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研究種目：挑戦的萌芽研究

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研究課題名(和文) 肺血管異常における TGF-β 関連遺伝子変化の包括的検索とその役割の検討

研究課題名(英文) A comprehensive analysis of the TGF-beta family genes in the patients with abnormal pulmonary vessels

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研究成果の概要(和文)：肺血管異常を示す症例をexomeシーケンスで検索し、TGF-β 関連遺伝子異常の有無を検索する。複数の症例で同一の遺伝子異常が見つかったら、その機能解析を施行する。BMPR1AでpP2T, CHRDでpM630L, GDF-3でpG213R, GDF-5でpS276A, GDF-7でpA330S, GDF-15でpV9L, pS48T, LEFTYでpD322A, pR33Q, NodalでpH165R, RGMAでpD399E, pD415E, pD423E, TGF-β R3でpS15F, Smad5でc1314_1315insC, が見つかった。これらの変異による構造変化に関して検討して行く必要があると考えられた。

研究成果の概要(英文)：Genomic DNA isolated from patients who has abnormal lung vessel structure has been investigated by exome sequencing. Non-synonymous variants found were as follows: pP2T in BMPR1A, pM630L in CHRD, pG213R in GDF-3, pS276A in GDF-5, pA330S in GDF-7, pV9L and pS48T in DGF-15, pD322A and pR33Q in LEFTY, pH165R in Nodal, pD399E, pD415E, and pD423E in RGMA, and c1314_1315insC in Smad5. The effects these variant gives to the pulmonary vessel structure should be investigated.

研究分野：呼吸器内科学

キーワード：肺血管異常 TGF-β エキソーム アミノ酸変異

1. 研究開始当初の背景

血管関連、結合組織関連疾患の原因遺伝子の検索は、大家系を中心とした解析により行われてきた。その結果、これらの疾患ではしばしば TGF- 関連遺伝子の異常が認められることが明らかになっている。具体的には、遺伝性出血性毛細血管拡張症 (Rendu-Osler-Weber 症候群), Loey-Dietz 症候群, 家族性胸部大動脈瘤, 原発性肺高血圧症, Marfan 症候群, Sphrintzen-Goldberg 症候群, Furlong 症候群, Camurati-Engelmann 病, 進行性骨化性線維異形成症, Hunter-Thompson 骨異形成症, Grebe 骨異形成症, 硬結性骨化症, Van Buchem 病, C 型短指症, A2 型短指症, 指節癒合症, 早発卵巣不全, ミューラー管遺存症, 内臓錯位, 口唇口蓋裂, 遺伝性ヘモクロマトーシス, 若年性ヘモクロマトーシス, 若年性ポリポーシス, 遺伝性非ポリポーシス大腸癌, Bannayan - Riley - Ruvalcaba 症候群, Cowden 病などが挙げられる。これほどの多くの疾患の原因が TGF- 関連遺伝子異常であることに驚かされる。これら疾患の多くは遺伝子の浸透率が低く, 疾患遺伝子を保有していても臨床所見を示さない人が多い。すなわち, 多数の患者を有する大家系を見つけるのは困難で, しばしば孤発例として観察されている。さらに, これら疾患には臨床症状の一部を有する「亜型」様病態が認められる。そのような患者では, 典型的症状を示す典型疾患と同一の遺伝子上に別の遺伝子変異を有することがしばしばである。

上記のような知識より, 疾患遺伝子が不明な血管関連, 結合組織関連疾患患者, さらに臨床的に典型例ではなく, 診断が困難な血管関連, 結合組織関連疾患患者について, TGF- 関連遺伝子を中心に検索すれば, 疾患遺伝子が見つかる可能性が高いのではないかと, という推察が可能である。しかしながら, TGF- 受容体, 細胞内シグナル伝達系, 補助分子を含めた関連遺伝子の数は数十に上り, 簡単に検索することは不可能であった。

