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Primary Hyperoxaluria Type 1 and Brachydactyly Mental Retardation Syndrome Caused by a Novel Mutation in *AGXT* and a Terminal Deletion of Chromosome 2

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Primary hyperoxaluria type 1 (PH1) is an autosomal recessive disorder caused by mutations in the alanine:glyoxylate aminotransferase (*AGXT*) gene, located on chromosome 2q37. Mutant *AGXT* leads to excess production and excretion of oxalate, resulting in accumulation of calcium oxalate in the kidney, and progressive loss of renal function. Brachydactyly mental retardation syndrome (BDMR) is an autosomal dominant disorder, caused by haploinsufficiency of histone deacetylase 4 (*HDAC4*), also on chromosome 2q37. It is characterized by skeletal abnormalities and developmental delay. Here, we report on a girl who had phenotypes of both PH1 and BDMR. PCR-sequencing of the coding regions of *AGXT* showed a novel missense mutation, c.32C>G (p.Pro11Arg) inherited from her mother. Functional analyses demonstrated that it reduced the enzymatic activity to 31% of the wild-type and redirected some percentage of the enzyme away from the peroxisome. Microsatellite and array-CGH analyses indicated that the proband had a paternal de novo telomeric deletion of chromosome 2q, which included *HDAC4*. To our knowledge, this is the first report of PH1 and BDMR, with a novel *AGXT* mutation and a de novo telomeric deletion of chromosome 2q. © 2012 Wiley Periodicals, Inc.

Key words: primary hyperoxaluria type 1; *AGXT*; brachydactyly mental retardation syndrome; *HDAC4*; novel mutation

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INTRODUCTION

Primary hyperoxaluria type 1 (PH1; OMIM 259900) is an autosomal recessive disorder characterized by increasing synthesis of oxalate, which accumulates in the form of insoluble calcium oxalate in the kidney and urinary tract and leads to marked hyperoxaluria,

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and progressive loss of renal function. The PH1 phenotype is caused by mutations in the alanine:glyoxylate aminotransferase (*AGXT*) gene, which maps to 2q37.3 [Nishiyama et al., 1990]. The gene product, enzyme AGT (EC 2.6.1.44), is liver-specific, requires pyridoxal phosphate as a cofactor and converts glyoxylate into glycine in the peroxisome [Danpure and Jennings, 1986]. Mutations in the *AGXT* decrease the enzyme function and lead to the conversion of glyoxylate into oxalate [Danpure and Rumsby, 2004], and eventually cause renal failure. The disease phenotype is heterogeneous in the age-of-onset, level of urinary oxalate, and rate of disease progression.

More than 150 mutations throughout the *AGXT* gene have been reported in PH1 (http://www.hgmd.cf.ac.uk, accessed March, 2012). The mutations are heterogeneous and the majority of patients are compound heterozygous for rare missense mutations. Functional studies of *AGXT* mutations have demonstrated that several result in a reduction of enzymatic activity, inhibition of protein dimerization and protein degradation. Notably, the most common mutation (p.Gly170Arg) causes an enzyme trafficking defect that results in most of the enzyme to be mis-localized to the mitochondria, where it is metabolically inactive [Coulter-Mackie and Lian, 2006; Djordjevic et al., 2010]. Some of the variants affect the enzyme function by reducing the protein dimerization and stability, reducing the enzyme activity, and rerouting the protein to the mitochondria [Danpure, 2006].

Brachydactyly mental retardation syndrome (BDMR; MIM 600430) has a wide range of clinical features including brachydactyly type E, developmental delay, behavioral problems, and neurological anomalies [Wilson et al., 1995]. The disorder was associated with deletions of the 2q37 region [Chaabouni et al., 2006], and was recently found to be caused by haploinsufficiency of histone deacetylase 4 (*HDAC4*) [Williams et al., 2010]. The HDAC4 protein belongs to the class IIa of histone deacetylases. It regulates genes involved in bone, muscle, neurologic, and cardiac development [Glenisson et al., 2007; Cohen et al., 2009; Sun et al., 2009]. In addition to the chromosomal deletion, splicing and frameshift mutations in the *HDAC4* gene were found in patients with BDMR [Williams et al., 2010].

Here, we report on a patient with both PH1 with BDMR. Molecular analysis showed that the pathology was caused by a novel missense mutation in the *AGXT* gene in one allele and a deletion of the telomeric region of chromosome 2, including the *HDAC4* gene, in the other allele.

