意語無し、言語理解は数語。対人的関心と軽度の人見知りはある。

症例４）　H.M　2歳女児　精神発達遅滞、二分口蓋垂裂、特徴的顔貌。
arr16p13.11p12.3(15,492,317-18,112,776)×3
診断：16p13.11 重複症候群

患児は、2歳女児。37歳の母と39歳の父から、在胎38週　で出生。出生時体重2946g、身長49cm、頭囲34cm。現在の身体計測値は、身長-1.2SD、体重-1.5SD、頭囲-0.7SD。

二分口蓋垂　薄い頭髪　薄い爪　流涙がないを認める。脳画像異常なし。眼科的合併症として斜視があり 1 歳時に治療。母は強迫神経症の通院歴。

症例５）　I.J.　1歳男児：鎖肛、著しい成長障害、小脳虫部低形成、
arr2p16.1p14(60,676,037-65,731,798)×1
診断：2p14p16.1 に約 5Mb の欠失、2p16.1-p15 欠失症候群（MIM612513）

在胎39週、27歳の母と29歳の父から出生時体重2484g、身長44.5cm、頭囲31cmで正常経腟分娩で出生。出生時に低位鎖肛と小頭を認めた。その後、僧帽弁逆流、頭蓋骨早期閉鎖、斜視、指関節の伸展制限を診断されている。成長障害が著しく、1歳6ヶ月時の身体計測値SDは、身長-6SD、体重-3.4SD、頭囲-5SDである。精神運動発達遅滞があり、1歳6ヶ月時に寝返り可、坐位不可。1時間毎に覚醒する睡眠障害がある。頭部MRIにて小脳虫部低形成を認める。
過去に報告がある 2p16.1-p15 欠失症候群（MIM612513）の欠失領域を含み、脳形成異常、指の形態など過去の報告例と類似しており検討中である。

症例6）　O.M.　4歳女児　臨床診断:多発奇形、精神遅滞、先天性心疾患、眼瞼裂狭小。
アレイ結果:arr 16p13.3(1,206,922-6,552,944) x 3
16p13.3 重複症候群

36歳の母と35歳の父から、在胎37週で出生。出生時体重1682g、身長41.5cm、頭囲29cm。

現在の身体計測値 SD は、身長-2.6SD、体重-1.6SD、頭囲-3.2SD。

特徴的身体所見として、彎曲した爪　内眼角贅皮　カール頭髪　眼瞼裂狭小を認める。循環器合併症としてファロー四徴症。眼科的合併症として眼瞼下垂　眼瞼裂狭小。耳鼻科的合併症として高度難聴（80-90db）

症例7）　H.T　8歳男児
特徴的顔貌、軽度精神遅滞、関節過伸展
アレイ結果：arr　Xp21.1　(32,466,962　-34,371,98) x3
診断:Xp21.1 に約 1.9Mb の欠失

本領域には、BMD/DMD筋ジストロフィーに関連するDMD遺伝子の領域を含む。MLPAでの検討で、Dp427C～エクソン29に重複を認める。重複領域に他のOMIM遺伝子は無く、本重複と臨床症状の関係は不明。

症例8）　K.F.　12歳男児
軽度精神遅滞、心房中隔欠損症、特徴的顔貌
arr 8p23.1 (7,753,524-11,841,90) x 1

出生時体重2690g、身長45.1cm、頭囲31cm。

現在の身体計測値SDは、身長-.5SD、体重-.5SD、頭囲-2SD。　特徴的身体所見として、第５指軽度短小、歯列不整,　cowlick hair 後頭部。第４指の屈曲制限135度。項部の生え際のUpsweetを認める。

症例9）　K.T.　眼瞼裂狭小、軽度精神遅滞、特徴的顔貌
arr 10q22.2q22.3(76,741,585-78,399,732) x 1

診断：10q22.2 に約 1.6Mb の欠失

6 歳男児。健康な両親（出生時母 27 歳、父 44 歳）の第 2 子として正期産にて出生。出生体重 3514g、身長 51cm、頭囲 35.5cm。新生児期には特記すべき異常や哺乳力不良は認められていない。3 ヶ月時に眼瞼下垂/眼裂狭小と特徴的顔貌を指摘。運動発達の遅れはなく始歩 11 ヶ月。1 歳時斜視が目立つようになる。2 歳時に眼瞼下垂に対して眼瞼形成術。3 歳時身長+1.5SD、体重+2SD、頭囲+0.1SD 。耳介は形成の異常があり耳介の位置は低く後方回転している。眉毛は薄く上方に凸である。鼻は低く鼻根部は幅広く扁平。頭髪の量は標準的である。眼瞼裂狭小、眼間開離を認める。四肢に特記すべき異常なし。母指及び母趾の大きさは他の指趾と比べて標準的な大きさ。歯牙早期萌出、及び軽度のエナメル質の低形成を認める。発達は始歩 11 ヶ月。2 歳児の KIDS 乳幼児発達スケールで総合発達指数 96（運動 108,　言語理解 84、表出言語 60 以下）。人なつっこい性格である。

