クレアチントランスポーター欠損症

知的障害
けいれん
自閉症
ADHD

運動機能障害
（筋緊張低下）

〈遺伝子検査〉
X染色体q28にある
*SLC6A8*遺伝子の変化による
〈遺伝形式〉X連鎖劣性遺伝

〈病態生理〉
クレアチントランスポーターの異常により、クレアチンを細胞の中に取り込めなくなる。

〈患者数〉
日本に約８０００人の患者さんがいると推定されます。
通常、男性が発症します．女性は遺伝子の変化があっても、通常無症状ですが、軽度の知的障害や学習障害を認めることがあります。

【解説】
- クレアチントランスポーター欠損症では、発達の遅れがみられます。
- 言葉の遅れがみられることが多く、３歳頃に初めての言葉が出ることが多いようです。
- 約６０%の方にけいれんを認めます。多くの患者さんでは、お薬によって発作をコントロールできます。
- 約５０%の方にADHD(注意欠陥多動性障害)、約４０%の方に自閉症の症状がみられます。
- 約６０%の方に、筋緊張の低下を始めとする運動機能の障害がみられます。筋緊張の低下は成長とともに改善することが多いです。

- X染色体のq28に局在する*SLC6A8*遺伝子の変化により、クレアチントランスポーターの機能に異常がでます。
- すると、クレアチンを脳の細胞の中に取り込めず、脳の細胞の中でクレアチンを利用できないことで様々な症状が生じると考えられています。

- 男性の知的障害の0.8-3.5%はクレアチントランスポーター欠損症と考えられ、頻度の高い疾患です。
- 約８０００人の患者さんが日本にいると推定されます。［Kamp 2014］

- 通常、X染色体を１本しか持たない男性に発症する病気で、女性の場合、遺伝子異常があっても無症状です（保因者といいます）。
- ただし、女性にも軽度知的障害や学習障害等の症状がみられることがあります。

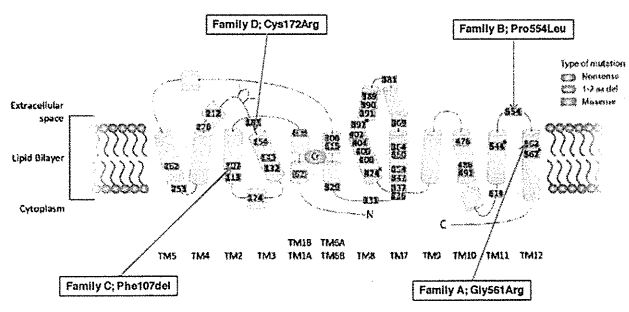
クレアチントランスポーター欠損症の診断

- 遺伝子検査
  - クレアチントランスポーター（輸送体）たんぱくを作るSLC6A8遺伝子の変異（X連鎖性遺伝）
- 病理
  - 特徴的な所見なし
- 頭部画像検査
  - 通常のMRI検査などでは特徴的な所見なし
  - MRスペクトロスコピーという特殊なMRI検査でクレアチンピークが低下
- 生化学検査
  - 尿中クレアチンと尿中クレアチニンの比が上昇（3以上）
  - 尿中グアノジノ酢酸は正常

【解説】
- クレアチントランスポーター欠損症は、クレアチンを脳内に取り込む輸送体（トランスポーター）の働きが悪いため、発達の遅れやけいれん、自閉症などの症状が見られます。ただし、その程度はさまざまで、また、同じような症状をおこす疾患は他にもたくさんあり、クレアチントランスポーター欠損症に特徴的な症状はありません。
- X染色体の中にあるSLC6A8遺伝子の変異によって起こります。遺伝形式はX連鎖性で男の子に発症する病気ですが、この遺伝子の変異をもつ女性にも症状が出現することがあります。
- 通常の脳の画像検査では特徴的な異常がありませんが、MRスペクトロスコピーという特殊な撮影法では脳内のクレアチンが少なくなっていることを知ることができます。

診断方法

患者で検出された変異の位置



大きな欠失を持つ家系には省かれている.

[From Van de Kamp, et al. J Med Genet. 2013]

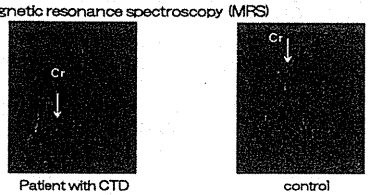
脳クレアチン欠乏症の診断

1.

deficiency		尿 GAA/C N	尿 GAA/C CR/CN	血清 GAA	血清 CR	血清 CN	髄液 GAA	髄液 CR	髄液 CN
AGAT		↓	↓	↓	no data		no data	→	
GAMT		↑	↓	↑↑	↓	↓～→	↑↑	↓	
SLC6A8	male	→	↑	→	?		no data	→	
	female	→	→～↑					?	

(GAA: guanidinoacetic acid, CR: creatine, CN: creatinine)

2. ^{1}H magnetic resonance spectroscopy (MRS)

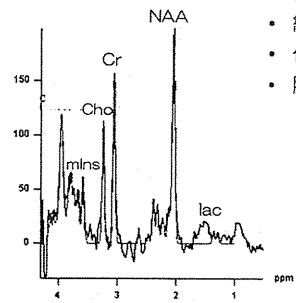


Patient with CTD　　control

decreased peak of creatine at basal ganglia

^{1}H -MR Spectoroscopy (MRS)

基底核での正常MRS波形



- 横軸を化学シフトの周波数
- 縦軸を信号強度
- 化学シフトの違いにより
- 脳内の代謝物を測定できる

『Proton MRSの臨床有用性コンセンサスガイド2013年度版』

MRSで測定される代表的な代謝物の意義

代謝物	化学シフト (ppm)	意義
NAA	2.02	神経細胞の高濃度に局在。 正常神経細胞密度に相関。
Cr	3.03	クレアチンとリン酸化クレアチンの総量を反映。 神経細胞やグリア細胞等の細胞密度に相関。
Cho	3.36	細胞膜代謝に関係するリン脂質の材料 となる代謝物
mIns	3.56	アストロサイトにおける濃度が高く、 グリア細胞増殖との相関が高い
lac	1.33	嫌気性解糖の結果生じる代謝物 エネルギー代謝障害の程度の指標

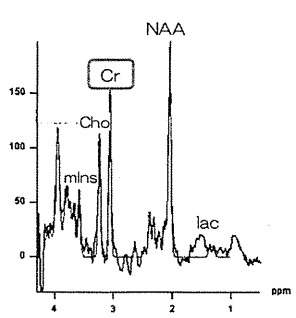
『Proton MRSの臨床有用性コンセンサスガイド2013年度版』より改変

【解説】

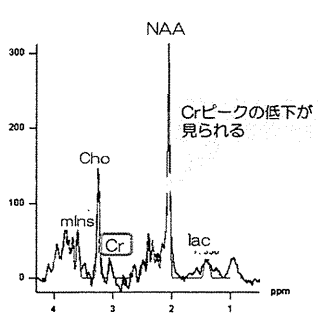
- MRSは磁場をかけた際の代謝物のプロトン原子核からの信号の周波数を解析し、その違いにより脳内の代謝物を測定することができます。つまり、脳の中の物質の量を推定できます。
- MRS波形で代表的なピークとして見られる物質を列挙しています。
- 脳クレアチン欠乏症で重要なクレアチンは神経細胞のエネルギーとして重要です。