MATERIALS AND METHODS

Patient

The proband was referred to King Chulalongkorn Memorial Hospital at 5 years of age after her older sister died at 6 years of age from end-stage renal failure. Autopsy showed a large amount of oxalate crystals in her kidneys. The proband was born at term with a birth weight of 3,040 g, to nonconsanguineous parents. She had epilepsy starting at the age of 2.5 years. She also had delayed development, attention deficit, and hyperactivity. At age 5 years, she could talk in single words, but not in sentences. Physical features included overweight, strabismus, short third, fourth, and fifth metacarpal bones, and short, proximally placed and overriding fourth toes, bilaterally (Fig. 1). Serum levels of BUN, creatinine, electrolytes, fasting blood glucose, calcium, phosphorus, lipids, and liver enzymes were normal. Urinalysis showed oxalate crystals and renal ultrasound showed bilateral medullary nephrocalcinosis. Chromosomal analysis with 400 band resolution was normal 46,XX. Using Stanford Binet Form, at chronological ages of 6 and 13 years, her IQs were 49 and 35, respectively. The diagnosis of PH1 was established by the presence of large amounts of oxalate and glycolate from urine organic acid analysis by gas chromatography–mass spectrometry. Within 3 months of treatment with high fluid intake, vitamin B6, and oral citrate, the urinary oxalate crystals and nephrocalcinosis disappeared. According to their parents, the deceased sister had abnormal digits and developmental delay with the speaking of only a few words at 6 years of age, similar to the proband.

AGXT Mutation Analysis

Written informed consent was obtained from each person included in the study. Genomic DNA was obtained from whole blood using a standard extraction method. All of the 11 exons and exon–intron boundaries of *AGXT* were amplified with primer pairs (see Supplementary Table I) and under PCR conditions as previously described [Monico et al., 2007]. The PCR products were directly sequenced and compared to the *AGXT* sequence in the database, RefSeq NG_008005.1.

For the p.Pro11Arg mutation analysis, PCR-RFLP was performed in the proband, both of her parents, and 54 unaffected Thais. The PCR products were amplified with primers for exon 1 of *AGXT* and were subsequently treated with *Fau*I (New England Biolabs, Beverly, MA).

Haplotype Analysis

Initially, three microsatellite markers (D2S367, D2S125, and D2S140) on chromosome 2p22.3 and 2q37.3 were selected from the Taiwan Polymorphic Marker Database (TPMD http://tpmd2.nhri.org.tw/tpmd/php-bin/index_en.php). Primer pairs and PCR conditions were shown in Supplementary Table I (see supporting information online). The PCR products were sent for size determination at Macrogen Inc. (Seoul, Korea). Analyses were performed by GeneMapper version 4.0 (Applied Biosystems, Foster City, CA).

To further investigate the haplotype, 12 microsatellite markers (D2S160, D2S347, D2S112, D2S2330, D2S117, D2S325, D2S2382, D2S126, D2S396, D2S206, D2S338, and D2S125) were selected to cover chromosome 2q13–2q37.3 using ABI Prism Linkage Mapping Set version 2.5. The fragment lengths of all loci were determined by Genescan, GeneMapper version 4.0 (Applied Biosystems, Foster City, CA).

Array Comparative Genomic Hybridization (CGH) Assay

Genomic DNA of the proband, her father, and a normal Thai control were sent to Macrogen Inc. for array-CGH analysis on chromosome 2 using NimbleGen 385K chip (Cat. No. B3733001-00-01), according to the company's instruction.