近年, 遺伝子工学の発達により, 全 exon 解析 (exome 解析) が安価に可能となった。しかし実際には, 20000 種類に及ぶヒト遺伝子をスクリーニングすると多数の遺伝子変化が見つかる。それらが遺伝子多型なのか遺伝子異常なのか, 判定は一般に困難である。すなわち, exome を散漫に検索しても, なかなか実際の疾患遺伝子には到達できない。狙いを絞って, 可能性の高い遺伝子異常を同定し,

異常遺伝子の機能解析を行なう必要がある。

本研究は, 疾患遺伝子候補を狙いを絞って検索し, 肺血管系異常の遺伝的背景を明らかにしようとするものである。

2. 研究の目的

本研究は, 疾患遺伝子候補を TGF- 関連遺伝子に狙いを絞って検索し, 肺血管系異常の遺伝的背景を明らかにしようとするものである。

偶然の発見により, 思いがけない疾患と関連している変異を見つける危険性を避けるため, 本研究では TGF- シグナル伝達系に関連した遺伝子のみを選択的に検索することとした。

3. 研究の方法

肺血管異常を示す症例は, 肺血管異常を示すことが知られている遺伝性疾患とは異なる症例とした。具体的には, CT 画像所見で, 肺血管の走行異常が複数箇所認められ, さらに既知の遺伝性疾患を示唆する身体所見を認めない症例とした。

肺血管異常を示す症例を exome シークエンスで検索した。得られたデータを全て閲覧することは避け, あらかじめ検索リストとして倫理委員会に提出した遺伝子のみを検索することとした。

Exome 解析は, 以下のように行った。まず, 倫理委員会の承認を得た同意書により, インフォームドコンセントのあと同意取得した患者から末梢血を採取した。末梢血からゲノム DNA を単離, Aligent 社の SURE select で exon に対応する塩基配列を補足し, 補足 DNA を PCR で増幅した。増幅産物のうち, 300 bp 付近に存在する DNA を分離, 回収し, Illumina 社の Genome Analyze Iix にて増幅産物を解析した。