症例 10) S.Y　1 歳男児　多発奇形/精神運動発達遅滞

arr　1q21.3q22(154,187,018-156,132,842)×1

診断:1q21.3 領域の 1.9Mb の欠失

在胎 40 週、出生時体重 2535g、身長 49cm、頭囲 31.5cm。1 歳時の身体計測値 SD は、身長-2SD、体重-2.4SD、頭囲-1SD。特徴的身体所見として、斜視　upsweep hair　停留精巣　陰嚢低形成　翼状頚　右前耳瘻孔を認める。脳画像は異常なし眼科的合併症として斜視。同領域の欠失は過去に報告例が 1 例ある。

D．考察

過去 3 年以内に通院歴がある症例 114 例から家族の同意の得られた 66 名をマイクロアレイ解析の対象とした。

その結果 10 例に病因と考えうるコピー数の異常を認めた。病院として有意なコピー数異常と考え得る症例のうち、OMIM に登録されている疾患は約半数であり、半数はその解釈を求められる。日常の小児科、小児の臨床遺伝外来での先天異常症の診療において患者にその結果をフィードバックするためには、患者家族自身がこの解釈が必要であるという結果の意義を理解する必要があり、十分に理解するためには遺伝カウンセラーの関わりも重要であろう。

E．結論

染色体 G 分染法及び全サブテロメア FISH 解析で異常の検出できない症例の約 15%にマイクロアレイ解析で異常を検出した。先天異常の臨床においてマイクロアレイ法の有用性は高いと考えられた。

F．健康危険情報

なし

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Paris, June 8 , 2013

H．知的財産権の出願・登録状況
該当無し

厚生労働科学研究費補助金（難治性疾患等克服研究事業）
分担研究報告書

診断未定多発奇形・発達遅滞を示す患者の病因解明

研究分担者　山本　俊至
東京女子医科大学統合医科学研究所・准教授

研究要旨
研究目的：診断未定多発奇形・発達遅滞を示す患者においては、微細な領域のゲノムコピー数異常が関わっていることが多い。これらの患者を対象にマイクロアレイを用いた解析を行うと17%程度で何らかの変異が認められる。本研究においては、診断未定多発奇形・発達遅滞を示す患者を対象とした網羅的ゲノムコピー数解析を行い、新たな疾患単位の同定を行った。
研究方法：多発奇形・発達遅滞を示す患者のうち、従来の G-band 法では異常が認められなかった診断未定患者を対象にマイクロアレイを用いた解析を行った。異常が認められた場合には、基本的に FISH 法で確認し、de novo の有無を調べるために両親解析を行った。なお、本研究は学内の倫理委員会の承認に基づいて行われ、対象者からは書面によるインフォームド・コンセントを取得して行った。
研究結果：2 人の患者において、過去に 1 例だけ報告のある 3p21.31 の微細欠失を認め新規症候群として報告した。15q22 の微細欠失患者を 1 名同定し、諸外国の計 5 名の共通欠失を示す患者情報を収集し、新規微細欠失症候群と認識できると考え、報告した。また、Xq22 の微細欠失を示す女性患者 1 名を同定し、諸外国から共通する症例をデータベース検索で明らかにし、計 5 名の genotype-phenotype 連関を解析して報告した。
結論：本研究により、これまで明らかになっていない染色体微細欠失症候群を新たに報告した。染色体微細欠失による臨床症状はまだ明らかでないことが多く、今後の症例を積み重ねて新たな疾患概念を確立させていくことが必要であると考えた。

A．研究目的

診断未定多発奇形・発達遅滞を示す患者においては、微細な領域のゲノムコピー数異常が関わっていることが多い。これらの患者を対象にマイクロアレイを用いた解析を行うと17%程度で何らかの変異が認められる。今年度、新たに診断未定多発奇形・発達遅滞を示す患者を対象とした解析を行った。

B．研究方法

(1) 実施計画と経過

多発奇形・発達遅滞を示す患者のうち、従来の G-band 法では異常が認められなかった診断未定患者を対象にマイクロアレイを用いた解析を行った。異常が認められた場合には、基本的に FISH 法で確認し、de novo の有無を調べるために両親解析を行った。なお、本研究は学内の倫理委員会の承認に基づいて行われ、対象者からは書面によるインフォームド・コンセントを取得して行った。

(2) 倫理面への配慮

本研究においては患者情報に基づく遺伝子解析を行うことから、個人情報に配慮する必要があるため、東京女子医科大学の倫理委員会の承認を得て、書面に基づく説明と書面によるインフォームド・コンセントを得て実施した。収集される検体には、二重連結可能匿名化番号を付与し、匿名化番号、同意書のコピー１部、および患者情報票のコピー１部について個人情報管理者が管理した。個人情報と匿名化後の ID を連結する対応表はコンピューターの外部記憶装置に保存し、鍵のかかるキャビネット内で個人情報管理者が保管した。試料等に関するデータベースをコンピューターを用いて取り扱う場合は、インターネットや他のコンピューターから切り離した状態で取り扱った。