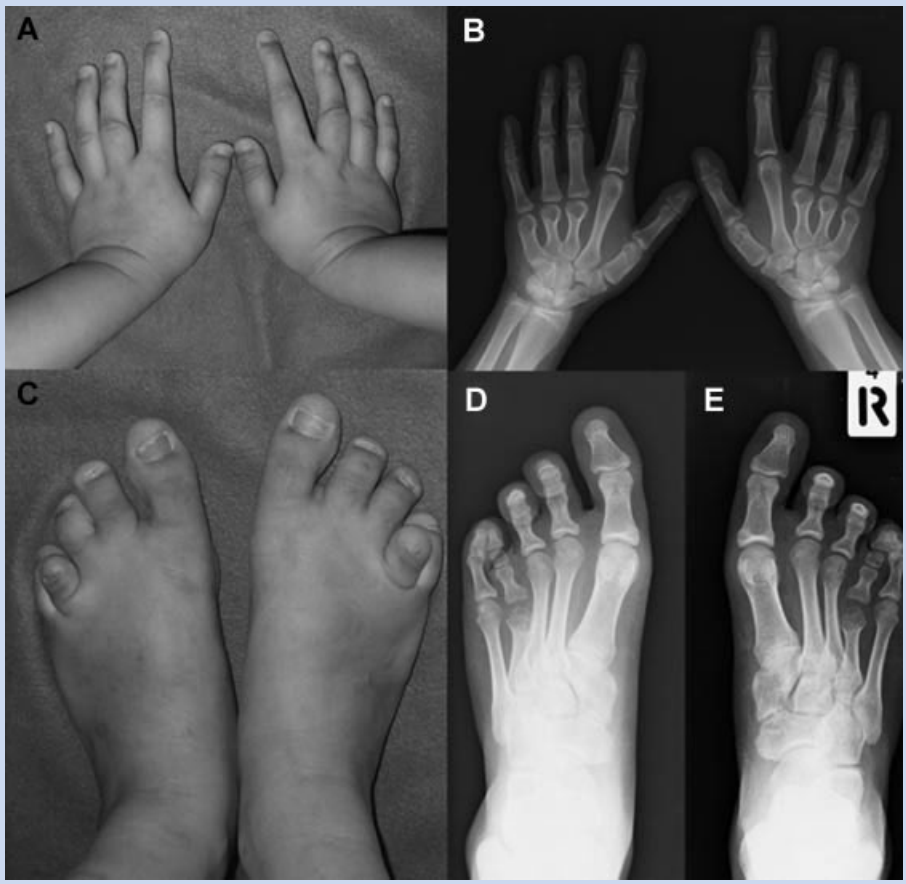

FIG. 1. Clinical features. Photographs of the hands (A) and feet (C). Radiographs of both hands (B), and left and right feet (D and E, respectively). Note the short third, fourth, and fifth metacarpal bones, and shortened and proximally placed fourth toes, bilaterally.

Generation of the *AGXT* Plasmids

The entire coding region of the *AGXT* gene was cloned from HepG2 (human liver) cells. Total RNA was extracted from HepG2 using QIAamp RNA Blood Mini Kit (Qiagen, Valencia, CA). Reverse transcription was performed using ImProm-II™ Reverse Transcriptase (Promega, Madison, WI). The entire coding region of *AGXT* was PCR amplified with a primer pair: AGXT-*Bam*HI-F and AGXT-*Eco*RI-R (see Supplementary Table I in supporting information online). PCR products were directly sequenced. The cloned gene was subsequently inserted into the pGEM plasmid (Promega) by TA cloning. The p.Pro11Arg mutation was generated using QuikChange Site-Directed Mutagenesis Kit (Stratagene, Santa Clara, CA). The wild-type and mutant clones were transferred into the pcDNA3.1/V5-HisB expression vector (Invitrogen, Carlsbad, CA).

Cell Culture and Transfection

Transformed African green monkey kidney fibroblasts (COS-7 Line from ATCC) were cultured in D-MEM/F-12 (Invitrogen) supplemented with 5% fetal calf serum. For transient transfection, cells were grown to ~80% confluence and transfected with 5 μg of plasmid DNA/1 × 10^6 cells using Lipofectamine (Invitrogen). Cells were grown for 48 hr prior to all subsequent assays.

Protein Isolation and Western Blot Analysis

Total protein lysates, electrophoresis, and western blotting were processed as previously described [Bakeberg et al., 2011]. Mouse anti-V5 monoclonal antibody (Invitrogen, Cat. No. 37-7500) and goat anti-mouse IgG2a (Abcam, Cambridge, MA, Cat. No. ab97241) were used as primary and secondary antibodies, respectively.

AGT Enzymatic Activity Assay

Cell collection and enzymatic activity assay were carried out as described [Rumsby et al., 1997]. The light absorbance at 340 nm was detected before and 5 min after addition of LDH with spectrophotometer (CE9500, Cecil Super Aquarius, Bath, UK).

Immunofluorescence Microscopy

Cells were prepared according to Masyuk et al. [2003]. The V5 signal was detected with mouse anti-V5 monoclonal antibody (Invitrogen, Cat. No. 37-7500) and AlexaFlour 594 goat anti-mouse

IgG2a (Invitrogen, Cat. No. A21135). Peroxisomes were detected with an antibody to catalase, a peroxisome marker (Abcam, Cat. No. ab1877) and AlexaFlour 488 donkey anti-rabbit IgG (Invitrogen, Cat. No. A21206).

