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Whole-Exome Sequencing Detected Mutations in Pediatric Patients with Atypical Hemolytic Uremic Syndrome in Taiwan

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Objectives: Although atypical hemolytic uremic syndrome (aHUS) is a genetic disorder, molecular defects are detected in only sixty percent of patients. We aim to dissect the genetic background by whole exome sequence and the clinical characteristics of pediatric patients with aHUS.

Methods: Patients with complement-dysregulation HUS treated at children's hospitals in Taiwan were investigated. Whole exome sequence was used to detect their genotype. Clinical characteristics and outcome were analyzed.

Results: Ten patients (6 male and 4 female) with mean age 5.2±5.0 years were enrolled. The age at onset ranged from 2 days to 11 years. Eighteen different mutations (17 missense, 2 nonsense, and 11 novel) on 7 complement and 3 coagulation genes were detected in all patients. The majority of mutation was heterozygous and S1191L on *CFH* were the recurrent mutation. Sixty percent of patients had multiple genetic mutations. Nine mutations were associated with genes known to be implicated in aHUS (*CFH, CFI, CD46, CFHR5, and DGKE*), while 4 and 5 mutations were detected on complement- (*C8B, C9, and MASP1*) and coagulation-associated (*VWF* and *CD36*) genes, respectively. *CD36* may be a candidate gene act as disease modifier for aHUS through the contribution of thrombosis by impairing the interaction with TSP-1 and ADAMTS 13 shown in simulation model. There were no statistical differences in clinical presentation and outcome between patients with and without multiple genetic defects and patients with and without combined genetic defects involved complement and coagulation systems.

Conclusions: Genetic defects on both complement and coagulation pathways play pathogenic roles on aHUS. *CD36* may be a novel candidate gene act as disease modifier of aHUS.