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Molecular genetic dissection and neonatal/infantile intrahepatic cholestasis using targeted next-generation sequencing

Introduction The etiologic diversity of neonatal/infantile cholestasis has been described previously. The most commonly identifiable etiologies are biliary atresia, genetic intrahepatic cholestasis, and metabolic diseases. Recent advances in the understanding of the molecular basis of cholestatic syndromes have enabled the classification of these syndromes and have offered an opportunity for the development of diagnostic methods that take into account the genetic makeup of neonatal/infantile intrahepatic cholestasis (NIIC).

Objectives Our aims were to ascertain a molecular genetic diagnosis for subjects with NIIC by the use of next-generation sequencing (NGS) and to perform a genotype-phenotype correlation.

Study design We recruited Japanese subjects with NIIC who had no definitive molecular genetic diagnosis. We developed a diagnostic custom panel of 18 genes, and the amplicon library was sequenced via NGS. We then compared clinical data between the molecular genetically confirmed subjects with NIIC.

Results We analyzed 109 patients with NIIC ("genetic cholestasis," 31 subjects; "unknown with complications" such as prematurity, 46 subjects; "unknown without complications," 32 subjects), and a molecular genetic diagnosis was made for 28 subjects (26%). The rate of positive molecular genetic diagnosis in each category was 22 of 31 (71%) for the "genetic cholestasis" group, 2 of 46 (4.3%) for the "unknown with complications" group, and 4 of 32 (12.5%) for the "unknown without complications" group. The grouping of the molecular diagnoses in the group with genetic cholestasis was as follows: 12 with Alagille syndrome, 5 with neonatal Dubin-Johnson syndrome, 5 with neonatal intrahepatic cholestasis caused by citrin deficiency, and 6 with progressive familial intrahepatic cholestasis or benign recurrent intrahepatic cholestasis with low gamma-glutamyl transpeptidase levels. Several clinical datasets, including age of onset, direct bilirubin, and aminotransferases, were significantly different between the disorders confirmed using molecular genetic diagnosis.

Conclusion Targeted NGS can be used for molecular genetic diagnosis in subjects with NIIC. Clinical diagnosis should be accordingly redefined in the view of molecular genetic findings.