RESULTS

Mutation Analysis

Molecular analysis by PCR-sequencing showed a novel mutation, c.32C>G, in exon 1 of the proband (Supplementary Fig. 1 in supporting information online). The nucleotide change was predicted to cause a missense mutation, p.Pro11Arg. The PCR-RFLP confirmed that the mother was heterozygous for c.32C>G, and the father was wild-type (Fig. 2A). The p.Pro11Arg was not found in the Human Gene Mutation Database nor in 108 alleles of unaffected Thai controls.

We further investigated the phenomenon by microsatellite analysis on the proband and her parents. The result demonstrated that the proband harbored only maternal alleles for two markers, D2S125 and D2S140, at the terminal region of chromosome 2. The immediate centromeric marker, D2S338, was non-informative,

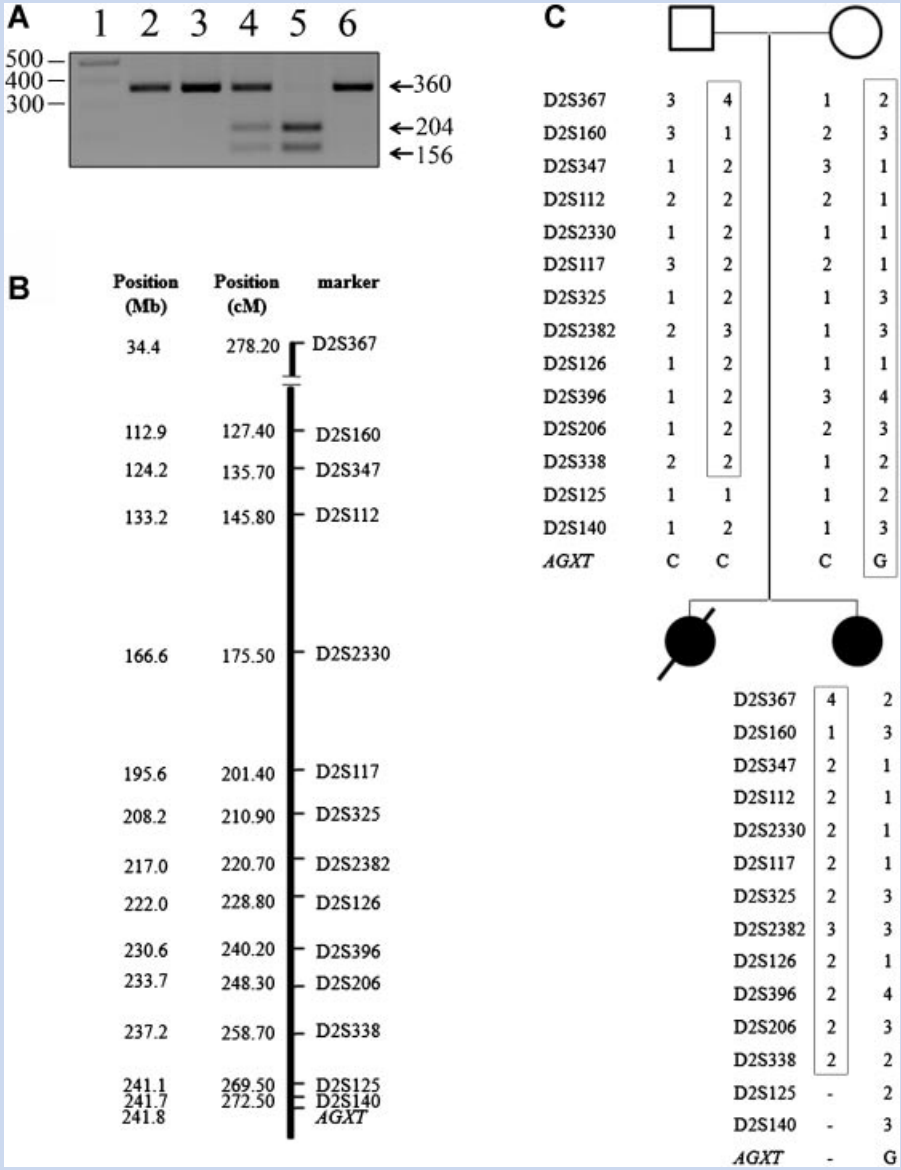

FIG. 2. PCR-RFLP and microsatellite marker analysis. A: PCR-RFLP analysis of the nucleotide change. Lane 1, 100-bp marker; lanes 2 and 6, unaffected controls; lane 3, father; lane 4, mother; lane 5, proband. In lane 5, *Fau*I digested the mutant allele of the proband into 204 and 156-bp products (arrows). The wild-type alleles do not harbor the recognition site, leaving the 360-bp PCR product intact. B: Map of microsatellite markers used in this study. The left panel indicates the distance between markers (cM) and position of each marker (Mb). C: Pedigree and haplotype of the proband, her parents and her deceased sister.

while other more centromeric markers showed normal biparental pattern of inheritance (Fig. 2B,C).

