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P814 CLINICAL CHARACTERISTICS AND GENE MUTATION ANALYSIS OF 148 CHILDREN WITH FANCONI ANEMIA IN CHINA

Topic: 12. Bone marrow failure syndromes incl. PNH - Clinical

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Background: Fanconi anemia (FA) is a rare autosomal recessive, X-linked (FANCB) or autosomal dominant (FANCR/RAD51) disease of bone marrow failure. Pathogenesis is mainly caused by gene mutation related to the FA pathway. At present, at least 23 genes have been discovered to play a role in the FA pathway. The gene mutations of FA have been reported in more and more countries. In China, there no large-scale cases have been reported.

Aims: In this study, we analyzed the clinical characteristics of 148 FA children from 20 provinces in China from October 2003 to October 2021. We explored the relationship between genotype and phenotype in 105 children with FA genotyping results. This is the largest series of subtyped Chinese Fanconi anemia patients to date, and the results will be helpful for future clinical management.

Methods: A total of 148 Fanconi anemia patients from 140 families were diagnosed by clinical phenotype, family history, chromosome breakage test induced by mitomycin C, Single cell gel electrophoresis experiment, targeted - sequence, whole exon sequencing, and MLPA method from October 2003 to October 2021. Since there were no genetic test results for the children before 2010, only the 105 patients after 2010 had gene sequencing results, which allowed genotyping. DNA damage repair defects were detected by MMC-induced Single cell gel electrophoresis and chromosome breakage experiments. Targeted-seq was used to identify the FA mutations of the patients. Multiplex ligation-dependent probe amplification (MLPA) was performed to detect large fragment deletions in patients with negative results in the targeted-seq but conforming to the FA by MMC-induced chromosome breakage experiments test and clinical manifestations. We performed WES of DNA samples from five patients and their parents.

Results: 1) The most common subtype of FA in China is FA-A, followed by FA-D2 and FA-P2) The most common deformities in FA-A patients are finger deformities and skin pigmentation, while heart deformities are more common in FA-D2/B/G/I/P subtypes. 3) The common mutations of FANCA are exon23c.2101A>G, exon28c.2778+1G>A, exon34c.3348+1G>A, exon21c.1844delC, and exon30 C2941T>G, which are different from Korea and Japan. 4) Homozygous nonsense mutation of exon32 c.3188G>A and exon29 c.2851C>T in FA-A likely benign, but the homozygous splicing mutation in exon29c.2852+1G>T is harmful. 4) Children with splicing and Del mutations of FANCD1 gene had poor clinical prognosis, while children with homozygous mutations of exon10c. 1792A>G is likely benign. 5) Cases of initial diagnosis of MDS or poor disease progression tend to occur in FA-B/C/E/G/J/L/M and FA-S subtypes. 6)Chromosome 1, 3, 7, and 8 abnormalities and mutations of SF3B1 P53 are related to disease progression.

Summary/Conclusion: We made a comprehensive description and analysis of the clinical characteristics and mutant genes of Children with FA in China. We proposed the mutation sites related to clinical prognosis and the cytogenetic abnormalities of disease progression, providing new data for our comprehensive understanding of FA. Our data will be useful for FA future menagement.