厚生労働科学研究費補助金 難治性疾患等政策研究事業(難治性疾患政策研究事業)
分担研究報告書

四肢形成不全の疾患概念と重症度分類法の確立に関する研究
遺伝子診断ならびに小児科領域からの疾患概念と重症度分類の確立支援

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研究要旨　本研究の目的は、遺伝子診断ならびに小児科領域からの四肢形成の疾患概念と重症度分類法の確立である。本年度は、全ゲノムアレイＣＧＨならびに全エクソーム解析を行い、世界 2 例目の IGF2 変異の同定、世界初の UBA2 変異の同定、ならびに、*DLX5* 変異、*TP63* 変異、*ROR2* 変異、PTCH1 変異、*PORCN* モザイクミスセンス変異を同定した。これらは、四肢形成不全発症機序の解明を通じて本研究の目的遂行に貢献するものである。

Ａ．　研究目的

本研究の目的は、遺伝子診断ならびに小児科領域からの四肢形成の疾患概念と重症度分類法の確立である。本年度は、遺伝子診断による裂手裂足症関連の発症機序を解明した。

Ｂ．研究方法

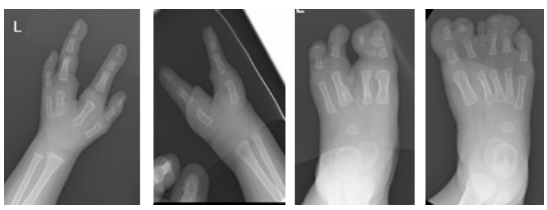
裂手裂足症を呈する患者 150 例以上を全国から集積し、全ゲノムアレイＣＧＨならびに全エクソーム解析を行い、その遺伝的原因を探索した。

（倫理面での配慮）

本研究の遂行にあたっては、ヒトゲノム・遺伝子解析研究に関する倫理指針を遵守し、検体の収集を含めた研究計画については、浜松医科大学倫理委員会の承認を得ている。検体は、書面によるインフォームド・コンセントを取得後に収集した。

Ｃ．研究結果

世界 2 例目の父性発現遺伝子 IGF2 変異の同定：シルバーラッセル症候群、裂手裂足症、性分化疾患を有する男児において、IGF2 の de novo 変異を同定し、メチル化感受性酵素を用いた解析でこれが、父由来染色体上に存在することを見出した（図１）。



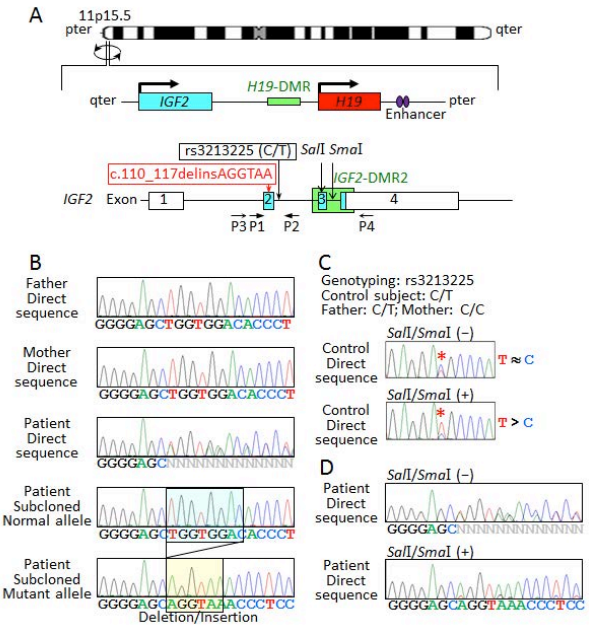
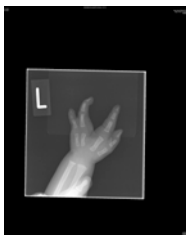