脳クレアチン欠乏症のMRS

基底核での正常MRS波形



基底核での患者MRS波形

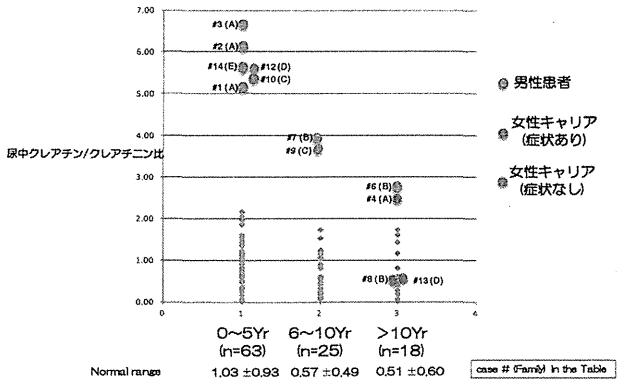


『Proton MRSの臨床有用性コンセンサスガイド2013年度版』

【解説】
脳クレアチン欠乏症で低下する脳内のクレアチン量をMRSにより明らかにすることができます。

Dezortova M, et al. ^{1}H MR spectroscopy as a diagnostic tool for cerebral creatine Deficiency. Magn Reson Mater Phy 21:327-332, 2008

尿中クレアチン/クレアチニン比106名のコントロール
およびSLC6A8遺伝子変異を持つ男性患者および女性保因者

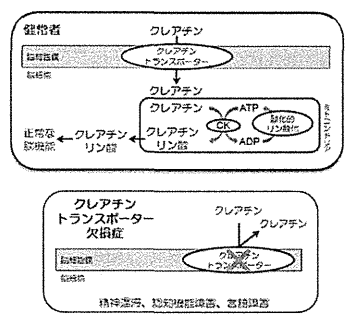


【解説】

- 4人の女性保因者のうち2名が軽度精神遅滞の症状を呈した。尿中Cr/Crn比は症状を呈した2例中1例は高値、もう一例および症状のない2例は正常値を示しました。
  - 女性における尿 Cr/Crn比は臨床症状と関連しませんでした。尿スクリーニングは男性のみで有効な手段であり、女性では注意が必要。［van de Kamp, *Clin Genet*, 2011］
- 男性における尿Cr/Crn比は、臨床症状の重症度とは関連ませんでした。
  - 本研究における尿サンプルは、様々な年齢で測定され、また、食事の影響を受けるため、複数回の計測が必要なこともあります。
- 本研究では、家族内、および家族間の臨床症状の多様性が示されました。責任遺伝子以外の遺伝要因や、環境要因の関与も指摘されています。［van de Kamp, J Med Genet, 2013］

将来性のある治療法

クレアチントランスポーター欠損症に対する治療戦略



Journal of Clinical Investigation
122: 2837-2846, 2012

ヒトクレアチントランスポーター欠損症に対する治療には、大きく分けて4種類の候補があり、そのいくつかについて報告がなされています。

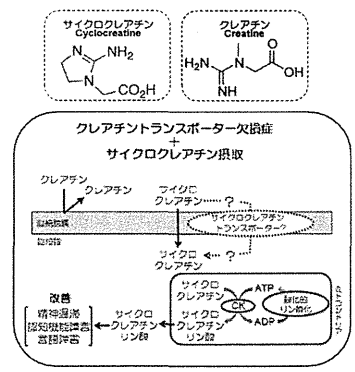
1）**クレアチン経口投与**は、一部を除き、効果が得られていません。その理由は、ニューロンの細胞膜上に発現すべきクレアチントランスポーターの欠損により、循環血液中のクレアチンをニューロン内部に輸送できなかったためと考えられています。効果が認められた一部の患者の特徴は、脳においてクレアチンが検出できるレベルにあること、および低年齢の投与開始が可能だったことです。しかしながら、その場合でも、臨床症状の完全な改善には至っていません。

2）**クレアチン類似物質経口投与**　以下の3点がポイントとなります。①クレアチントランスポーターが欠損していても、何らかの経路をへてニューロン内部に取り込まれること、②ニューロンに取り込まれたのち、リン酸化されて直接的エネルギー源であるATPを合成する能力を有すること、③　②の結果、認知機能を含む脳機能の改善につながる物質であることです。さらに、ヒト摂取の安全性が確認されている物質が、より望ましいと考えられます。

3）**脳におけるクレアチン合成の促進**　ヒトおよびマウスの脳には、2種類のクレアチン合成酵素が発現していることから、正常な脳はクレアチン合成能を有する可能性が指摘されています。しかしながら、^{1}H-MRSを用いた測定において、ヒト患者の脳クレアチンレベルは検出限界以下を示しているという事実から、必要十分量のクレアチン合成は患者脳では難しいことが伺われます。

4）**遺伝子治療**　安全性が保障されていない等の理由により、これまでのところ報告されておりません。

クレアチントランスポーター欠損症に対する
サイクロクレアチン治療の可能性



Kurosawa Y, et al. Journal of Clinical Investigation 122: 2837-2846, 2012

【解説】
ヒト患者の動物モデルである“クレアチントランスポーター遺伝子ノックアウトマウス“を対象に実施した、**サイクロクレアチン(cyclocreatine)**経口投与試験では、9週間の投与後、ニューロンにサイクロクレアチンが取り込まれていたことが確認されました。さらに、磁気共鳴分光法（^{31}P-MRS）を用いた測定により、そのサイクロクレアチンはリン酸化されていたことがわかり、ATP合成能を有していた可能性が高いと考えられています。また、同一マウスによる各種認知機能検査では、サイクロクレアチンを9週間経口投与した後に、空間認知能力、短期記憶力などに大幅な改善を認め、そのレベルは対照群のマウスと比べても遜色のないものでした。

サイクロクレアチンはまた、悪性腫瘍の治療薬候補と考えられていた時期があり、アメリカ合衆国でヒトを対照としたPhase I Studyが既に終了しており、ヒト摂取の安全性に関するデータが報告されています。また、いくつかの親油性クレアチン類似物質も、ヒト患者線維芽細胞などを用いた試験により、治療薬候補としての可能性が示されています。

現時点においては、クレアチン経口投与が唯一の選択肢であり、サイクロクレアチン等のクレアチン類似物質経口投与が、近い将来における治療の最有力候補と考えられています。

X連鎖性知的障害
X-LINKED INTELLECTUAL DISABILITY

知的障害 (Intellectual disability: ID) とは

定義

A. 全般的知能の欠陥：概ねIQ（知能指数）＜70
B. 年齢、性別および社会文化的背景が同等の仲間たちと比べて、日常の適応機能が障害されている
C. 発症は発達期の間　（DSM-5）

	IQ
軽度	50~70
中等度	40~50
重度	20~40
最重度	~20

頻度

一般人口における割合1～3%

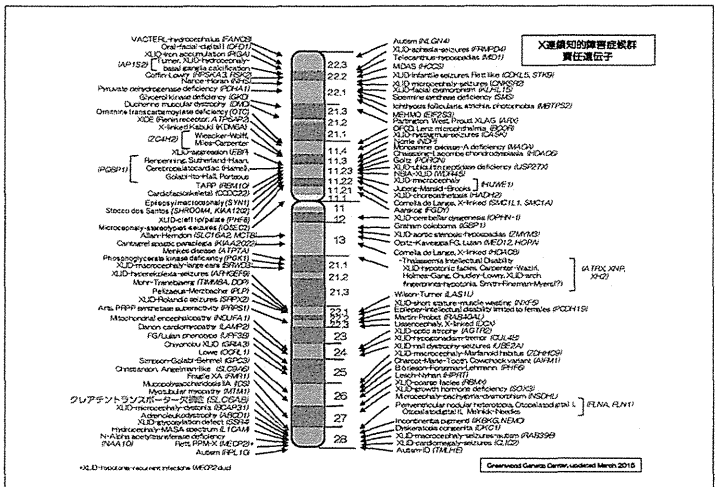
男：女＝1.3～1.4：1

原因

遺伝要因
- 染色体異常症
- 単一遺伝子疾患（＞700遺伝子）
  - 常染色体優性ID
  - 常染色体劣性ID
  - X連鎖性ID ← ID男性の5～10%を占める
- 多因子遺伝疾患