To analyze the possibility that the proband had a chromosomal deletion, array-CGH analysis was performed on chromosome 2 with NimbleGen 385K chip. *HDAC4* is located at chr2:239,985,140-239,989,318 and *AGXT* is located at chr2:240,865,911-242,604,169. The result showed that the proband had a chromosomal deletion from position 238,094,544 to telomere while the father's chromosomes were intact (Supplementary Fig. 2 in supporting information online), inferring that the proband had both the *HDAC4* and *AGXT* genes deleted.

Protein Expression Analysis

The effect of p.Pro11Arg on AGT protein expression was analyzed by western blotting. GAPDH was used as a loading control. The results showed that while the empty vector did not express AGT, as demonstrated by the antibody to the V5 epitope tag, the mutant still expressed the AGT protein at 46 kDa at similar intensity as the wild-type (Fig. 3A).

AGT Enzymatic Activity

To analyze the effect of the mutation on the enzymatic activity, the semiautomated alanine:glyoxylate aminotransferase assay was performed. The enzyme activity was calculated from the amount of pyruvate generated from the reaction. The HepG2 cells, which expressed endogenous AGT, showed a low level of enzyme activity, while the untransfected COS-7 cells, which were used as a negative control, showed no activity. This finding was similar to COS-7 cells transfected with the empty vector. The COS-7 cells transfected with the p.Pro11Arg mutant generated AGT with the activity of 1.01 ± 0.25 μmol/h/mg, which was significantly lower than those transfected with the wild-type *AGXT* (3.21 ± 0.26 μmol/h/mg), *P* value < 0.01 (Fig. 3B).

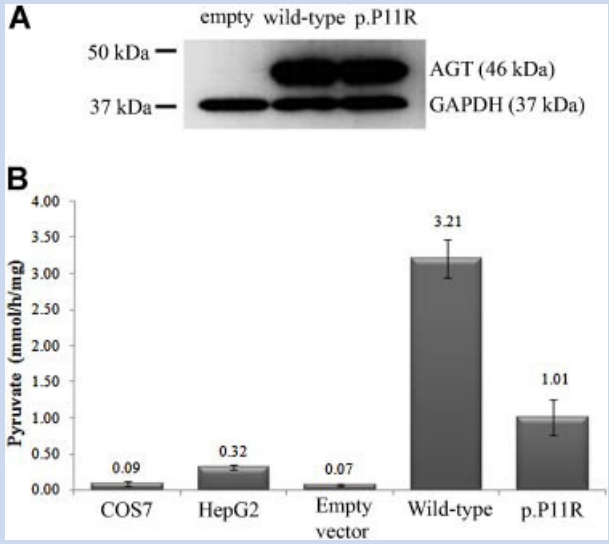

FIG. 3. Effects of the p.Pro11Arg mutation on the enzyme function. A: Western blotting showed that the mutation did not affect the protein expression as the mutant construct expressed the protein in COS-7 cells at the expected molecular weight of 46 kDa. B: The mutation greatly reduced the enzyme activity as cells transfected with the mutant construct had significantly lower activity compared to the wild-type. COS7 = untransfected COS-7 cells; HepG2 = untransfected HepG2 cells; empty vector, wild-type, p.Pro11Arg = COS-7 cells transfected with the empty vector, wild-type *AGXT*, and p.Pro11Arg mutant, respectively.

AGT Subcellular Localization

The wild-type and mutant protein subcellular localization was analyzed by immunofluorescence with anti-V5 monoclonal antibody (Supplementary Fig. 3 in supporting information online). While almost all of the signals from the wild-type and catalase (a peroxisomal marker) overlapped, the signals from the p.Pro11Arg mutant did not.