Exome シークエンス後に注目して解析する遺伝子は, TGF- シグナル伝達系に属する以下の遺伝子である。

Activin A, Activin B, ACVR1, ACVR1B, ACVR1C, ACVR2, ACVR2B, ACVRL1, AMHR2, BAMBI, BMP-1, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8a, BMP-8b, BMP-10, BMP-15, BMPR1A, BMPR1B, BMPR2, CHRDL1, CRIP1, CRIP2, CRIP3, CRIP4, CRIP5, CRIP6, CRIP7, CRIP8, CRIP9, CRIP10, CRIP11, CRIP12, CRIP13, CRIP14, CRIP15, CRIP16, CRIP17, CRIP18, CRIP19, CRIP20, ENG, FST, GDF-1, GDF-2, GDF-3, GDF-4, GDF-5, GDF-6, GDF-7, GDF-8, GDF-9a, GDF-9b, GDF-10, GDF-11, GDF-12, GDF-13, GDF-14, GDF-15, HJV, Inhibin A, Inhibin B, LEFTY1, LEFTY2, LEFTY3, LEFTY4, LEFTY5, LEFTY6, LEFTY7, LEFTY8, LEFTY9, LEFTY10, LEFTY11, LEFTY12, LEFTY13, LEFTY14, LEFTY15, LEFTY16, LEFTY17, LEFTY18, LEFTY19, LEFTY20, LEFTY21, LEFTY22, LEFTY23, LEFTY24, LEFTY25, LEFTY26, LEFTY27, LEFTY28, LEFTY29, LEFTY30, LEFTY31, LEFTY32, LEFTY33, LEFTY34, LEFTY35, LEFTY36, LEFTY37, LEFTY38, LEFTY39, LEFTY40, LEFTY41, LEFTY42, LEFTY43, LEFTY44, LEFTY45, LEFTY46, LEFTY47, LEFTY48, LEFTY49, LEFTY50, LEFTY51, LEFTY52, LEFTY53, LEFTY54, LEFTY55, LEFTY56, LEFTY57, LEFTY58, LEFTY59, LEFTY60, LEFTY61, LEFTY62, LEFTY63, LEFTY64, LEFTY65, LEFTY66, LEFTY67, LEFTY68, LEFTY69, LEFTY70, LEFTY71, LEFTY72, LEFTY73, LEFTY74, LEFTY75, LEFTY76, LEFTY77, LEFTY78, LEFTY79, LEFTY80, LEFTY81, LEFTY82, LEFTY83, LEFTY84, LEFTY85, LEFTY86, LEFTY87, LEFTY88, LEFTY89, LEFTY90, LEFTY91, LEFTY92, LEFTY93, LEFTY94, LEFTY95, LEFTY96, LEFTY97, LEFTY98, LEFTY99, LEFTY100, LEFTY101, LEFTY102, LEFTY103, LEFTY104, LEFTY105, LEFTY106, LEFTY107, LEFTY108, LEFTY109, LEFTY110, LEFTY111, LEFTY112, LEFTY113, LEFTY114, LEFTY115, LEFTY116, LEFTY117, LEFTY118, LEFTY119, LEFTY120, LEFTY121, LEFTY122, LEFTY123, LEFTY124, LEFTY125, LEFTY126, LEFTY127, LEFTY128, LEFTY129, LEFTY130, LEFTY131, LEFTY132, LEFTY133, LEFTY134, LEFTY135, LEFTY136, LEFTY137, LEFTY138, LEFTY139, LEFTY140, LEFTY141, LEFTY142, LEFTY143, LEFTY144, LEFTY145, LEFTY146, LEFTY147, LEFTY148, LEFTY149, LEFTY150, LEFTY151, LEFTY152, LEFTY153, LEFTY154, LEFTY155, LEFTY156, LEFTY157, LEFTY158, LEFTY159, LEFTY160, LEFTY161, LEFTY162, LEFTY163, LEFTY164, LEFTY165, LEFTY166, LEFTY167, LEFTY168, LEFTY169, LEFTY170, LEFTY171, LEFTY172, LEFTY173, LEFTY174, LEFTY175, LEFTY176, LEFTY177, LEFTY178, LEFTY179, LEFTY180, LEFTY181, LEFTY182, LEFTY183, LEFTY184, LEFTY185, LEFTY186, LEFTY187, LEFTY188, LEFTY189, LEFTY190, LEFTY191, LEFTY192, LEFTY193, LEFTY194, LEFTY195, LEFTY196, LEFTY197, LEFTY198, LEFTY199, LEFTY200, LEFTY201, LEFTY202, LEFTY203, LEFTY204, LEFTY205, LEFTY206, LEFTY207, LEFTY208, LEFTY209, LEFTY210, LEFTY211, LEFTY212, LEFTY213, LEFTY214, LEFTY215, LEFTY216, LEFTY217, LEFTY218, LEFTY219, LEFTY220, LEFTY221, LEFTY222, LEFTY223, LEFTY224, LEFTY225, LEFTY226, LEFTY227, LEFTY228, LEFTY