C．研究結果

本研究により 3p21.31 微細欠失症候群、15q22 微細欠失症候群、Xq22 微細欠失症候群の疾患概念を新たに確立し、報告した。

D．考察

本研究によって、過去に報告の無い３つの染色体微細欠失症候群を確立することができた。マイクロアレイ染色体検査は世界的に普及しつつあるが、まだ確立されていない疾患概念が存在すると考えられ、さらに研究を進めていく必要がある。その場合、データベースによるデータ公開と諸外国との共同研究は益々重要となると思われる。

E．結論

今回、診断未定多発奇形・発達遅滞を示す女性患者２名において、お互いに重なり合う微細欠失を 3p21.31 領域に認めた。この領域の欠失は過去に１例だけ報告があるが、臨床症状には共通した極めて特徴的な所見があり、新規症候群として認識されると考えられた。

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G. 知的所有権の取得状況

1. 特許取得
なし
2. 実用新案登録
なし
3. その他

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ．研究成果の刊行物・別刷

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Expression Analysis of a 17p Terminal Deletion, Including *YWHAE*, but not *PAFAH1B1*, Associated With Normal Brain Structure on MRI in a Young Girl

Keisuke Enomoto,[1,2] Yasuhiro Kishitani,[1] Makiko Tominaga,[1] Aki Ishikawa,[1] Noritaka Furuya,[1] Noriko Aida,[3] Mitsuo Masuno,[4] Ken-Ichiro Yamada,[5] and Kenji Kurosawa[1,6]*

[1]Division of Medical Genetics, Kanagawa Children's Medical Center, Yokohama, Japan

[2]Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University Graduate School of Medical and Dental Science, Tokyo, Japan

[3]Department of Radiology, Kanagawa Children's Medical Center, Yokohama, Japan

[4]Genetic Counseling Program, Graduate School of Health and Welfare, Kawasaki University of Medical Welfare, Yokohama, Japan

[5]Department of Pediatrics, Hiratsuka City Hospital, Hiratsuka, Japan

[6]Kanagawa Children's Medical Center, Institue for Clinical Research, Yokohama, Japan

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Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide (*YWHAE*), on chromosome 17p13.3, has been shown to play a crucial role in neuronal development. The deletion of *YWHAE*, but not platelet-activating factor acetylhydrolase, isoform 1b, subunit 1 (*PAFAH1B1*), underlies a newly recognized neurodevelopmental disorder, characterized by significant growth retardation, developmental delay/intellectual disability (DD/ID), distinctive facial appearance, and brain abnormalities. Here, we report on a girl with a terminal deletion of 17p13.3, including *YWHAE* but not *PAFAH1B1*, showing normal brain structure on MRI. She had mild developmental delay, a distinctive facial appearance, and severe growth retardation despite normal growth hormone levels, which was improved by growth hormone therapy. Expression analysis of *YWHAE* and *PAFAH1B1* yielded results consistent with array CGH and FISH results. These results indicate that the dosage effect of *YWHAE* varies from severe to very mild structural brain abnormalities, and suggest that the expression of *YWHAE* is associated with a complex mechanism of neuronal development.

Key words: *YWHAE*; *PAFAH1B1*; microdeletion 17p13.3; growth retardation

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Am J Med Genet Part A 158A:2347–2352.

INTRODUCTION

Deletions of 17p13.3 result in the neuronal migration disorders including lissencephaly and variable structural disorders of the brain [Dobyns et al., 1993]. Haploinsufficiency of platelet-activating factor acetylhydrolase, isoform 1b, subunit 1 (*PAFAH1B1*) and tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide (*YWHAE*), genes located in this region, are responsible for Miller–Dieker syndrome, which is characterized by lissencephaly, distinctive facial appearance, and severe neurological dysfunctions [Cardoso et al., 2003].

Recently, it has been shown that patients with deletion of *YWHAE*, but not *PAFAH1B1*, have significant growth retardation, developmental delay/intellectual disability (DD/ID), distinctive facial appearance, and brain abnormalities [Nagamani et al., 2009; Bruno et al., 2010; Mignon-Ravix et al., 2010; Schiff et al., 2010; Shimojima et al., 2010; Tenney et al., 2011]. These results indicated that the *YWHAE* plays a crucial role in neuronal development [Toyo-oka et al., 2003]. The structural abnormalities

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*Correspondence to:
Kenji Kurosawa, M.D., Ph.D., Division of Medical Genetics, Kanagawa Children's Medical Center, 2-138-4 Mutsukawa, Minami-ku, Yokohama 232-8555, Japan. E-mail: kkurosawa@kcmc.jp

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