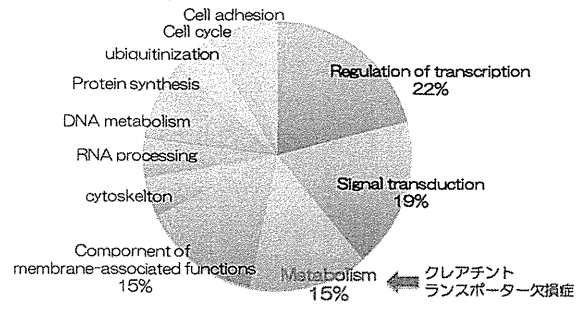
環境・後天的要因（周産期異常、感染症、頭部外傷など）

【解説】
- IDの原因はさまざまですが、少なくとも半数以上の患者さんで原因不明といわれています。
- しかし、重度IDはID患者の0.3～0.5%ですが、その多くが単一遺伝子疾患（メンデル遺伝病）であると報告されています。
- 一方、軽度IDの原因は多因子遺伝疾患や環境要因が複雑に関与していると考えられています。
- 単一遺伝子疾患の中でも、X連鎖性IDはID男性の5～10%の原因であると報告されており重要です。



【解説】
- X染色体上に責任遺伝子が存在し、神経学的、身体的、生化学的な特徴を伴う知的障害をX連鎖知的障害症候群といいます。
- 1966年の脆弱X症候群の細胞遺伝学的研究いよる発見から始まり、X連鎖知的障害症候群研究は発展し、現在では100以上のX連鎖知的障害責任遺伝子が同定されています。

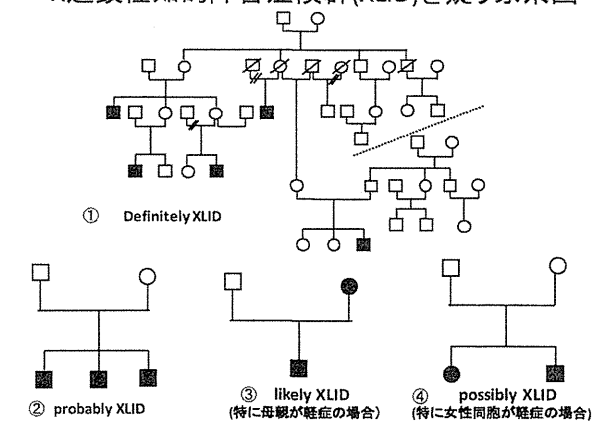
X連鎖性知的障害の責任遺伝子がコードするタンパクの機能分類（102遺伝子）



[Lubs HA, et al. *AJHG*, 2012]

（注意：AGAT欠損症、GAMT欠損症は常染色体劣性遺伝性疾患）

X連鎖性知的障害症候群(XLID)を疑う家系図



X連鎖性疾患は、ふつう、男性のみが発症します．

次のような家系図の場合、X連鎖性疾患を疑います．

① 家系内の複数の男性患者がその母親を介してつながっています．この場合、確実にX連鎖性（definitely X-linked)と考えられます．

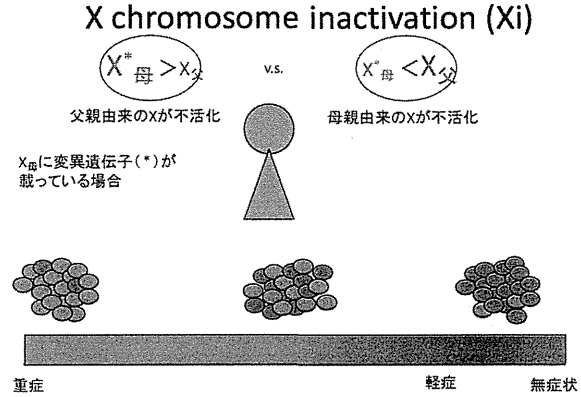
② 複数の男性同胞が患者の場合、X連鎖性の可能性が高い（probably X-linked)と考えます．（注意；他の遺伝形式の可能性もあります）

③ 男性患者とその母親が軽度罹患の場合、X連鎖性の可能性があります．（likely X-linked)．（注意；他の遺伝形式の可能性もあります）

④ 男性患者とその女性同胞母親が軽度罹患の場合、X連鎖性の可能性があります．（possibly X-linked)．（注意；他の遺伝形式の可能性もあります）

②～③はX連鎖性が確実というわけではなく、他の遺伝形式の可能性もあります．どのタイプの場合も、ミトコンドリア病の可能性があります．また、常染色体優性遺伝の場合、浸透率、表現度などを考慮すると、複雑になります．

X染色体不活化
X chromosome inactivation (Xi)



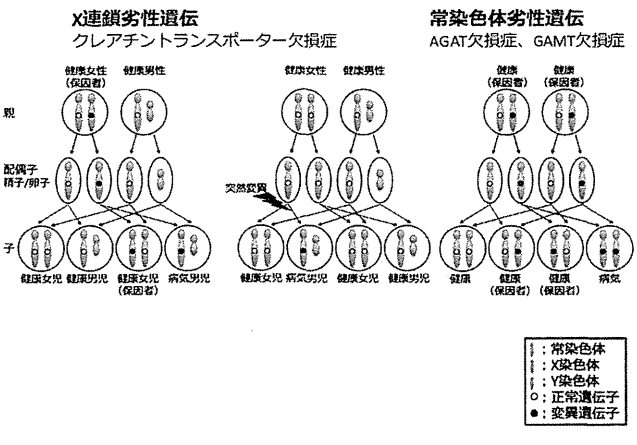
【解説】X染色体の不活化

女性は2本のX染色体、男性は1本のX染色体をもっています．
X染色体上にある遺伝子の変化では、通常、男性が発症します．女性の場合、X染色体上にある1つの遺伝子に変化が起きても、もう一方の遺伝子が正常であれば、機能としては困らないので、発症しない、と考えます．

しかし、女性でも、様々な症状で発症することが示されています．
これは、2本のX染色体のどちらか一方のX染色体は働いていない状態（不活化）ことが原因です．ですから、変化をもつ遺伝子が不活化したX染色体上にあり、もう一方の正常の遺伝子が活性化したX染色体上にあれば、正常と同じように機能します．しかし、逆の場合、すなわち、変化をもつ遺伝子が活性化したX染色体上にあり、もう一方の正常の遺伝子が不活化したX染色体上にあれば、正常に機能できなくなります．

変化をもつ遺伝子が活性化したX染色体にあるのか、あるいは、不活化したX染色体にあるかは、細胞によって異なっています．ですから、変化をもつ遺伝子が活性化したX染色体に載っている細胞を多くもっている女性では、発症する可能性がある、ということになります．（図の場合、変異をもつ遺伝子は母親由来のX染色体上にあるため、父親由来のX染色体が不活化している細胞を多くもっている女性では発症する、と考えられます．）

クレアチントランスポーター欠損症では、遺伝子の変化自体が X染色体不活化に影響を与えないため、他のX連鎖性疾患にくらべ、女性が発症しやすいと考えられています．また、このことは、無症状の女性でも、遺伝子変異をもっている可能性があることを意味しています．海外の報告では、一般女性の0.024%が遺伝子変異をもつ保因者である、と推定しています．[DesRoches CL, Gene. 2015]



【解説】
脳クレアチン欠乏症にはX連鎖劣性遺伝形式のクレアチントランスポーター欠損症と
常染色体劣性遺伝形式のAGAT欠損症とGAMT欠損症があります。

X連鎖劣性遺伝
男性の染色体は1本なので、その遺伝子に変異が起こると病気になります。
女性は2本持っているため、1本の遺伝子に変異が起きても通常無症状(保因者）です。
しかし、X染色体不活化というメカニズムのため（ページ参照）、女性でも病気になることがありますが、通常男性患者より軽症です。
母親が保因者の場合（図）、次のお子さんに関して、男児の半分（50%）は病気になり、女児の半分（50%）は保因者になります。
母親が保因者ではなく、突然変異の可能性もあり(図)、その場合は次のお子さんが病気になる確率は一般と同じと考えられています。