229, LEFTY230, LEFTY231, LEFTY232, LEFTY233, LEFTY234, LEFTY235, LEFTY236, LEFTY237, LEFTY238, LEFTY239, LEFTY240, LEFTY241, LEFTY242, LEFTY243, LEFTY244, LEFTY245, LEFTY246, LEFTY247, LEFTY248, LEFTY249, LEFTY250, LEFTY251, LEFTY252, LEFTY253, LEFTY254, LEFTY255, LEFTY256, LEFTY257, LEFTY258, LEFTY259, LEFTY260, LEFTY261, LEFTY262, LEFTY263, LEFTY264, LEFTY265, LEFTY266, LEFTY267, LEFTY268, LEFTY269, LEFTY270, LEFTY271, LEFTY272, LEFTY273, LEFTY274, LEFTY275, LEFTY276, LEFTY277, LEFTY278, LEFTY279, LEFTY280, LEFTY281, LEFTY282, LEFTY283, LEFTY284, LEFTY285, LEFTY286, LEFTY287, LEFTY288, LEFTY289, LEFTY290, LEFTY291, LEFTY292, LEFTY293, LEFTY294, LEFTY295, LEFTY296, LEFTY297, LEFTY298, LEFTY299, LEFTY300, LEFTY301, LEFTY302, LEFTY303, LEFTY304, LEFTY305, LEFTY306, LEFTY307, LEFTY308, LEFTY309, LEFTY310, LEFTY311, LEFTY312, LEFTY313, LEFTY314, LEFTY315, LEFTY316, LEFTY317, LEFTY318, LEFTY319, LEFTY320, LEFTY321, LEFTY322, LEFTY323, LEFTY324, LEFTY325, LEFTY326, LEFTY327, LEFTY328, LEFTY329, LEFTY330, LEFTY331, LEFTY332, LEFTY333, LEFTY334, LEFTY335, LEFTY336, LEFTY337, LEFTY338, LEFTY339, LEFTY340, LEFTY341, LEFTY342, LEFTY343, LEFTY344, LEFTY345, LEFTY346, LEFTY347, LEFTY348, LEFTY349, LEFTY350, LEFTY351, LEFTY352, LEFTY353, LEFTY354, LEFTY355, LEFTY356, LEFTY357, LEFTY358, LEFTY359, LEFTY360, LEFTY361, LEFTY362, LEFTY363, LEFTY364, LEFTY365, LEFTY366, LEFTY367, LEFTY368, LEFTY369, LEFTY370, LEFTY371, LEFTY372, LEFTY373, LEFTY374, LEFTY375, LEFTY376, LEFTY377, LEFTY378, LEFTY379, LEFTY380, LEFTY381, LEFTY382, LEFTY383, LEFTY384, LEFTY385, LEFTY386, LEFTY387, LEFTY388, LEFTY389, LEFTY390, LEFTY391, LEFTY392, LEFTY393, LEFTY394, LEFTY395, LEFTY396, LEFTY397, LEFTY398, LEFTY399, LEFTY400, LEFTY401, LEFTY402, LEFTY403, LEFTY404, LEFTY405, LEFTY406, LEFTY407, LEFTY408, LEFTY409, LEFTY410, LEFTY411, LEFTY412, LEFTY413, LEFTY414, LEFTY415, LEFTY416, LEFTY417, LEFTY418, LEFTY419, LEFTY420, LEFTY421, LEFTY422, LEFTY423, LEFTY424, LEFTY425, LEFTY426, LEFTY427, LEFTY428, LEFTY429, LEFTY430, LEFTY431, LEFTY432, LEFTY433, LEFTY434, LEFTY435, LEFTY436, LEFTY437, LEFTY438, LEFTY439, LEFTY440, LEFTY441, LEFTY442, LEFTY443, LEFTY444, LEFTY445, LEFTY446, LEFTY447, LEFTY448, LEFTY449, LEFTY450, LEFTY451, LEFTY452, LEFTY453, LEFTY454, LEFTY455, LEFTY456, LEFTY457, LEFTY458, LEFTY459, LEFTY460, LEFTY461, LEFTY462, LEFTY463, LEFTY464, LEFTY465, LEFTY466, LEFTY467, LEFTY468, LEFTY469, LEFTY470, LEFTY471, LEFTY472, LEFTY473, LEFTY474, LEFTY475, LEFTY476, LEFTY477, LEFTY478, LEFTY479, LEFTY480, LEFTY481, LEFTY482, LEFTY483, LEFTY484, LEFTY485, LEFTY486, LEFTY487, LEFTY488, LEFTY489, LEFTY490, LEFTY491, LEFTY492, LEFTY493, LEFTY494, LEFTY495, LEFTY496, LEFTY497, LEFTY498, LEFTY499, LEFTY500, LEFTY501, LEFTY502, LEFTY503