DISCUSSION

Here, we describe the first patient with PH1 and BDMR. The diagnosis of PH1 was confirmed by the presence of oxalate and glycolate in urine organic acid analysis. This patient also had brachydactyly type E, developmental delay, and behavioral problems, which was consistent with described symptoms of BDMR [Williams et al., 2010]. The sequencing results showed only the mutant c.32C>G (p.Pro11Arg) allele in the proband. Her mother was heterozygous for the mutation while the father was wild-type.

Phenotypically, besides PH1, the proband also had BDMR. This led us to hypothesize that our patient inherited the p.Pro11Arg from her mother, while the paternal allele was deleted. It was substantiated by the findings from microsatellite analysis, which showed that, for the two most telomeric markers, D2S125 and D2S140, no paternal alleles were present in the proband. This suggested a deletion at least from the D2S125 marker (241.1 Mb) to the q terminus of chromosome 2. The other possibility is that the proband has a segmental maternal uniparental isodisomy. Luedi et al. [2007] reported that the 2q37.3 region harbored some imprinted genes, both for the paternal and maternal alleles. Therefore, array-CGH analysis was performed and confirmed the terminal deletion in one copy of chromosome 2 in the proband.

There has been no previous report of cases with BDMR and PH1. Some large deletions in the *AGXT* gene have been reported in PH1 patients, but none of them showed BDMR symptoms [Nogueira et al., 2000; Coulter-Mackie et al., 2001; Monico et al., 2007]. We suggest that those previously described deletions were within the *AGXT* gene and therefore left the *HDAC4* gene intact. There has been a report of a patient with PH1 caused by a frameshift mutation and maternal isodisomy of the telomeric end of chromosome 2 [Chevalier-Porst et al., 2005]. The uniparental disomy was verified by the presence of two copies of the gene, analyzed by quantitative PCR. Again, no symptoms of BDMR were described, suggesting that there was no defect in the *HDAC4* gene.

A novel mutation, p.Pro11Arg, was identified in this study. The functional analysis of this mutation showed that it reduced the

enzymatic activity to about 31% of the wild-type. The mutation also directed some percentage of the enzyme away from the peroxisome where it converted glyoxylate into glycine. Taken together, we demonstrate that the p.Pro11Arg change is a pathogenic mutation. This mutation, combined with the telomeric deletion of chromosome 2, caused the PH1 phenotype in the proband and presumably her deceased sister. Recurrent paternal de novo mutations in siblings have been previously reported in achondroplasia [Sobetzko t al., 2000], although it was a point mutation in that case. Paternal origin of de novo microdeletions has been reported in some diseases, such as Sotos syndrome and spinal muscular atrophy [Wirth et al., 1997; Miyake et al., 2003]. It has been proposed that in males, the rate of recombination is increased at telomeres compared with centromeres [Wirth et al., 1997; Broman et al., 1998; Miyake et al., 2003]. As the proband's sister was reported to have similar phenotypes, it remained possible that she harbored the same deletion suggesting recurrent paternal de novo microdeletions. Unfortunately, her DNA sample was unavailable for studies. An alternative explanation is that the father harbors a mosaic deletion in his germline. We did not analyze sperms to assess this hypothesis.

Previously, three different amino acids have been described at residue position 11 of AGT. Proline (the major allele) and leucine (the minor allele), are considered wild-type, while histidine is the only previously reported mutation at this position [Williams et al., 2009]. It is well established that the p.Pro11Leu change found in the minor allele redirects about 5% of the protein toward the mitochondrial matrix, along with other effects such as reduction of enzyme stability and activity. It has been proposed that AGT targeting is an evolutionary adaptation to dietary factors, both in animals (*Carnivora*) and in humans [Birdsey et al., 2004; Caldwell et al., 2004]. The protein tends to target to the mitochondria in carnivores, the peroxisome in herbivores, and both the mitochondria and peroxisome in omnivores. The p.Pro11His variant was found to cause a 45% reduction in AGT enzymatic activity [Williams et al., 2009]. It would be especially interesting to further investigate the subcellular targets of both the p.Pro11Arg and p.Pro11His mutants.

In summary, we report the first patient with PH1 and BDMR. The proband had a paternal de novo telomeric deletion of chromosome 2q including the *HDAC4* and *AGXT* genes, and a novel missense mutation, p.Pro11Arg, inherited from the mother. The point mutation occurred at the amino acid residue important in the evolution of *Carnivora*. It reduced the enzymatic activity to about 31% of the wild-type and directed some percentage of the enzyme away from the peroxisome, proving its causation.

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