常染色体劣性遺伝
両親がそれぞれ1つずつ遺伝子の変異をもっており、両方ともお子さんに伝わることで病気になると考えられます。
次のお子さんが病気になる確率は男女関係なく4/1（25%）です。

症例

自験例について：クレアチントランスポーター欠損症

発達の遅れで受診

周産期歴　特記事項なし
発達歴
あやし笑い　2か月　定頸　5か月　寝返り4か月
遅い遣い 10か月 坐位 12か月 つかまり立ち 10か月
つたい歩き 11か月 ひとり立ち・自立歩行 2歳過ぎ
有意語未

発育 体重は-2SDで推移し、1歳に入って正常範囲に入ってきた　身長は正常下限－2SD前後を推移

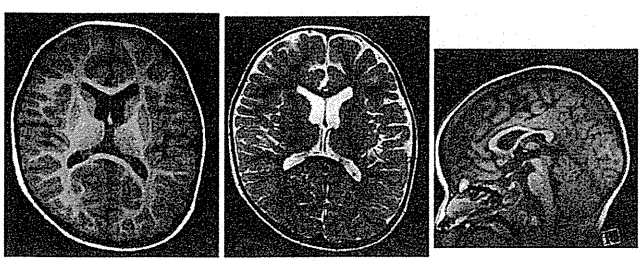
神経学的所見に異常ない

血清Creatinine　2回測って　0.11～0.12 mg/dL

【解説】
脳クレアチン欠乏症では血清クレアチニンは正常低め～低値を示すことが知られており、自験例でも低めでした。

Jiddeke M. van de Kamp, et al. X-linked creatine transporter deficiency: clinical aspects and pathophysiology. J Inherit Metab Dis 37:715-733, 2014

自験例：頭部MRIで異常なし



T1強調画像
水平断

T2強調画像
水平断

T1強調画像
矢状断

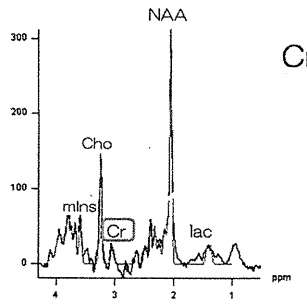
【解説】
MRIの通常のシーケンスでは異常を検出できませんでした。
過去の報告でも、異常がないか、軽度の信号異常や、脳梁が薄い、脳室の軽度拡大など、非特異的所見しかみられません。

尿中クレアチン/クレアチニン比 6以上と上昇を認め、尿中GAA正常から、クレアチントランスポーター欠損症が疑われました。

Jiddeke M. van de Kamp et al. X-linked creatine transporter deficiency: clinical aspects and pathophysiology. J Inherit Metab Dis 37:715-733, 2014

自験例：MR Spectroscopy

基底核での患者MRS波形



Crピークの低下

脳クレアチン欠乏症の患者さんやご家族のための社会的資源

- 療育手帳
  - 対象
  - ：認定基準を満たす知的障害をもつ人
  - 内容
  - ：障害の認定、税金の控除や交通費の割引など
- 身体障害者手帳
  - 対象
  - ：認定基準を満たす身体障害をもつ人
  - 内容
  - ：障害の認定、装具などの福祉機器の交付、医療費の助成、税金の控除や交通費の割引など
- 特別児童扶養手当（20歳未満）
- 障害児福祉手当（20歳未満）
- 特別障碍者手当（20歳以上）
- 障害基礎年金（20歳以上）
  - 対象
  - ：認定基準を満たす障害をもつ人
  - 内容
  - ：手当、年金の支給
- 自立支援医療
  - 対象
  - ：てんかんと診断され通院治療を受けている人
  - 内容
  - ：外来医療費の軽減
- 高額療養費制度
  - 対象
  - ：医療費が一定額をこえた人
  - 内容
  - ：医療費の払い戻し
- 介護保険
  - 対象
  - ：認定基準を満たす身体障害をもつ人
  - 内容
  - ：障害の認定、装具などの福祉機器の交付、医療費の助成、税金の控除や交通費の割引など

【解説】

- 障害の程度や収入などによって、利用できる内容や程度が異なることがあります。
- 詳しくは、通院している病院の医療福祉相談室、お住まいの市町村の担当窓口、保健所などにご相談ください。
- なお、2016年2月の時点では、本疾患は
- 特定疾患治療研究事業
- 小児慢性特定疾患治療研究事業
- による医療助成の対象には含まれていません。

ハンドブック作成に関わった先生

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  - 相田典子
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  - 後藤知英
  - 露崎　悠
  - 新保裕子
- 神奈川県立精神医療センター芹香病院
  - 加藤秀一
- 自治医科大学　小児科
  - 小坂　仁
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  - 和田敬仁

敬称略

II. 研究成果の刊行に関する一覧表

書籍

著者署名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kato H, Miyake F, Shimbo H, Ohya M, Sugawara H, Aida N, Anzai R, Takagi M, Okuda M, Takano K, Wada T, Iai M, Yamashita S, Osaka H.	Urine screening for patients with developmental disabilities detected a patient with creatine transporter deficiency due to a novel missense mutation in SLC6A8.	Brain Dev	36	630-633	2014
Akiyama T, Osaka H, Shimbo H, Nakajiri T, Kobayashi K, Oka M, Endoh F, Yoshinaga H.	A Japanese adult case of guanidinoacetate methyltransferase deficiency.	JIMD	12	665-669	2014
van de Kamp JM, Errami A, Howidi M, Anselm I, Winter S, Phalin-Roque J, Osaka H, van Dooren SJ, Mancini GM, Steinberg SJ, Salomons GS.	Genotype-phenotype correlation of contiguous gene deletions of SLC6A8, BCAP31 and ABCD1.	Clin Genet	87	141-147	2015
野崎 章仁、熊田知浩、柴田実、藤井達哉、和田敬仁、小坂仁.	尿中クレアチン/クレアチニン比と家族歴より診断に至ったクレアチントランスポーター欠損症の1家系　本邦3家系目.	脳と発達	47	49-52	2015
和田敬仁	脳クレアチン欠乏症候群	小児科臨床	79	290	2016

III. 研究成果の刊行物・別刷

ELSEVIER

Brain & Development xxx (2013) xxx–xxx

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Urine screening for patients with developmental disabilities detected a patient with creatine transporter deficiency due to a novel missense mutation in *SLC6A8*

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Abstract

Creatine transporter deficiency (CTD) is an example of X-linked intellectual disability syndromes, caused by mutations in *SLC6A8* on Xq28. Although this is the second most frequent genetic cause of intellectual disabilities in Europe or America after Fragile X syndrome, information on the morbidity of this disease is limited in Japan. Using the HPLC screening method we have established recently, we examined samples of urine of 105 patients (73 males and 32 females) with developmental disabilities at our medical center. And we have found a family with three ID boys with a novel missense mutation in *SLC6A8*. This is the second report of a Japanese family case of CTD. A systematic diagnostic system of this syndrome should be established in Japan to enable us to estimate its frequency and treatment.

Keywords: Intellectual disability; X-linked; Mental retardation; Creatine deficiency syndrome; Urine screening

1. Introduction

Cerebral creatine deficiency syndromes (CCDSs) are a group of inborn errors of creatine metabolism, including two autosomal recessive disorders that impair the biosynthesis of creatine, arginine:glycineamidinotransferase deficiency (MIM 602360) and guanidinoacetate-methyltransferase deficiency (MIM 601240), and the X-linked disorder, creatine transporter deficiency (CTD; MIM 300036). The common clinical features of CCDSs are intellectual disability, delayed language, autistic behavior and epilepsy [1].