, LEFTY504, LEFTY505, LEFTY506, LEFTY507, LEFTY508, LEFTY509, LEFTY510, LEFTY511, LEFTY512, LEFTY513, LEFTY514, LEFTY515, LEFTY516, LEFTY517, LEFTY518, LEFTY519, LEFTY520, LEFTY521, LEFTY522, LEFTY523, LEFTY524, LEFTY525, LEFTY526, LEFTY527, LEFTY528, LEFTY529, LEFTY530, LEFTY531, LEFTY532, LEFTY533, LEFTY534, LEFTY535, LEFTY536, LEFTY537, LEFTY538, LEFTY539, LEFTY540, LEFTY541, LEFTY542, LEFTY543, LEFTY544, LEFTY545, LEFTY546, LEFTY547, LEFTY548, LEFTY549, LEFTY550, LEFTY551, LEFTY552, LEFTY553, LEFTY554, LEFTY555, LEFTY556, LEFTY557, LEFTY558, LEFTY559, LEFTY560, 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LEFTY661, LEFTY662, LEFTY663, LEFTY664, LEFTY665, LEFTY666, LEFTY667, LEFTY668, LEFTY669, LEFTY670, LEFTY671, LEFTY672, LEFTY673, LEFTY674, LEFTY675, LEFTY676, LEFTY677, LEFTY678, LEFTY679, LEFTY680, LEFTY681, LEFTY682, LEFTY683, LEFTY684, LEFTY685, LEFTY686, LEFTY687, LEFTY688, LEFTY689, LEFTY690, LEFTY691, LEFTY692, LEFTY693, LEFTY694, LEFTY695, LEFTY696, LEFTY697, LEFTY698, LEFTY699, LEFTY700, LEFTY701, LEFTY702, LEFTY703, LEFTY704, LEFTY705, LEFTY706, LEFTY707, LEFTY708, LEFTY709, LEFTY710, LEFTY711, LEFTY712, LEFTY713, LEFTY714, LEFTY715, LEFTY716, LEFTY717, LEFTY718, LEFTY719, LEFTY720, LEFTY721, LEFTY722, LEFTY723, LEFTY724, LEFTY725, LEFTY726, LEFTY727, LEFTY728, LEFTY729, LEFTY730, LEFTY731, LEFTY732, LEFTY733, LEFTY734, LEFTY735, LEFTY736, LEFTY737, LEFTY738, LEFTY739, LEFTY740, LEFTY741, LEFTY742, LEFTY743, LEFTY744, LEFTY745, LEFTY746, LEFTY747, LEFTY748, LEFTY749, LEFTY750, LEFTY751, LEFTY752, LEFTY753, LEFTY754, LEFTY755, LEFTY756, LEFTY757, LEFTY758, LEFTY759, LEFTY760, LEFTY761, LEFTY762, LEFTY763, LEFTY764, LEFTY765, LEFTY766, LEFTY767, LEFTY768, LEFTY769, LEFTY770, LEFTY771, LEFTY772, LEFTY773, LEFTY774, LEFTY775, LEFTY776, LEFTY777, LEFTY778, LEFTY779, LEFTY780, LEFTY781, LEFTY782, LEFTY783, LEFTY784, LEFTY785, LEFTY786, LEFTY787, LEFTY788, LEFTY789, LEFTY790, LEFTY791, LEFTY792, LEFTY793, LEFTY794, LEFTY795, LEFTY796, LEFTY797, LEFTY798, LEFTY799, LEFTY800, LEFTY801, LEFTY802, LEFTY803, LEFTY804, LEFTY805, LEFTY806, LEFTY807, LEFTY808, LEFTY809, LEFTY810, LEFTY811, LEFTY812, LEFTY813, LEFTY814, LEFTY815, LEFTY816, LEFTY817, LEFTY818, LEFTY819, LEFTY820, LEFTY821, LEFTY822, LEFTY823, LEFTY824, LEFTY825, LEFTY826, LEFTY827, LEFTY828, LEFTY829, LEFTY830, LEFTY831, LEFTY832, LEFTY833, LEFTY834, LEFTY835, LEFTY836, LEFTY837, LEFTY838, LEFTY839, LEFTY840, LEFTY841, LEFTY842, LEFTY843, LEFTY844, LEFTY845, LEFTY846, LEFTY847, LEFTY848, LEFTY849, LEFTY850, LEFTY851, LEFTY852, LEFTY853, LEFTY854, LEFTY855, LEFTY856, LEFTY857, LEFTY858, LEFTY859, LEFTY860, 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TGF- β R3, Smad1, Smad2, Smad3, Smad4, Smad5, Smad6, Smad7.

