Pusan National University
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Rare cases of ornithine transcarbamylase deficiency and variant Turner syndrome

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INTRODUCTION

- Turner syndrome, a condition that affects only girls and women, result when the X chromosome is missing or partially missing
- Ornithine transcarbamylase (OTC) deficiency, the most common inherited urea cycle disorder, is transmitted as a partially dominant X-linked trait.
- The *OTC* gene maps to Xp21.1 and spans approximately 73 kb, containing 10 exons and 9 introns.
- OTC deficiency is diagnosed using a combination of clinical findings and biochemical testing, while confirmation is often done using molecular genetics techniques.
- Here, we report two girls diagnosed with OTC deficiency and Partial Xp deletion.

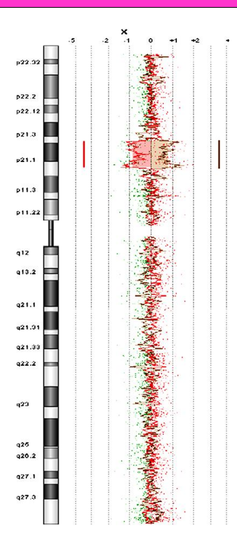

Table 1
Genes deleted in our patient and their functional implications.

Gene involved		Functional implications	Chromosomal loci	Clinical phenotype of our patient	Tissue specific expression
XK	Kell blood group precussor (McLeod syndrome)	Controls synthesis of the Kell blood group antigen. Associated with McLeod syndrome, characterized by neuromuscular and haematopoeitic abnormalities	Xp21.1	Asymptomatic	High levels in skeletal muscle, heart, brain, and pancreas; low levels in placenta, lung, liver, and kidney
CYBB	Cytochrome b-245, beta polypeptide	CYBB deficiency causes chronic granulatamatous disease(CGD) with defect in phagocytic NADPH oxidase killing of intracellular microorganisms	Xp21.1	Carrier	Lymph node, connective tissue, blood, spleen, trachea, pituitary gland
DYNLT3	Dynein, light chain, Tctex-type (T-complex-associated testis expressed1-like)	Protein binding	Xp21	NA	Oesaphagus, nerve, kidneys, adrenal gland, bladder, trachea, brain
SYTL5	Synaptotagmin-like 5	May act as Rab effector protein and play a role in vesicle trafficking. Binds phospholipids	Xp21.1	NA	Ear, mouth, skin, tracheas, embryonic tissue, muscle, prostate, lungs, testes, eyes
SRPX	Sushi-repeat –containing protein, X-linked	May be involved in phagocytosis during disk shedding, cell adhesion to cells other than the pigment epithelium or signal transduction	Xp21.1	NA	Retina, vascular, heart, umbilical cord, nerve, placenta, connective tissue, uterus, adrenal glands
RPGR	Retinitis pigmentosa GTPase regulator, transcript variant A	X-linked retinitis pigmentosa, associated with other phenotypes such as cone-rod and macular degenerations and primary ciliary dyskinesia	Xp21.1	Asymptomatic	Outer segments of rod, cone photoreceptors and transitional zone of motile cilia in airway epithelia, heart, brain, placenta, lung, liver, muscle, kidney
OTC	Ornithine transcarbamylase	Catalyzes formation of citrulline from carbamyl phosphate and ornithine. OTC deficiency causes hyperammonemia	Xp21.1	Symptomatic	Liver, kidney, intestine

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CASE 1

Brief HX
A 15-years-girl was diagnosed with OTC deficiency on the basis of clinical and biochemical findings including hyperammonemia (426 μmol/L), high level of glutamine and low citrulline in plasma and increased orotic acid in urine at 13 months of age. No mutation of OTC gene was identified by Sanger sequencing. Although ammonia was well-controlled with low protein diet and ammonia scavenging agents, the patient showed intellectual disability and autistic-like behavior. Subsequently, karyotyping was performed in the patient because she demonstrated profound short stature (-3.5 SDS) and primary amenorrhea. High resolution chromosome study revealed a large deletion within chromosome X, bands p21.1 to p11.4. Thyroid function test, hearing test, kidney US and EchoCG were normal.

Past Hx
GA 36+3 wks – 1075 g – C/Sec, 1st baby

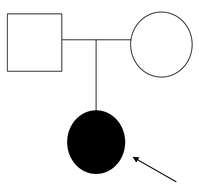

Table 1. Biochemical findings in patient 1.