CTD is caused by mutations in *SLC6A8* on Xq28, and reported to constitute 1% of males with ID of unknown etiology [2] or 2.1% of male with nonsyndromic X-linked intellectual disability (XLID) [3]. Although this is the second most frequent genetic cause of intellectual disabilities in Europe or America after Fragile X syndrome, only one case report of a Japanese patient

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http://dx.doi.org/10.1016/j.braindev.2013.08.004

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with a deletion of the *SLC6A8* gene has been published by Osaka [4], and we have little information on the frequency of this disease in Japan.

To diagnose the three types of CCDs, we have established a new simple HPLC screening method to determine the concentrations of guanidinoacetic acid (GAA), creatine (CR), and creatinine (CN) in urine [5]. Here we report the second case of Japanese familial case of CTD with a novel missense mutation of the *SLC6A8* gene.

2. Case report

The proband is a six-year-old boy, who was referred to our medical center because of his psychomotor retardation and delayed speech at age 4 years 11 months. He was born after an uneventful and full-term pregnancy. He sat until 12 months and walked at 22 months. He had no overt dysmorphism. He had febrile seizures three times. He could speak only a few words. His language comprehension was much better than expression, and he could obey several simple orders. His cognitive function seems to be that of a 3–4 years old. His neurological examination showed no abnormal findings, including pyramidal, extrapyramidal, or cerebellar signs. At 6 years and 4 months old, his height was 112.7 cm (−0.6 S.D.), and weight 18.8 kg (−0.7 S.D.), and head circumference 47.8 cm (−2.2S.D.), suggesting relative acquired microcephalus. He had no apparent autistic features.

The clinical pictures of the patient, his two younger brothers and mother are summarized. (Fig. 1 and Table 1).

We detected an abnormal pattern in the patient's urine by the HPLC method, showing CR/CN ratio was extremely high and GA within normal range, during the examination of the urine samples of 105 patients (73 males and 32 females) with developmental disabilities at our medical center.

These results prompted us to suspect a diagnosis of CTD. The urines of his two brothers and their mother also showed abnormal pattern. (Fig. 2).

^{1}H-MRS, examined using 3.0T MR system at the left basal ganglia of the index case showed a marked reduction of brain creatine peak. Brain T2-weighted and FLAIR MRI showed a high signal at the left trigone, and hypoplasia of the corpus callosum.

Genetic analysis of genomic DNA and cDNA from the patient showed a novel missense mutation in the exon 12 of the *SLC6A8* gene [c.1681G>C; p.Gly561Arg]. The two brothers had the same mutation. This glycine is a highly conserved amino acid among the creatine transporters of several species (chimpanzee, cattle, dog, mouse, rat and zebrafish). This amino acid substitution was not registered in the SNP database, and we did not find this substitution in 50 controls. Therefore this mutation is likely to be a pathogenic mutation for this family. Their mother has the same mutation heterogeneously.

3. Discussion

This is the second report of a Japanese familial case of CTD with a novel missense mutation of the *SLC6A8* gene, diagnosed by our new screening method of urinary GAA concentration and CR/CN ratio for individuals with developmental disabilities.

Several reviews have been published to characterize the clinical, laboratory, molecular, and imaging profiles of CTD, and the patients can presented with various symptoms, including growth disorder, hypotension, pyramidal/extrapyramidal findings, and attention deficit

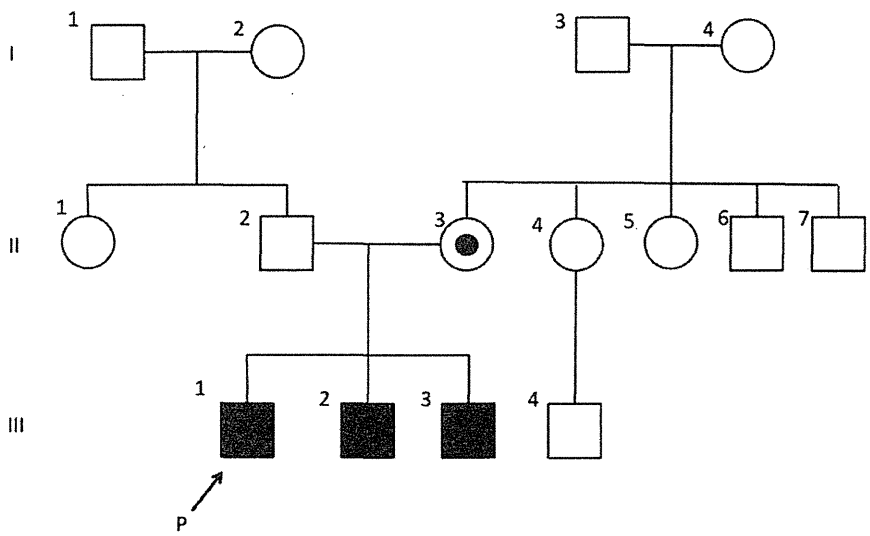

Fig. 1. Pedigree chart of the family.

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Table 1
Clinical features of the family.

	III-1; 6 Yr	III-2; 4 Yr	III-3; 2 Yr	II-3; 29 Yr
Gestational age	38.6 w	38.5 w	40.6 w	40 w
Birth Wt/HC	2776 g/32.5 cm	2632 g/–	2882 g/–	2960 g/NA
Present Wt/Ht/HC (S.D.)	−0.6/−0.7/−2.2	−0.4/−1.7/NA	−2.2/−3.4/−4.2	−2.1/−2.2/NA
Walking	24 months	22 months	24 months	18 months
Language development	Words only	5 words only	One words only	16 months
Meaningful words	Perception > Expression 24-months	Perception > Expression 20-months	Perception > Expression 21-months	
Seizure (Onset)	Febrile Sz (5 Yr)	Febrile Sz (2 Yr 10 Mo)	Febrile Sz Status (11 Mo) Epilepsy (1.5 Yr)	Epilepsy (14 Yr)
EEG	No Sz discharge	Not done	No Sz discharge	P/O-dominant diffuse Sp&W
Brain MRI/CT	Hypoplasia of corpus callosum	Normal (CT only)	Delayed myelination, hypoplasia of corpus callosum, small pituitary grand	Normal
Characteristics	Obey a simple order, understand his situation, good memory of sight information	Obey a simple order	Restless, hyperactive	Poor at putting in order, easy to be deceived
Creatine/Creatinine (mg/dl)	55.2/10.9	175.7/27.5	110.3/16.5	294.0/131.6
Ratio	5.07	6.39	6.7	2.23

Yr, year(s); Wt, weight; HC, head circumference; w, week(s); Ht, height; NA, not assessed; EEG, electroencephalogram; Sz, seizure; Mo, month(s); P/O, Parietal and occipital cortex; Sp&W, spike and waves; MRI, magnetic resonance imaging; CT, computed tomography.