これらの遺伝子の TGF- β シグナル伝達系中の位置を以下の図に示す。

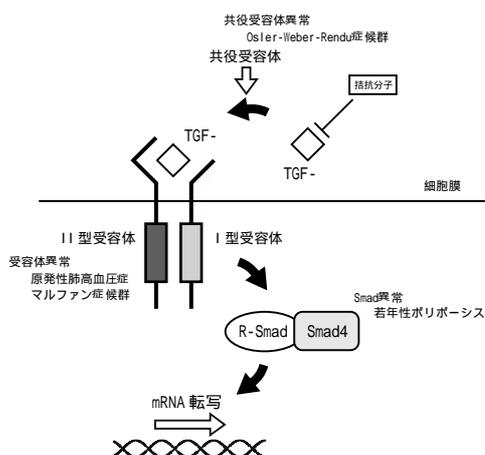


図1 TGF- β シグナル伝達系と遺伝疾患

TGF- β シグナル伝達系分子異常は、多数の疾患の原因となる。発生異常、間葉系の異常が見られるものが多い

4. 研究成果

多数の variant が検索対象遺伝子の intron や 5' non-coding region, 3' non-coding region で見いだされた。さらに、アミノ酸置換を生じない variant が多数見いだされた。しかしながら、これらの variant がタンパク機能に直接大きな影響を与える可能性は低いと考え、検索の範囲をアミノ酸置換を生じる変異、すなわち、non-synonymous variant に限定した。

BMP-2 で pS37A, BMP-4 で pV152A, BMP-8b で pM84V, BMP15 で c782_783insTCT, BMPRI1A で pP2T, CHRDL で pM630L, GDF-3 で pG213R, GDF-5 で pS276A, GDF-7 で pA330S, GDF-15 で pV9L, pS48T, LEFTY で pD322A, pR33Q, Nodal で pH165R, RGMA で pD399E, pD415E, pD423E, TGF- β R3 で pS15F, Smad5 で c1314_1315insC, が見つかった主要な non-synonymous 変異であった。

これらの non-synonymous では、必ずしもアミノ酸変異として大きなもの馬鹿裏ではない。特に BMP-4 で見られたバリンからアラニンのように、おそらく大きな構造変化を生じないと想定されるものもあり、全てを詳細

な検索の対象とする必要はないものと考えられた。

この中で興味深いものは、BMP15 の c782_783insTCT, Smad5 の c1314_1315insC であった。Genome 中に見られる variant のうち、塩基挿入は大きな影響を与えると一般的に想定されているものである。さらに、c1314_1315insC は、アミノ酸の open reading frame をずらす塩基挿入であり、この患者では Smad5 は機能を失っていると考えられた。

これらの変異による構造変化に関して検討して行く必要があると考えられた。

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)

[雑誌論文](計 0 件)

[学会発表](計 0 件)

[図書](計 0 件)

[産業財産権]

出願状況(計 0 件)

名称:

発明者:

権利者:

種類:

番号:

出願年月日:

国内外の別:

取得状況(計 0 件)

名称:

発明者:

権利者:

種類:

番号:

取得年月日:

国内外の別:

[その他]

ホームページ等

6. 研究組織

(1)研究代表者

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研究者番号:

(3)連携研究者

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研究者番号: