子を候補遺伝子として、疾患関連多型について生物学的製剤反応遺伝子の検索を行った結果、PTPRC 上の rs10919563 で有意な関連を認めた ( $P < 0.05$ )。rs10919563 は欧米での検討でも生物学的反応性と有意な関連を認めており、結果の信頼性は高いと言える。本研究により、投与前のスクリーニングでこの多型解析を行うことで、生物学的製剤不応例となるリスクを軽減できる可能を示すことが出来た。

研究成果の概要（英文）：

We tried to detect the genes that associated with response to biologic agents using disease-associated polymorphisms as candidate, and found that a SNP, rs10919563, on PTPRC gene is significantly associated with response to biologic agents ( $P < 0.05$ ). Since the SNP is also known as anti-TNF- $\alpha$  therapy response polymorphism in Caucasian, it seems to be a reliable result.

交付決定額

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	直接経費	間接経費	合計
2008 年度	2,200,000	660,000	2,860,000
2009 年度	1,000,000	300,000	1,300,000
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研究分野：医歯薬学

科研費の分科・細目：外科系臨床医学・整形外科学

キーワード：リウマチ病学

## 1. 研究開始当初の背景

関節リウマチ (RA) は多関節に慢性炎症を生じる全身性自己免疫疾患であり、その本態は滑膜に存在する免疫系細胞とサイトカインによる複雑な応答システムの異常である。病勢の進行とともに関節構造が破綻し、日常生活動作を著しく障害する。社会活動、家庭生活にも支障をきたし、平均余命が短縮するという報告もある。有病率が 0.5%前後と比較的頻度の高い疾患でもあるため、社会的、経済的な負担も問題となっている。

RA における治療の主役は薬物治療である。これまで主に疾患修飾性抗リウマチ薬 (DMARDs) とステロイド剤が使われてきたが、2003 年にインフリキシマブが関節リウマチに適応追加となり、2005 年にエタネルセプトが承認されて以来、生物学的製剤が目覚ましい効果をあげ、以前に比べ RA の疾患活動性の制御は容易になりつつある。しかし、RA 患者は薬物を長期に渡り投与されることもあって副作用が無視できないことが多く、また患者によっては治療反応性が悪いことも少

なくない。特に生物学的製剤は重症感染症などの副作用が一定の割合で発生するため、RA患者に対して一律に用いることは不相当と考えられている。加えてメソトレキサートをはじめとする従来のDMARDsに比べ薬剤費が非常に高価であり、今後ますます加速する高齢化社会においては医療経済上の観点からも無用な投薬は避ける必要がある。以上の状況からオーダーメイド医療の要望が高まっている。薬剤反応性遺伝子型に基づく薬理効果予測、副作用予測が可能となれば、生物学的製剤投与前に患者個人に応じたリスクとベネフィットを判断でき、効果的経済的な薬剤選択、治療選択が可能となる着想するに至った。

## 2. 研究の目的

本研究の全体構想はRAにおける包括的なオーダーメイド医療の実現であり、その中で本研究計画はRA治療の根幹の一部を担う生物学的製剤に対する薬剤反応性遺伝子の同定を目的とした。

## 3. 研究の方法

これまでにDNAを収集済みの患者に加え、当施設で生物学的製剤を投与している患者からDNAを収集し、生物学的製剤投与患者におけるDNAコホートを組織した。

既知の疾患感受性遺伝子を候補遺伝子とし、ハップマップを用いて候補遺伝子をカバーするタグSNPを選択して、TaqMan法を用いて遺伝子型同定を行い、Rソフトウェアパッケージを用いて遺伝統計解析を行った。

## 4. 研究成果

PTPRC上のrs10919563で有意な関連を認めた( $P < 0.05$ )。今後はこの情報をもとにオーダーメイド医療を推進していきたい。

## 5. 主な発表論文等

(研究代表者、研究分担者及び連携研究者には下線)

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[その他]

ホームページ等

<http://www.twmu.ac.jp/IOR/JointSurgery/>

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