Published in final edited form as:
Mol Genet Metab. 2008 August ; 94(4): 498–502. doi:10.1016/j.ymgme.2008.04.011.

Complex Management of a Patient with a Contiguous Xp11.4 Gene Deletion Involving Ornithine Transcarbamylase: A Role for Detailed Molecular Analysis in Complex Presentations of Classical Diseases

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Abstract

A male infant was diagnosed prenatally with a partial ornithine transcarbamylase (*OTC*) gene deletion and managed from birth. However, he displayed neurological abnormalities and developed pleural effusions, ascites and anasarca not solely explained by OTC deficiency (OTCD). Further evaluation of the gene locus using exon-specific PCR and high density SNP array copy number analysis revealed a 3.9Mb deletion from Xp11.4 to Xp21.1 including five additional gene deletions, three causing the known genetic diseases: Retinitis pigmentosa (RP3), X-linked chronic granulomatous disease (CGD) and McLeod syndrome. The case illustrates (1) the complexities of managing a patient withneonatal onset OTCD, CGD, RP3 and McLeod syndrome, (2) the need for detailed evaluation in seemingly "isolated" gene deletions and (3) the clinical utility of high density copy number analysis for rapidly characterizing chromosomal lesions.

Keywords

ornithine transcarbamylase; OTC; Xp11.4 to Xp21.1 deletion; granulomatous disease, chronic; CGD; CGH; copy number analysis; retinitis pigmentosa; RP3; McLeod syndrome

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Introduction

Ornithine transcarbamylase deficiency (OTCD; OMIM 311250), an X-linked disorder, is the most common inherited defect of ureagenesis, affecting 1:14,000 births [1]. Most mutations are 'private' single nucleotide substitutions or small insertions or deletions [2–4]. OTCD perturbs urea cycle function and results in variable degrees of hyperammonemia depending on the extent of enzyme deficiency. Complete OTCD in a male infant is usually lethal or results in severe brain damage in survivors due to delay in diagnosis and treatment. When an OTCD diagnosis is known prior to the birth of the child, prospective treatment has been successful [5]. Recent studies have suggested a role for liver transplantation in the management of severe OTCD [6–10] although long-term data are not yet available.

When engaging in the treatment of severe neonatal OTCD understanding the extent of the genomic lesion is critical, as demonstrated by the cases of two brothers with neonatal OTCD resulting from an Xp11.4-p21.1 contiguous gene deletion also including chronic granulomatous disease (CGD; OMIM 306400), Retinitis pigmentosa (RP3; OMIM 312610), and McLeod syndrome (OMIM 314850).

Methods

Case reports

Patient 1 was a term male born via normal vaginal delivery. At birth he demonstrated lethargy and a weak cry. Subsequently, he developed poor feeding, emesis, and progressive tachypnea and cyanosis. He was intubated. and shortly afterward went into coma. Blood ammonia was 1154 μmol/ml (normal 9–33 μmol/ml). Plasma amino acid and urine orotic acid analysis suggested OTCD. The patient died on the 5th day of life. Molecular analysis of the OTC gene revealed a partial gene deletion involving exons 1–8 (of 10 total). The mother was a vegetarian by choice and reported intolerance of dairy. She had a history of occasional headaches. She also reported frequent respiratory tract infections and an "eye problem" not treatable with corrective lenses. Similar symptoms were not present in any other family members. The mother deferred carrier status testing after the death of patient 1. Four years later she presented in the first weeks of pregnancy. Chorionic villus sampling (CVS) confirmed a male fetus, however, *OTC* gene evaluation was delayed by maternal cell contamination. Final prenatal diagnosis confirmed the presence of the *OTC* deletion in the fetus and the mother as a carrier. Her ammonia levels remained normal during pregnancy, but rose to 230 μmol/L postpartum.

