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I. 知的所有権の出願・取得状況

なし

J. その他

なし

厚生労働科学研究費補助金　肝炎等克服緊急対策研究事業
C型肝炎を含む代謝関連肝がんの病態解明及び治療法の開発等に関する研究
分担研究報告書

NASHとC型肝炎の病態形成における臨床病理学的および遺伝的要因に関する研究

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研究要旨：肝生検で診断した888例のNAFLDをMatteoni分類に従い組織学に4つのタイプに分類し、網羅的遺伝子関連解析(GWAS)を行い、22番染色体上に存在するpatatin like phospholipase domain containing 3(*PNPLA3*)のrs738409のSNPがNASHの発症・進展（脂肪蓄積、線維化）の感受性遺伝子である事が判明した。さらに*PNPLA3*のrs738409のSNPはNASH肝発癌にも関係している事が明らかになった。また、肝生検で診断した276例のC型肝炎を対象にTaqMan PCRで*PNPLA3*のrs738409のSNPを解析すると、rs738409のSNPはC型肝炎の脂肪蓄積と線維化進展にも関与している事が判明した。Matteoni分類に従い分類したNAFLD症例を対象にproteome解析、metabolome解析を行い、血液生化学的に単純性脂肪肝(NAFL)とNASHを鑑別する方法を検討中であり、5642例の糖尿病患者の肝障害の実態を明らかにしてきたが、現在5年経過後の肝発癌や予後を解析中である。

A. 研究目的

NAFLDの2割前後がNASHに進展すると言われ、進行したNASHからはしばしば肝癌が発症する。NASH発症・進展や発癌の遺伝的背景は明らかでない。また単純性脂肪肝(NAFL)とNASHの簡便な血液生化学的鑑別法も未だない。糖尿病患者では高率にNAFLDを合併するが、多数例で予後を解析した報告は無く、その長期予後を明らかにする。またC型肝炎の多くは進展するが、肝機能が正常で予後良能な症例も30%前後存在し、かつC型肝炎では半数近くに脂肪蓄積が見られる。脂肪蓄積は線維化進展例に多く、その遺伝的背景は明らかでない。NASH, C型肝炎における脂肪蓄積、線維化進展、発癌に関与する遺伝的要因を明らかにし、NAFLとNASHの血液生化学的鑑別法の作成を目的とした。

B. 研究方法

1. NASHの検討：肝生検で診断した888例のNAFLDをMatteoni分類に従い組織学的にtype 1～4に分類し、脂肪蓄積、炎症、線維化の程度や患者背景・臨床検査成績を解析し、コントロール2524例とともに網羅的遺伝子関連解析(GWAS)を施行した（京

都大学ゲノム疫学解析センター松田文彦教授との共同研究）（表 1, 2)。また NASH 肝癌 58 例での GWAS も行った。

2. C 型肝炎の検討：肝生検で grade, stage, steatosis の程度などを解析した C 型肝炎 276 例を対象に、NAFLD の GWAS 検討で NASH 発症・進展の感受性遺伝子として同定された 22 番染色体上の遺伝子 patatin-like phospholipase domain containing 3(*PNPLA3*)の rs738409 の SNP 解析を TaqMan PCR で検討した(表 3)。

3. 肝生検で診断した NAFLD280 を Matteoni 分類し従い分類し、血清を用いて proteome 解析、metabolome 解析を行い、NAFL, NASH の鑑別法の作成を試みた。

4. 糖尿病 5642 例の肝障害の実態を明らかにしてきたが(J Gastroenterol 2013)、最初の集計から 5 年近く経過しており、糖尿病患者の NAFLD の肝発癌を含む長期予後を明らかにする。

（倫理面の配慮）

遺伝子解析を含む本臨床研究に関しては済生会吹田病院と京都府立医科大学の倫理委員会の承認を受けた。患者の同意を得たうえで、採血を行った。

C. 研究結果

(1)当初 NAFLD529 例に網羅的遺伝子関連解析(GWAS)を行い *PNPLA3* の rs738409 の SNP(I148M)が NASH 発症・進展感受性遺伝子と報告したが、Matteoni type 3 の症例数が少なかったため(PLoS ONE 2012)、今回 NASH 肝癌 58 例を含む NAFLD397 例を追加し,888 例 NAFLD(control2525 例)と 58 例の NASH 肝癌で GWAS を行った。その結果 I148M は type 4 NASH に特異的(p-value 1.34×10^{-29}, HWE $p<10^{-7}$)かつ発癌感受性遺伝子である事が判明した（図 1,表 4）(p-value 1.7×10^{-9})（論文作成中）。

(2)I148M は C 型肝炎の線維化、脂肪蓄積にも関与している事も明らかになった（図 2）(J Gastroenterol in press)。

(3)肝生検で診断した NAFLD280 例での proteome, metabolome 解析から、NAFL と NASH で有意差のある血清生化学的マーカーが複数みつたっており、それらを組み合わせて現在その鑑別法を作成中である。

(4)5642 例の糖尿病患者のフォローが約 5 年経過しており、肝発癌症例もかなりみられ、現在肝発癌を中心に長期予後を解析中である。

考察

Matteoni らは NAFLD を組織学的に 4 つの type に分類し、予後の解析から type 1,2 が NAFL で type 3,4 が NASH と分類した。NAFLD の 20%前後が NASH に進展すると言われ、進行した NASH からはしばしば肝癌が発症する。しかし、NAFLD から NASH へ進展や NASH 発症・進展、NASH 肝発癌における遺伝的要因は充分明らかにされていなかった。今回肝生検で診断した多数例の NAFLD を組織学的に 4 つのタイプに分類し GWAS を行い、遺伝的には type 3 は type1, type 2 と同じで、典型的な NASH である type 4 の発症・進展と肝発癌のみに *PNPLA3* の rs738409 の SNP が深く関与していることが明らかになった。また C 型肝炎では 50%前後に脂肪蓄積が見られ、脂肪蓄