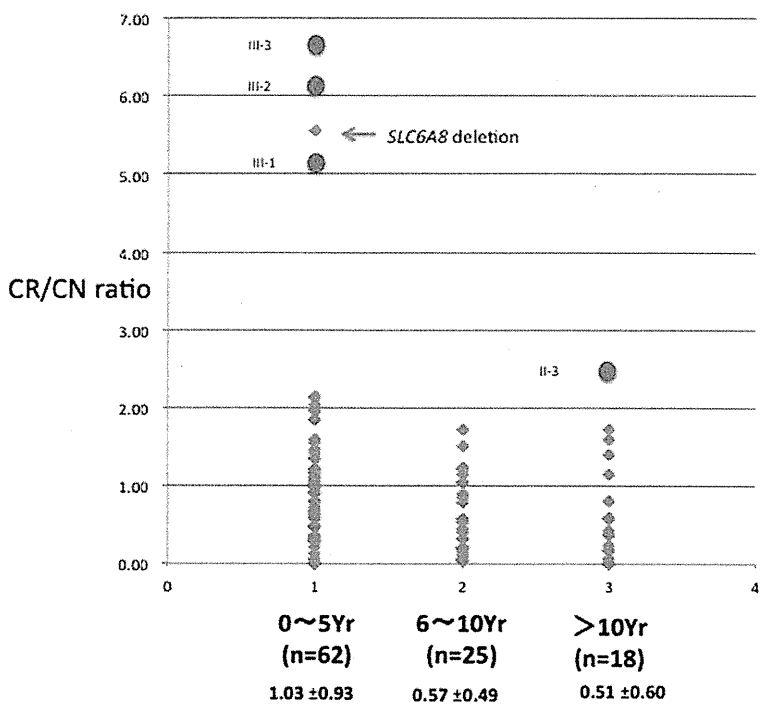

Fig. 2. The distribution of the ratio of creatine (CR)/creatinine (CN) by age of normal controls and the family. "SLA6A8 deletion" is the patient reported by Osaka [4]. (Yr, years; *n*, number).

hyperactivity disorder (ADHD) have been reported [1]. Our patients of the family presented with a broad spectrum of clinical phenotypes and relatively mild intellectual disability without autistic features or extrapyramidal abnormal movement, and they had expressive language disorder rather than receptive language disorder. Their relatively mild phenotype may suggest that their creatine transporter has some residual activity, although we have not confirmed it yet. Our result indicates that short stature and acquired relative microceph-

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aly may be a good indication to suspect CTD as a diagnosis for patients with ID.

Up to now, no treatments had been established for CTD, although oral supplementation of creatine monohydrate is known to be effective for GAMT and AGAT deficiency. Recently it was reported that the creatine analog, cyclocreatine, improved the cognitive abilities of brain-specific *Slc6a8* knockout mouse, and this might be a therapeutic agent in the near future [6].

Female carriers of X-linked CTD can commonly manifest, although usually less severely than affected males, as the mother of our index case presents. There is no consistent skewing of X-inactivation in peripheral tissues, indicating that there is no selection against CTD [7]. We emphasize the utility of our screening method for patients of CCDSs because of its cost performance, although the screening method may not be suitable for detecting female patients with CTD because of the high rate of false positive results [8].

The family was diagnosed during the examination of the urine samples of 105 patients with developmental disabilities at our medical center by our screening HPLC method. Considering that CTD is a frequent cause of intellectual disabilities in Europe or America, many patients in Japan should remain to be diagnosed. We have to develop systematic strategies for diagnosis, treatment and prevention of CCDSs as early as possible, because CCDSs are potentially treatable disorders [9].

Acknowledgements

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JIMD Reports
DOI 10.1007/8904_2013_245

CASE REPORT

A Japanese Adult Case of Guanidinoacetate Methyltransferase Deficiency

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Abstract Guanidinoacetate methyltransferase (GAMT) deficiency is a rare disorder of creatine synthesis resulting in cerebral creatine depletion. We present a 38-year-old patient, the first Japanese case of GAMT deficiency. Developmental delay started after a few months of age with a marked delay in language, which resulted in severe intellectual deficit. She showed hyperactivity and trichotillomania from childhood. Epileptic seizures appeared at 18 months and she had multiple types of seizures including epileptic spasms, brief tonic seizures, atypical absences, complex partial seizures with secondary generalization, and "drop" seizures. They have been refractory to multiple antiepileptic drugs. Although there have been no involuntary movements, magnetic resonance imaging revealed T2 hyperintense lesions in bilateral globus pallidi. Motor regression started around 30 years of age and the patient is now able to walk for only short periods. Very low serum creatinine levels measured by enzymatic method raised a suspicion of GAMT deficiency, which was confirmed by proton magnetic resonance spectroscopy and urinary guanidinoacetate assay. *GAMT* gene analysis revealed that the patient is a compound heterozygote of c.578A>G, p.Gln193Arg and splice site mutation, c.391G>C, p.Gly131Arg, neither of which have been reported in the literature. We also identified two aberrant splice products from the patient's cDNA analysis. The patient was recently started on supplementation of high-dose creatine and ornithine, the effects of which are currently under evaluation. Although rare, patients with developmental delay, epilepsy, behavioral problems, and movement disorders should be vigorously screened for GAMT deficiency, as it is a treatable disorder.

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Introduction

Guanidinoacetate methyltransferase (GAMT; OMIM 601240) deficiency is a rare autosomal recessive disorder of creatine synthesis resulting in cerebral creatine depletion (Stöckler et al. 1994, 1996b). Guanidinoacetate (GAA) accumulates in body fluids. Symptoms of GAMT deficiency usually emerge after a few months of life, such as intellectual disability, speech delay, autistic behaviors, epileptic seizures, and involuntary movements (Mercimek-Mahmutoglu et al. 2006). Making a diagnosis of GAMT deficiency is challenging; nonetheless, early diagnosis is crucial because this disorder is treatable (Stöckler et al. 1996a). Only approximately 80 cases have been reported to date, mostly from Europe and the Middle East. Here we report on the first Japanese patient with GAMT deficiency with two novel gene mutations.

Case Report

The patient, a 38-year-old female with intractable epilepsy and severe mental retardation, was born at full term with a birth weight of 3,260 g. There were no pre- or perinatal complications. She is the third of four children of Japanese non-consanguineous healthy parents. The first child, a boy, started having epileptic seizures after 1 year of age with unknown cause and died at 28 years of age at an institution for the mentally handicapped. The other two children have been healthy.

Although the patient showed a social smile by 3 months and head control by 4 months of age, her development has been delayed since then. She sat alone at 14 months, walked alone at around 20 months, and became able to take the stairs one step at a time with support around 5 years of age. She has spoken no meaningful words and gained little language comprehension. Her medical chart at 7 years of age described her as speechless, unable to follow verbal commands, but able to run and walk up the stairs one step at a time without support. She showed no involuntary movements. She was hyperactive and had trichotillomania. Neuropsychological assessment at 7 years 7 months by analytic test for development in infancy and childhood (Enjoji and Yanai 1961) demonstrated her developmental quotient was 14. Around 30 years of age, she was unable to walk for a long time but was able to take the stairs with support. At 32 years of age, she was no longer able to run. Currently, at 38 years of age, the patient has severe intellectual deficit with no speech or language comprehension. She still has trichotillomania. Her transport is mostly by wheelchair, although she is able to walk slowly for short periods. Her muscle tone is normal and there are no involuntary movements.

The onset of epilepsy was at around 18 months of age, characterized by epileptic spasms and brief tonic seizures. At 2 years of age, atypical absences appeared. Despite therapy with multiple antiepileptic drugs, the patient continued to have these seizures until 15 years of age, when her seizures were suppressed by valproic acid and clonazepam. When they recurred at 20 years of age, her seizures were characterized by consciousness impairment with head and body version to left followed by generalized tonic-clonic convulsions lasting up to 1 minute, suggesting complex partial seizures with secondary generalization. At around 23 years, brief "drop" seizures occurring in clusters started. She has continued to have these seizures since then, although she has been tried on multiple antiepileptic drugs including phenobarbital, valproic acid, clonazepam, phenytoin, clobazam, topiramate, lamotrigine, and levetiracetam.

Electroencephalograms (EEGs) at 2–12 years of age showed a slow background activity, generalized 1.5–2.5 Hz slow spike-wave bursts and some multifocal spikes, consistent with Lennox-Gastaut syndrome. EEGs after adolescence showed multifocal spike-waves with anterior head predominance and intermittent generalized slow spike-waves. The most recent EEG at 38 years of age demonstrated background slowing and no spikes during wakefulness but intermittent focal polyspikes and polyspike-waves over bilateral anterior and left posterior head regions during sleep.

Laboratory blood tests demonstrated low levels of serum creatinine (5–7 μmol/L by enzymatic method; normal range 40–71 μmol/L). Subsequent tests using enzymatic methods demonstrated serum creatine levels were below detection limit (normal range 23–92 μmol/L). Proton magnetic resonance spectroscopy (^{1}H-MRS) demonstrated absent creatine peak (Fig. 1a). Brain magnetic resonance imaging (MRI) demonstrated T2 high-intensity lesions in globus pallidi (Fig. 1b). Analysis of urinary creatine metabolites by weak-acid ion chromatography (Wada et al. 2012) demonstrated elevated GAA (548.53, 782.52 mmol/mol creatinine; normal 3–78 mmol/mol creatine (Almeida et al. 2004)) and creatine below detection limit. These findings suggested GAMT deficiency.

Genomic DNA analysis of the *GAMT* gene (Suppl. Table 1) showed a compound heterozygosity for two novel point mutations, an exonic splicing mutation c.391G>C located at the last nucleotide of exon 3 and a missense mutation c.578A>G, p.Gln193Arg in exon 6 (Fig. 2a). Analysis of cDNA revealed two aberrantly spliced transcription products at the allele of splicing mutation (Fig. 2b, c). One transcript had the complete exon 3 (64-bp) deletion by exon skipping and the other transcript was aberrantly spliced at exon 2 involving intron 2 insertion (44-bp) followed by exon 3 skipping, resulting in a 20-bp deletion. Both transcripts are expected to result in frame shift and premature termination of p.Val110Glyfs*30 and p.Ile111Profs*73, respectively. A novel A to G transition on exon 6 (c.578A>G) results in the replacement of arginine by glutamine at position 193 (p.Gln193Arg). This missense variation was not found in 100 control alleles. Glutamine193 is highly conserved in evolution (Fig. 2d), suggesting this mutation represents a pathogenic mutation.

This patient was recently started on supplementation of high-dose creatine and ornithine, and its effects are currently under evaluation.

Discussion

We reported on the first Japanese case of an adult patient with GAMT deficiency. Cases have been reported mostly from Europe and the Middle East (Mercimek-Mahmutoglu et al. 2006).

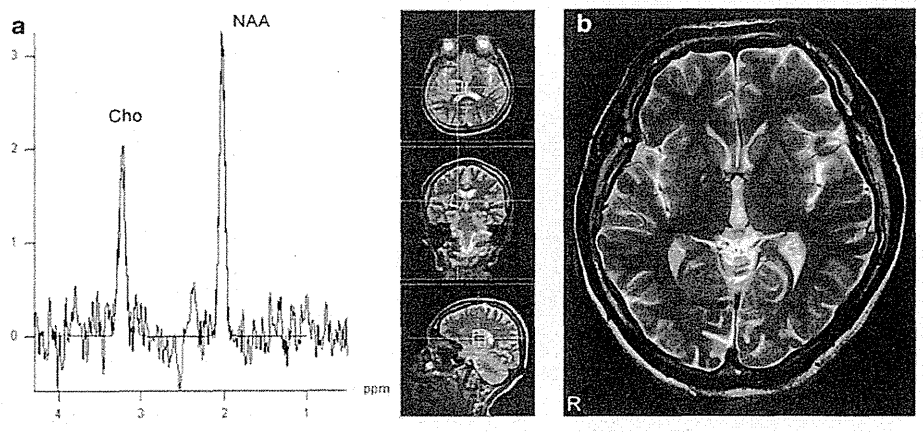

Fig. 1 MR spectroscopy and MRI from the patient with GAMT deficiency. (**a**) ^{1}H-MRS at the right basal ganglia demonstrates absence of creatine peak. (**b**) T2-weighted brain MRI shows high-intensity lesions in bilateral globus pallidi. *Cho* choline; *NAA* N-acetylaspartate

Compared with cases in the literature, our patient showed similar MRI findings and clinical course, with severe intellectual deficit, intractable epilepsy, behavioral problems, but she lacked involuntary movements. Although no definite progression of symptoms was seen during adolescence and young adulthood, motor regression slowly started around 30 years of age. This suggests GAMT deficiency can be slowly progressive if untreated.

Onset of symptoms in GAMT deficiency is from a few months to young childhood (Longo et al. 2011). Intellectual disability is seen in all cases and is severe (IQ < 35) in the majority, especially with profound speech disturbance (Mercimek-Mahmutoglu et al. 2006). Epilepsy is the second most frequent symptom, intractable in most cases, and partially responsive to antiepileptic drugs in two thirds (Leuzzi et al. 2013). Various types of seizures, such as generalized tonic-clonic seizures, absences, myoclonic seizures, myoclonic-astatic seizures, and partial seizures with secondary generalization, have been reported (Leuzzi et al. 2013). Involuntary movements, behavioral problems, and abnormal MRI signals in globus pallidi are seen in some cases. Adult cases that help to understand the natural history of GAMT deficiency are scarce (Schulze et al. 2003; Caldeira Araújo et al. 2005). Progression of neurological deficits, such as paraparesis, hypertonia, and rigidity, has been reported in some cases (Caldeira Araújo et al. 2005).

GAMT gene analysis revealed a compound heterozygosity of two novel mutations: c.391G>C splice donor site of exon 3 and c.578A>G, p.Gln193Arg in exon 6. The former led to two abnormal transcripts lacking exon 3, resulting in a premature stop codon. Reverse transcription polymerase chain reaction detected a higher expression level of the allele with the c.578A>G mutation, which implies the degradation of mRNA from the allele with the splice site mutation by nonsense-mediated mRNA decay (Fig. 2b). Gln193Arg substitution by the latter mutation is presumed to destabilize the tertiary structure of GAMT (Komoto et al. 2002) by increasing the bulkiness and changing the neutral to a positively charged residue, as Gln193 is situated in the middle of α-helix and protrudes into this enzyme.

Making a diagnosis of GAMT deficiency is challenging, because of its nonspecific symptoms and limited access or capacity of ^{1}H-MRS. GAA assay may not be readily available. While not as specific as GAA, measurement of creatinine is helpful, as creatinine can be low in GAMT deficiency (Verhoeven et al. 2000). It should be warned that creatinine may also be low in patients with decreased muscle volume. Another caveat is that creatinine measurement by Jaffé method is not as sensitive in detecting GAMT deficiency as the enzymatic method or high-performance liquid chromatography (Verhoeven et al. 2000). Our patient showed low levels of serum creatinine as determined by enzymatic method, which directed us to the diagnosis of GAMT deficiency. The assay of creatine and creatinine is also important to detect creatine transporter 1 deficiency, another type of cerebral creatine deficiency, as the urinary creatine/creatinine ratio is elevated in this disorder (Salomons et al. 2003; Verhoeven et al. 2005). GAA is a more sensitive marker than creatine and creatinine in GAMT deficiency and arginine: glycine amidinotransferase deficiency, the other type of cerebral creatine deficiency (Verhoeven et al. 2005). Therefore, blood and urine tests of creatinine, creatine and GAA should be a part of the workup for developmental delay and/or epilepsy with unknown cause, if creatine and GAA measurements are available.