Patient 2 was delivered at 38 weeks gestation and was noted to be hypotonic. Within 45 minutes of life, he was started on intravenous fluids (dextrose and intralipids) and ammonia scavengers (sodium phenylacetate, sodium benzoate and arginine hydrochloride). His ammonia was 125 μmol/L at 2 hours of life (normal <100). Plasma glutamine was 1087 μmol /L (normal 422–849) with normal ornithine and arginine levels; citrulline was <2.0 μmol /L (normal 0–35) and an initial urine orotic acid level was normal. Albumin was 2.1 g/dL (normal 2.6–3.6) at 2:35 hours of life. Within 12 hours of life, tremors and bilateral ankle cloni were noted. Ammonia levels were easily managed with only mild increases as the dietary protein intake reached 1.7 g/kg/d. Despite relatively well-controlled ammonia levels, the neurologic status was significant for agitation and minimal responsiveness. Several electroencephalograms and a brain MRI were normal. At three weeks of age, he developed pleural effusions and transudative abdominal ascites that progressed to frank anasarca, bowel edema, hepatomegaly and sloughing of skin. Ultrasound of the liver was normal. There was minimal improvement of the anasarca with diuretics and no evidence of unusual enteric or renal protein losses. Initially, the edema was thought to be due to hypoalbuminemia. However, increased protein intake and intravenous albumin normalized the serum albumin level but the anasarca only improved moderately and worsened again with subsequent infections. Postnatal analysis of the *OTC* gene confirmed the

deletion of the first 8 of the 10 *OTC* exons. Given the presence of neurologic findings despite rather well-controlled ammonia levels and the persistent edema not easily explained by OTCD, we hypothesized that the deletion encompassed more than just *OTC* and initiated further analysis of the *OTC* locus in this patient.

Study subjects were enrolled in an IRB-approved protocol of written informed consent at the Children's Hospital of Philadelphia.

Genomic Analysis

Whole genome SNP genotyping was performed using the Illumina (San Diego, CA) Infinium HumanHap550 Beadchip Array according to the manufacturer's protocol. Targeted copy number analysis was performed for Xp by analyzing the B-allele frequency and log R ratio tracts of the accompanying Illumina BeadStudio software (ver. 2.3) as described in [11]. For the X chromosome in a male, deletions result in log R ratios below -1 and B allele frequencies < 0.5 for all SNP's involved.

Amplification of exons of all genes residing in the interval was done by PCR. PCR primers were designed using ExonPrimer (http://ihg.gsf.de/ihg/ExonPrimer.html) and Primer3 [12] accessed via an interface with the UCSC Genome Browser [13] to amplify *OTC* exons 1, 9, and 10, *RPGR* exon 1, *SYTL5* exon 16, *CYBB* exon 13, *XK* exon 2, *PRRG1* exon 3, *TMEM47* exon 2, and *DMD* exon 3. Primer sequences are available upon request. Amplifications were performed with Amplitaq Gold™ (Applied Biosystems, Branchburg, NJ) and products visualized via electrophoresis on a 2% agarose gel.

Results and Discussion

Molecular genetic results

The Illumina Infinium HumanHap550 Beadchip array confirmed and further delineated the *OTC*/Xp deletion of Patient 2 (Figure 1A). SNPs were identified that defined the maximal and minimal size of the deletion (Supplementary Table 1). The telomeric breakpoint was 975kb centromeric of the Duchenne muscular dystrophy gene (*DMD*) and the centromeric breakpoint was within intron 8 of *OTC* (Figure 1) establishing the deletion to be between 3.925 and 3.940Mb in size, spanning from Xp11.4 to Xp21.1. PCR analysis of exons of seven genes between Xp11.4 and p21.1 (cen-*OTC, RPGR, SYTL5, CYBB, PRRG1* and *TMEM47, DMD*-tel) confirmed that exons 9 and 10 of *OTC* and exon 3 of the *DMD* gene were present and that *OTC* exons 1–8, and exons of each of the five other known genes in the interval were absent (Supplementary Figure 1). The deletion thus included *RPGR*, the retinitis pigmentosa GTPase regulator, mutations of which cause X-linked RP3 with recurrent respiratory infections; *SYTL5*, synaptotagmin-like 5, which binds several Rab proteins and may serve as a Rab effector protein [14] involved in vesicular traffic; *CYBB*, cytochrome b-245, Beta polypeptide, mutations of which cause X-linked CGD, due to deficiency of NADPH oxidase resulting in inability to generate superoxide radicals for pathogen killing; *XK*, the Kell red cell antigen, defects of which cause McLeod syndrome with anemia, acanthocytosis, transfusion complications, late-onset neuromuscular symptoms and chorea; *PRRG1*, transmembrane gamma-carboxyglutamic acid protein 1, which is highly expressed in the spinal cord, and *TMEM47*, transmembrane protein 47, highly expressed in the brain (Figure 1 and Table 1A).

Implications of gene deletions for clinical management

OTCD might have been cured by liver transplant [6–9] but anasarca, respiratory compromise and fungal sepsis made the patient unsuitable for immediate consideration. Patient 2 developed *Candida glabrata* sepsis at 11 weeks of age that precipitated disseminated intravascular coagulation (DIC), hypotension, renal insufficiency and oliguria. Clinical testing demonstrated

lack of an oxidative burst confirming chronic granulomatous disease. Infectious disease complications were assumed to be worsened by the patients CGD. Allogenic bone marrow transplant following myeloablative conditioning was considered, but deferred due to poor clinical status. Furthermore, he was felt to be at high risk of rejection due to the deletion of the *XK* gene, a red cell antigen, which also results in McLeod syndrome, . To treat his CGD acutely, granulocyte infusions were conducted while Amphotericin B was administered to treat the fungemia. The patient showed signs of a cytotoxic response to this regimen developing marked hyperammonemia despite IV ammonia scavengers and hemodialysis. Interferon gamma administration was also considered but not used due to concerns that it could worsen the cytotoxic response. He subsequently died at 12 weeks of age.

Comparison with other Xp11.4-Xp21.2 deletion cases

The contiguous gene deletion present in these two brothers manifested with a complex but definable clinical picture and their course poignantly illustrates the challenges in managing a neonate with a contiguous gene deletion involving Xp11.4-Xp21.1. These patients manifested OTCD, CGD , RP3, McLeod syndrome and had potentially disease causing deletions of at least 3 additional genes.

Several patients with deletions of Xp11.4-Xp21.2 have been reported. These cases are well-known and were instrumental in identifying the *NR0B1* (*DAX1*), *GK*, *DMD*, *CYBB*, and *RPGR* genes (Figure 1, Table 1; and references therein). In addition, a number of cases resulted in neonatal lethal OTCD caused by deletions of *OTC*, but minimal further analysis was performed [2–4,34,35] . Upon review of the literature, the two cases reported here appear to be the only males reported with a deletion of Xp11.4-Xp21.2 centromeric of *DMD* and including *OTC*. Interestingly, deletions that arose telomeric to *OTC* through *DMD* resulted in only mild, if any, mental retardation (i.e. loss of *CYBB*, *RP3*, and *XK*, Table 1, Section B). Patient 2 showed neurological abnormalities from birth despite of only mildly increased ammonia levels. Although speculative, it is possible that the altered neurological status in our patients may have been due to the involvement of the *TMEM47* or *PRRG1* gene as they show high levels of expression in the brain and spinal cord, respectively or an early sign of McLeod syndrome.

With the improving ability to manage OTCD medically and with earlier liver transplantation, it will be important to characterize individuals with phenotypes caused by contiguous gene deletions that include *OTC* to accurately assess their risk regarding liver transplantation and to facilitate management. As outlined above, the combination of OTC, CGD and McLeod results in a very complicated clinical scenario, with limited therapeutic choices for effective management.

These cases underscore the necessity of detailed molecular analysis to clarify the extent of a genomic lesion for clinical management. The advent of widely available high-density copy number array analysis has immensely facilitated our ability to quickly delineate deletion breakpoints, an analysis previously very time consuming and only possible in research laboratories but not applicable in clinical care. As demonstrated in Patient 2, clinicians can now rapidly and easily determine whether disease-causing genes are deleted in a given patient and appropriately adjust management. Furthermore, it is likely that as this technology becomes engrained in clinical practice, we will learn that microdeletions of individual and contiguous genes are more common than previously appreciated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Additional Abbreviations

BAC, bacterial artificial chromosome; SNP, single nucleotide polymorphism.

Acknowledgments

We thank the family who participated in this study. We thank Nancy Spinner, Brian Thiel and the staff of the Center for Applied Genomics for technical assistance. This work was supported by several National Institutes of Health awards: an NHLBI HL074731, a GCRC 2M01RR000240, an NIGMS T-32 Training Award, and an NIH Rare Diseases Clinical Research Center grant (5U54RR019453). Institutional funds were also provided by the Children's Hospital of Philadelphia.

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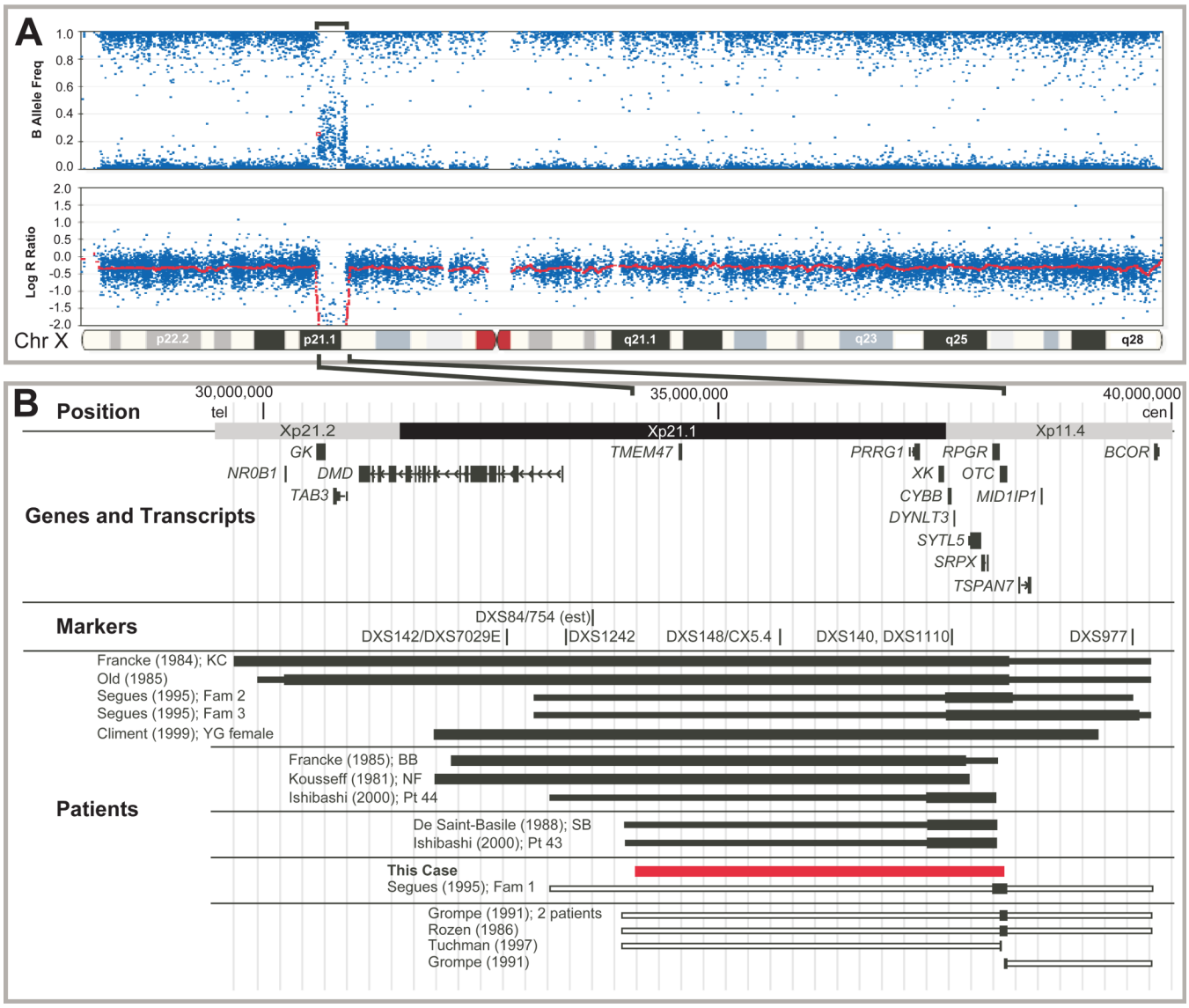

Figure 1. Comparison of Xp11.4-21.2 deletions

A. B-Allele frequencies (top) and Log R ratios (bottom) of SNP copy number analysis for Patient 2. The deleted region is indicated by brackets above and expanded below to show the genomic region. B. Genomic position is indicated at the top with chromosome bands alternately shaded. Genes and selected transcripts are indicated. Markers from previous studies used to compare deletions are indicated. The extent of reported deletions are represented by solid bars to indicate deletions proven by cytogenetic or molecular analysis (wider portion) or by clinical features (narrow portion). Open bars represent additional regions that may be deleted but are undefined molecularly and the patients died too early to define clinically. Authors and specific patients are indicated to the left of each deletion. Patients are clustered as in Table 1B.

Table 1

Summary of Xp11.4-p21.1 genes and deletions.

A. Genes involved in patients Xp11.4-p21.1 deletion (this report)

Involved Gene		Functional Implications
TMEM47	Transmembrane protein 47	Expressed in brain at high levels
PRRG1	Transmembrane gamma-carboxyglutamic acid protein 1	Expressed in the spinal cord
LANCL3	LanC lantibiotic synthetase component C-like 3	Unknown
**XK*	Membrane transport protein XK	Kell blood group 'precursor substance' (Kx). Mutations associated with McLeod syndrome, characterized by neuromuscular and hematopoietic abnormalities
**CYBB*	Cytochrome b-245, beta polypeptide	CYBB deficiency causes chronic granulomatous disease (CGD) with decreased phagocyte (NADPH oxidase-dependent) killing of intracellular bacteria
DYNLT3	Dynein light chain Tctex-type 3 (T-complex-associated testis-expressed 1-like)	Unknown
SYTL5	Synaptotagmin-like 5	May play a role in vesicle trafficking[14–16]. Expressed in placenta and liver.
SRPX	Sushi-repeat-containing protein, X-linked	May be involved in phagocytosis
**RPGR*	Retinitis pigmentosa GTPase regulator isoform C	Mutations cause 'X-linked retinitis pigmentosa' (XLRP)
**OTC*	Ornithine carbamoyltransferase	Catalyzes formation of Citrulline from carbamyl phosphate and ornithine Deficiency causes urea cycle disorder with hyperammonemia

B. Summary of Xp11.4-p21.1 deletions.

Category	Authors/Case	Involved Genes	Clinical Features	Comments
B1. Deletions approx 10Mb including more than *DMD* through *OTC*				
	[17–19] (KC)	*NR0B1* through *OTC* (complex rearrangement)	Female heterozygote	
	[20]	*NR0B1*through *OTC*	Male neonatal lethal with AHC, GKD and OTCD	
	[21] (Families 2 and 3)	*DMD* through *OTC*	Male neonatal lethal OTCD	
	[22] (YG)	*DMD* through *OTC*	Female with only OTCD symptoms	
B2. Deletions >5Mb from *DMD* telomeric to *OTC*				
	[18,19,23–25] (BB)	*DMD* through *RPGR*	Male with DMD, CGD, retinal pigment atrophy, anemia, acanthocytosis, mild MR. Also had intestinal pseudoobstruction, chronic abdominal distension and diarrhea. Mild MR. Died at 15y due to MVA.	Case facilitated identification of dystrophin [26] and X-linked CGD [27]
	[23,28,29] (NF)	*DMD* through *CYBB*	Male with CGD, McLeod, choroidoretinal atrophy	Used in identification of *CYBB*
	[30] (Patient 44)	?*DMD* through *RPGR*	Male with McLeod, CGD, retitinis pigmentosa and muscle weakness	
B3. Deletions <5Mb centromeric of *DMD* including *OTC*				
→	This report	*TMEM47* through *OTC*	Severe neonatal OTCD, CGD during lifetime, died at 3 mo.	
	[21]/ (Family 1)	*RPGR* (?*SRPX*) through *OTC*	Female with OTCD, died at 22 mo.	
B4. Deletions <5Mb from centromeric of *DMD* to telomeric of *OTC*				
	[31] (SB)	Likely *TMEM47* through *RPGR*	CGD, McLeod and choroidoretinal atrophy	Case allowed identification of *RPGR* as causing RP3 and *XK* as causing McLeod [23,32,33]
	[30] (Patient 43)	*XK* through *RPGR*	Male with McLeod, CGD and retitinis pigmentosa	
B5. Uncharacterized Deletions reported involving terminal exons of *OTC*				
	[34] (2 patients) [3] (1 patient) [4] (1 patient)	*OTC* exons 1-10	Severe neonatal OTCD	
	[35] (1 patient)	*OTC* ~ exons 1-10	Severe neonatal OTCD	Excluded markers L1.28 and 754
	[2]	*OTC* exons 1-3	Severe neonatal OTCD	

B. Summary of Xp11.4-p21.1 deletions.

Category	Authors/Case	Involved Genes	Clinical Features	Comments
	[4]	*OTC* exons 1-8	Severe neonatal OTCD	
	[4]	*OTC* exons 1-9	Severe neonatal OTCD	
	[34]	*OTC* exons 9-10	Severe neonatal OTCD	

* Genes with demonstrated clinical relevance to the management of patients in this family..

Abbreviations: *NRB01=DAX1*, AHC=adrenal hypoplasia congenita, GKD=glycerol kinase deficiency, OTCD=ornithine transcarbamylase deficiency, CGD=chronic granulomatous disease, MR=mental retardation, MVA=motor vehicle accident