	Patient data	Normal range
Plasma ammonia	426	10-50 μmol/L
Plasma glutamine	6015	246-1182 μmol/L
Plasma citrulline	22	3-35 μmol/L
Plasma arginine	60	12-133μmol/L
Urine orotic acid	> 6	0.20-6.00 mmol/mol Cr
LH	3.58	mIU/mL
FSH	5.27	mIU/mL
Estradiol	6.01	pg/mL

46,X,del(X)(p11.4p21.1)

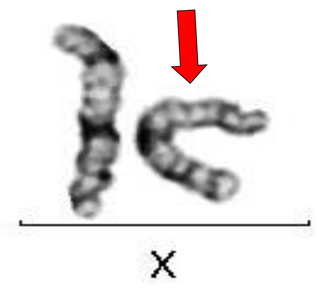

Figure 1. The high resolution chromosome study was revealed a large deletion within chromosome X, bands p21.1 to p11.4.

CASE 2

Brief HX
A 3 year-old girl was presented with lethargy and vomiting. At that time, plasma ammonia increased to 308 μmol/L (normal range <50 μmol/L) and the additional results of plasma amino acid analysis and urinary orotic acid were compatible with OTC deficiency. Targeted sequencing of OTC gene was normal, then multiplex ligand probe analysis revealed all nine exons deleted. As short stature (-2.3 SDS) and pigmented retinopathy were observed in the subject, the CGH microarray was performed additionally. We confirmed a deletion within chromosome X, bands p21.1 to p11.4, about 5Mb. Thyroid function test, hearing test, kidney US and EchoCG were normal.

Past Hx
GA 32+2 wks – 1660 g – C/Sec (1st baby in triplets)

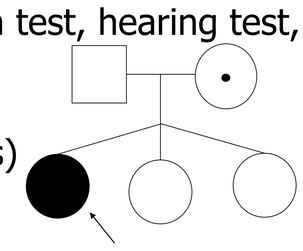

Table 2. Biochemical findings in patient 2.

	Patient data	Normal range
Plasma ammonia	308	10-50 μmol/L
Plasma glutamine	1066.1	254-823 μmol/L
Plasma citrulline	15.8	1-46 μmol/L
Plasma arginine	32.5	10-140 μmol/L
Urine orotic acid	61.74	0.20-6.00 mmol/mol Cr

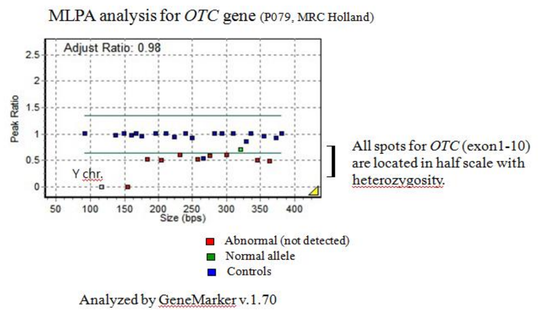

Figure 2. A multiplex ligation-dependent probe amplification (MLPA) analysis showed complete deletion from exon 1 to 10 of *OTC* gene.

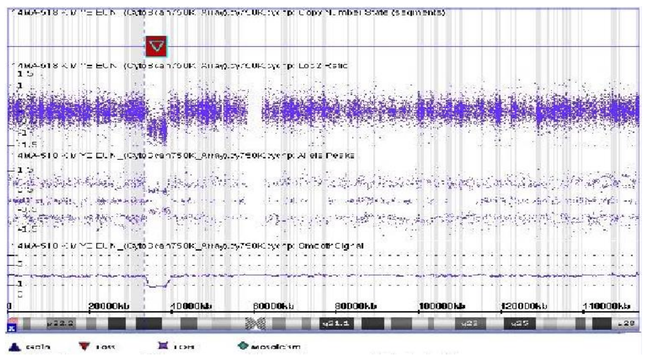

Figure 3. A array-comparative genomic hybridization (CGH) results, the *red box* indicates the deleted region between Xp21 to p11.4. The breakpoint positions were between 94,128,569 pb and 99,104292 pb.

CONCLUSION

- We described two girls with rare inborn error metabolism disorder, OTC deficiency due to partial Xp deletion.
- The application of high resolution molecular genetic techniques such as MLPA and array-CGH allows the identification of chromosomal rearrangements, such as large deletions.
- Further evaluations will be needed to elucidate the role of X-linked genes in Turner syndrome.

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