Early diagnosis is crucial to achieve a favorable outcome in GAMT deficiency. Ideally, treatment should be initiated as early as possible before the creatine pool supplied from maternal body during gestation becomes

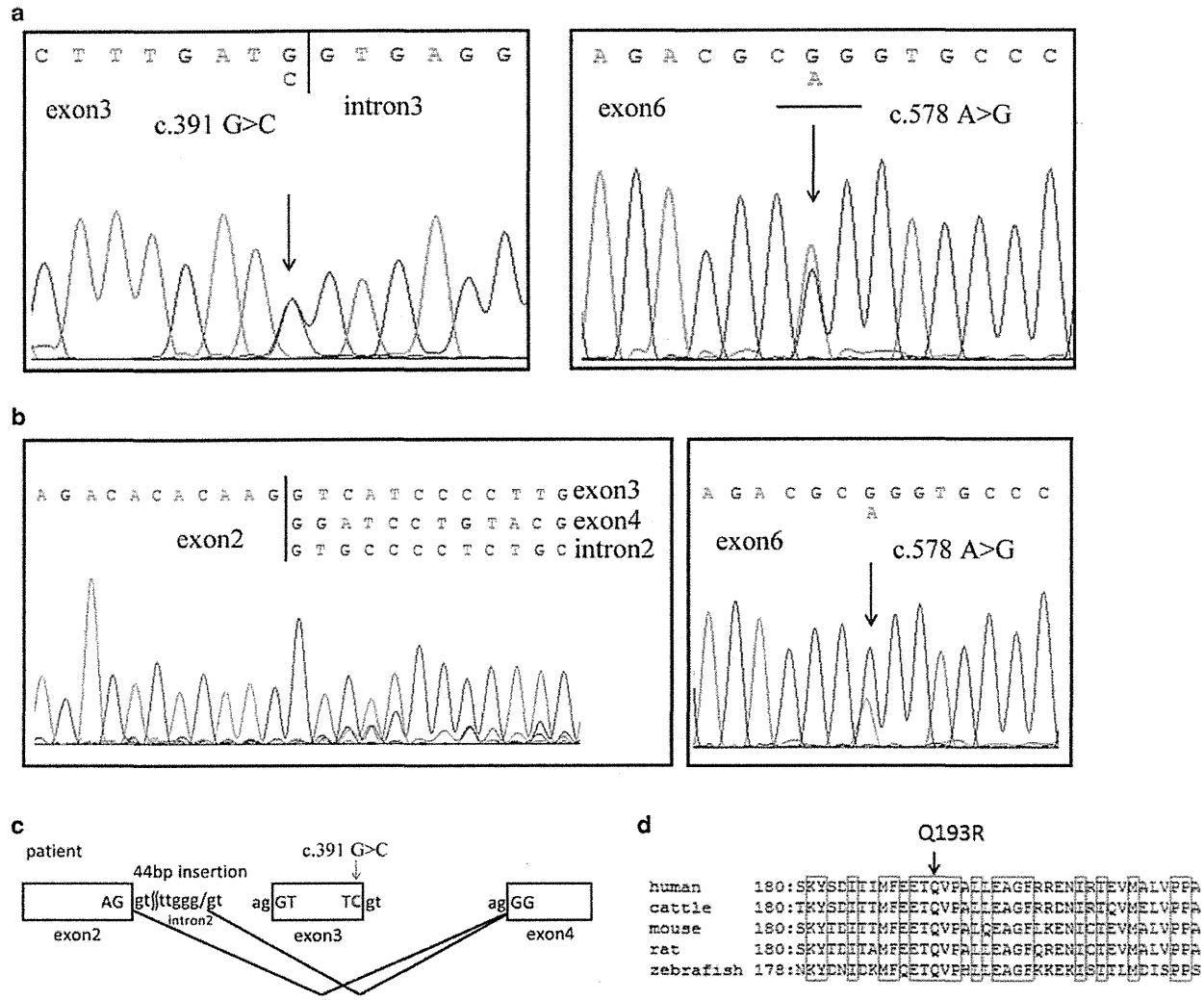

Fig. 2 Genetic analysis of the mutation in *GAMT*. (**a**) Chromatogram of genomic DNA analysis in a patient shows the heterozygote of c.391G>C (*left*) and c.578A>G (*right*). (**b**) cDNA analysis in the patient shows two aberrantly spliced transcription products (*left*) and c.578A>G (*right*). (**c**) c.391G>C mutation causes two aberrant splicing products: one with complete exon 3 (64-bp) skipping and the other involving intron 2 insertion (44-bp) followed by exon 3 skipping. (**d**) Aligned GAMT amino acid sequence of the patient with several other animals, revealing Gln193 is highly conserved among species

depleted and clinical symptoms appear. Presymptomatic treatment has been shown to be successful in achieving normal development (Schulze et al. 2006; El-Gharbawy et al. 2013). Even when diagnosed later, creatine supplementation with reduction of GAA by arginine restriction and ornithine supplementation can alleviate symptoms and prevent further progression of the disease (Schulze et al. 2001). GAMT deficiency is a good candidate for neonatal mass screening. Elevated GAA levels in neonatal blood (Schulze et al. 2006; El-Gharbawy et al. 2013) and amniotic fluid (Cheillan et al. 2006) have been reported, and validity of these tests needs to be elucidated.

In conclusion, we presented a 38-year-old patient, the first Japanese case of GAMT deficiency with two novel gene mutations. We should always include this disorder on the list of differential diagnoses when seeing patients with neurological symptoms such as intellectual disability, epilepsy, behavioral problems, and involuntary movements, since GAMT deficiency is a treatable disorder.

Take-Home Message

A 38-year-old patient, the first Japanese case of guanidinoacetate methyltransferase deficiency with two novel gene

mutations (splice site mutation and missense mutation) was reported.

Compliance with Ethics Guidelines

Contributions of Individual Authors

Tomoyuki Akiyama, Hitoshi Osaka, Hiroko Shimbo, and Tomoshi Nakajiri: Drafting/revising the manuscript for content, analysis, and interpretation of data

Katsuhiro Kobayashi, Makio Oka, Fumika Endoh, and Harumi Yoshinaga: Drafting/revising the manuscript for content

Guarantor for the Article

Tomoyuki Akiyama

Details of Funding

None

Details of Ethics Approval

This study was approved by the ethics board at Kanagawa Children's Medical Center.

Conflict of Interest

Tomoyuki Akiyama, Hitoshi Osaka, Hiroko Shimbo, Tomoshi Nakajiri, Katsuhiro Kobayashi, Makio Oka, Fumika Endoh, and Harumi Yoshinaga declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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Short Report

Genotype–phenotype correlation of contiguous gene deletions of *SLC6A8*, *BCAP31* and *ABCD1*

van de Kamp J.M., Errami A., Howidi M., Anselm I., Winter S., Phalin-Roque J., Osaka H., van Dooren S.J.M., Mancini G.M., Steinberg S.J., Salomons G.S. Genotype–phenotype correlation of contiguous gene deletions of *SLC6A8*, *BCAP31* and *ABCD1*. Clin Genet 2015: 87: 141–147. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2014

The *BCAP31* gene is located between *SLC6A8*, associated with X-linked creatine transporter deficiency, and *ABCD1*, associated with X-linked adrenoleukodystrophy. Recently, loss-of-function mutations in *BCAP31* were reported in association with severe developmental delay, deafness and dystonia. We characterized the break points in eight patients with deletions of *SLC6A8*, *BCAP31* and/or *ABCD1* and studied the genotype–phenotype correlations. The phenotype in patients with contiguous gene deletions involving *BCAP31* overlaps with the phenotype of isolated *BCAP31* deficiency. Only deletions involving both *BCAP31* and *ABCD1* were associated with hepatic cholestasis and death before 1 year, which might be explained by a synergistic effect. Remarkably, a patient with an isolated deletion at the 3′-end of *SLC6A8* had a similar severe phenotype as seen in *BCAP31* deficiency but without deafness. This might be caused by the disturbance of a regulatory element between *SLC6A8* and *BCAP31*.

Conflict of interest

The authors have no conflict of interest.

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Key words: clinical genetics – creatine transporter deficiency – deletion – intellectual disability – liver disease – metabolic disorders – neurology – X-linked adrenoleukodystrophy

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