図 1. 裂手裂足症患者における世界 2 例目の父性発現遺伝子 IGF2 変異。

世界初の UBA2 変異の同定：裂手裂足症、性分化疾患を有する男児において見出された（図２）。



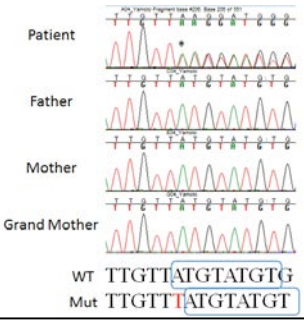
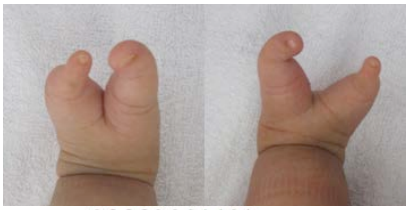
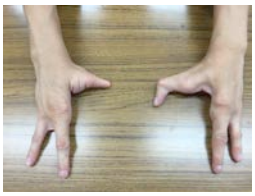


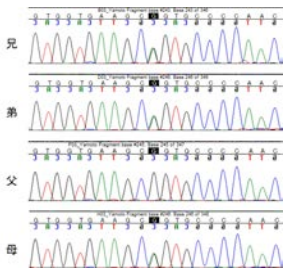
図２．患者のレントゲン写真と同定された c.1324dupT,p.(Tyr442Leufs*17)変異

DLX5 変異変異の同定：NM_005221.5: c.557A>G, p.(Gln186Arg)　*de novo* のミスセンス変異を認めた（下図）。

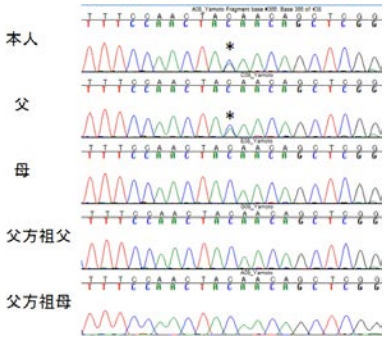


TP63 変異の同定：NM_003722.4:c.728G>A, p.(Arg243Gln)を兄・弟・母に上記変異を認めた（下図）。

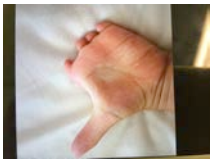


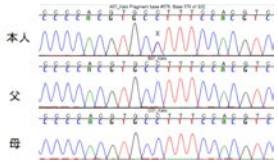


ROR2 変異の同定：NM_004560.3: c.2265C>A, p.(Tyr755*)　本人・父にヘテロ接合性のナンセンス変異を認める（下図）。

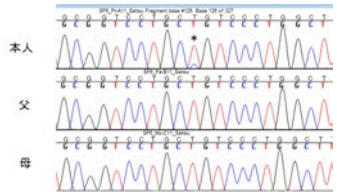


PTCH1 変異の同定：NM_000264.3: c.4244C>T,p.(Pro1415Leu)
本人に de novo のヘテロ接合性のミスセンス変異を認める。（下図）。





PORCN モザイクミスセンス変異の同定：NM_203475.2:c.1055T>C, p.(Leu352Pro) de novo のモザイク変異が本人に認められる（下図）。



D．考察

本研究により、四肢形成不全を招く遺伝的原因おの多様性が明らかとなってきた。特に、IGF2 や UBA2 などの現在まで裂手裂足症を招きうるとは考えられていなかった遺伝子変異が同定されたことの意義は大きい。これらの成果は、四肢形成不全ン発症機序の解明を通じて本研究の目的遂行に貢献するものである。

E．結論

全ゲノムアレイＣＧＨならびに全エクソーム解析を行い、世界 2 例目の IGF2 変異の同定、世界初の UBA2 変異の同定、ならびに、*DLX5* 変異、*TP63* 変異、*ROR2* 変異、PTCH1 変異、*PORCN* モザイクミスセンス変異を同定した。これらは、四肢形成不全ン発症機序の解明を通じて本研究の目的遂行に貢献するものである。

F．健康危険情報

総括研究報告書にまとめて記載

G．研究発表

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2. 学会発表
省略

H．知的財産権の出願・登録状況
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