積は線維化進展例に多いが、*PNPLA3* (rs738409)の SNP が C 型肝炎における脂肪蓄積と線維化進展に関与していることが明らかになった。
また、糖尿病患者では高頻度に肝障害を合併し、その多くが NAFLD であるが、糖尿病患者の長期予後に及ぼす NAFLD の影響は充分に明らかでない。5642 例の糖尿病患者をフォローしており、NAFLD からの肝発癌や糖尿病患者の長期予後に及ぼす NAFLD の影響を検討中である。また metabolome 解析、proteome 解析から、NAFL と NASH の血液生化学的鑑別法も作成中である。

E. 結論

22 番染色体上に位置する *PNPLA3* は NASH 発症・進展のみならず肝発癌の感受性遺伝子である。また C 型肝炎の脂肪蓄積や線維化進展にも PNPLA3 の SNP が関与している。

F. 健康危険情報

NAFLD/NASH の発症・進展のみならず、NASH 肝発癌にも遺伝的素因が関与していることが明らかになり、治療法の選択や肝癌早期発見のツールとしても有益な情報である。また C 型肝炎で肝硬変・肝癌に進展する例は30%前後と考えられており、今回の結果は C 型肝炎患者の予後推定に役立つ可能性が高い。

研究発表

1. 論文発表

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H. 知的所有権の出願・取得状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

特記事項なし

表1. Genotype Quality Control
(追加解析分)

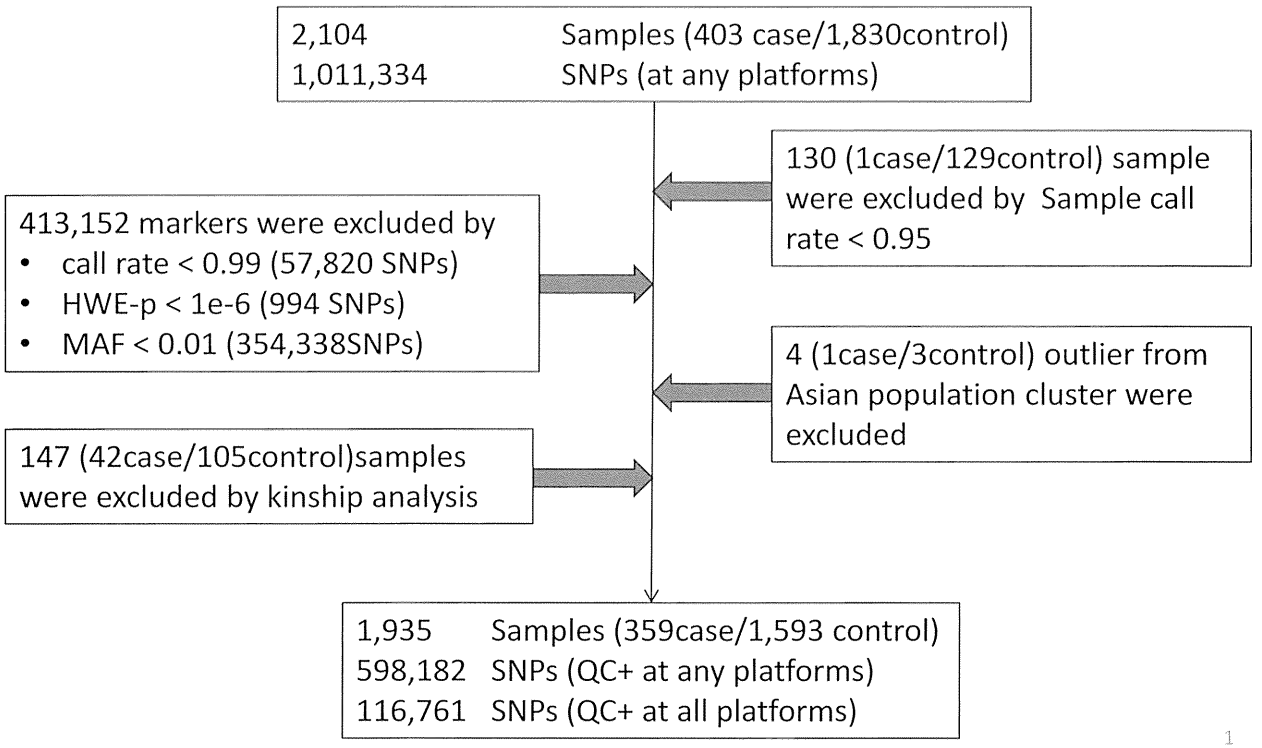

表2. 患者背景
（初回解析分と今回の追加解析のNAFLD, NASH肝肝癌の全症例）

		追加解析分	2回分の合計
Disease	NAFLD/Control	359/1593	888/2525
NASH-HCC		46	58
Matteoni分類	1/2/3/4	32/60/64/186	130/134/105/499
Brunt stage	1/2/3/4	86/48/60/29	251/123/164/56
Brunt grade	1/2/3	126/97/33	322/233/80