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Clinical Features, Response to Treatment, Prognosis, and Molecular Characterization in Korean Patients with Inherited Urea Cycle Defects

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Abstract

The urea cycle, consisting of a series of six enzymatic reactions, plays key roles to prevent the accumulation of toxic nitrogenous compound and synthesize arginine de novo. Five well characterized diseases have been described, resulting from an enzymatic defect in the biosynthesis of one of the normally expressed enzyme. This presentation will focus on two representative diseases; ornithine transcarbamylase(OTC) deficiency and citrullinemia(argininosuccinate synthetase deficiency). OTC deficiency is one of the most common inborn error of urea cycle, which is inherited in X-linked manner. We identified 17 different mutations in 20 unrelated Korean patients with OTC deficiency; L9X, R26P, R26X, T44I, R92X, G100R, R141Q, G195R, M205T, H214Y, D249G, R277W, F281S, 853 del C, R320X, V323M and 10 bp del at nt. 796-805. These mutations occur at well conserved nucleotide sequences across species or CpG hot spot. The L9X and R26X lead to the disruption of leader sequences, required for directing mitochondrial localization of the OTC precursor. Their phenotypes are severe, and neonatal onset. The G100R, R277W and V323M mutations were uniquely identified in patients with late onset OTC deficiency. The other genotypes are associated with neonatal onset. Out of 20 patients with OTC deficiency, only 6 patients are alive; two were liver transplanted, and normal in growth and development at 2, 4 years after transplantation respectively. Citrullinemia is an autosomal recessive disease, caused by the mutations in the argininosuccinate synthetase(ASS) gene. We identified in 3 major mutations in 11 unrelated Korean patients with citrullinemia; G324S, IVS6^{-2} A to G, and 67 bp ins at nt 1125-1126. Among these, the 67 base pair insertion mutation is novel. The allele frequency of each mutation is; G324S(45%), IVS6-2 A to G(32%), and 67 base pair insertion(14%). All patients are diagnosed at neonatal or infantile age. Interestingly, two patients presented with stroke like episode. Out of 11 patients, 5 patients died. Among 6 patients alive, one patient was successfully liver transplanted.

Subjects & Methods

- 35 patients diagnosed at AMC during march/1994 - June/2002
- Biochemical assay
- Molecular asssay
- Retrospective medical record review
- Mail questionnaire
- Telephone interview

Results

Table 1. Genotype-Phenotype Correlations in Korean Families with OTC deficiency

Families	Onset(Sex/Age)	Outcome(Age)	Genotype
#1 (OSK)	neonatel (M)	died (6 days)	R 141 Q
#2 (YYJ)	late (F/9 months)	died (10 years)	R 320 X
#3 (LKH)	neonatel (M)	died (10 months)	H 214 Y
#4 (SIK)	neonatel (M)	died (28 days)	?
#5 (CEK)	neonatel (M)	died (2 months)	R 26 X
#6 (KJH)	neonatel (M)	alive (10 months)	R 26 P
#7 (SYJ)	neonatel (M)	died (3 months)	L 9 X
#8 (KYL)	neonatel (M)	died (13 days)	F 281 S
#9 (PHK)*	neonatel (M)*	alive (3 years)*	D 249 G
#10 (KEH)	neonatel (M)	died (14 days)	M 205 T
#11 (KMS)	neonatel (M)	died (18 days)	del C at nt.853
#12 (KTH)	late (M/11 months)	alive (2 years)	V 323 M
#13 (CWI)	neonatel (M)	died (18 days)	R 320 X
#14 (HKY)*	late (F/9 months)*	alive (2 years)*	G 195 R
#15 (SSM)	neonatel (M)	died (29 days)	R 92 X
#16 (CWJ)	neonatel (M)	died (18 days)	R 141 Q
#17 (LIH)	late (M/8 months)	alive (2 years)	G 100 R
#18 (HR)	late (M/10 months)	alive (1 years)	R 277 W
#19 (KSS)	late (F/16 months)*	died (2 years)*	T 44 I
#20 (PHW)	neonatel (M)	alive (2 months)	10bp del at nt.796-805

*Liver transplanted

Table 2. Allele Frequency of the Each Mutation Identified in the ASS Gene of 11 Korean Patients with Citrullinemia

Mutation	Number of mutated alleles (Allele frequency: %)
G324S	10 (46)
IVS6-2 A-G	7 (32)
67bp insertion	3 (14)
Undetermined	2
Total	22

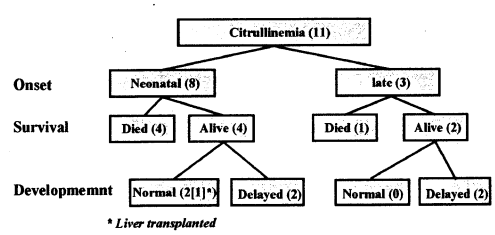

Fig. 2. Clinical outcome of Citrullinemia.

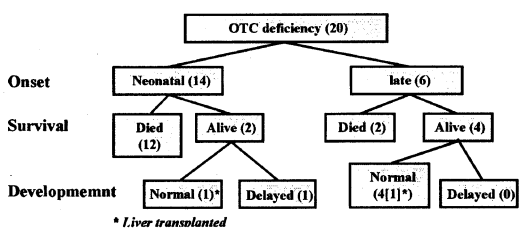

Fig. 1. Correlation between onset of symptoms and outcome of OTC deficiency.

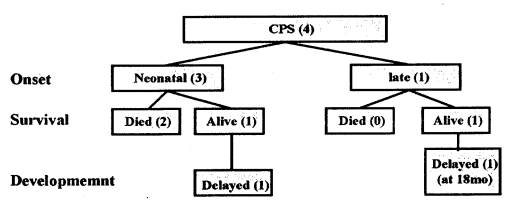

Fig. 3. Clinical outcome of 4 patients with CPS deficiency.

Conclusion

1. We identified 17 different mutations in 20 unrelated Korean patients with OTC deficiency; L9X, R26P, R26X, T44I, R92X, G100R, R141Q, G195R, M205T, H214Y, D249G, R277W, F281S, 853delC, R320X, V323M, and 10bp del at nt.796-805. These mutations occur at well conserved nucleotide sequences across species or CpG hot spot.

2. The L9X, R26X, and R26P lead to the disruption of leader sequences, required for directing mitochondrial localization of the OTC precursor. Their phenotypes are severe, and neonatal onset. The G100R, R277W, and V323M mutations were uniquely identified in patients with late onset OTC deficiency. The other genotypes are associated with neonatal onset.

3. Out of 20 patients with OTC deficiency, only 6 patients are alive; two were liver transplanted, and normal in growth and development at 1,3 years after liver transplantation respectively.

4. We identified 3 major mutations in 11 unrelated Korean patients with citrullinemia; G324S, IVS6-2 A-G, and 67bp ins at nt.1125-1126. Among these, the 67bp insertion mutation is novel. The allele frequency of each mutation is; G324S(46%), IVS6-2 A-G(32%), and 67bp ins(14%).

5. All patients are diagnosed at neonatal or infantile age. Interestingly, two patients presented with stroke like episode. Interestingly, two patients presented with stroke like episode. Out of 11 patients, 5 patients died. Among 6 patients alive, one patient was successfully liver transplanted.

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