Molecular pathology selected abstracts

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Common genetic variants contribute to risk of rare severe neurodevelopmental disorders

November 2018—The traditional paradigm broadly classifies genetic diseases into rare disorders caused by a single gene variant and common disorders caused by complex interplay among multiple genes. However, recent research has shown that penetrance and disease phenotype, even in disorders thought to be monogenic, are affected by common genetic variation. The authors performed a genome-wide association study (GWAS), in which they compared the common genetic variants (defined as having a minor allele frequency of five percent or greater in the general population) in 6,987 patients with severe neurodevelopmental disorders to 9,270 ancestry-matched controls. The patients were part of the Deciphering Developmental Disorders study and had such disorders as global developmental delay, intellectual disability, cognitive impairment, learning disabilities, and autism spectrum disorders. Eighty-eight percent of the patients also had abnormalities in at least one other organ system, and all disorders exhibited clinical severity such that they were thought likely to be monogenic. While no single variant showed significant association with the disorders, the authors found that 7.7 percent of the variance in risk for neurodevelopmental disorders was due to common genetic variation. The authors used this initial discovery GWAS to calculate a polygenic risk score by summing the contribution from all the examined variants. They then analyzed a validation cohort of an independent set of 728 trios comprised of a child with a neurodevelopmental disorder plus both parents. In these trios, it was found that the polygenic risk score was overtransmitted to the children with neurodevelopmental disorders, confirming the results. The authors then examined whether the polygenic risk score was associated with other neuropsychiatric disorders, cognitive and educational traits, and physical traits. They found that the polygenic risk score was negatively correlated with a genetic predisposition to higher educational attainment and intelligence and positively correlated with genetic risk of schizophrenia. No correlation was found between the polygenic risk score and other "negative-control" diseases, such as coronary artery disease or type 2 diabetes. Overall, these results suggest that common genetic variation plays a vital role in the clinical phenotype of severe neurodevelopmental disorders and brain development in general. This study emphasizes that it's necessary to consider background genetic variation to achieve complete understanding of genetic diseases.

Niemi MEK, Martin HC, Rice DL, et al. Common genetic variants contribute to risk of rare severe neurodevelopmental disorders. *Nature.* 2018. doi:10.1038/s41586-018-0566-4.

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Clearance of mutations after bone marrow transplantation for myelodysplastic syndrome

Myelodysplastic syndromes are a heterogeneous group of diseases with variable outcomes characterized by ineffective hematopoiesis. They are subclassified based on hematopoietic lineages exhibiting dysplasia, percentage of blast cells in the marrow, and defining molecular events. While treatments are available or in clinical trials, the only curative therapy for myelodysplastic syndrome (MDS) is hematopoietic stem cell transplantation. After transplant, monitoring for residual or recurrent disease includes evaluating bone marrow by morphologic examination, flow cytometry, and chimerism testing. The authors of this study used next-generation sequencing to identify mutations found in pretransplant marrow and assessed whether these mutations could serve as high-sensitivity molecular markers for residual/recurrent disease in the post-transplant setting. They subjected bone marrow and control skin samples from 90 consecutive patients with MDS to enhanced exome sequencing in which additional probes for 285 genes commonly mutated in MDS and acute myeloid leukemia had been added. In 86 of

the 90 patients, at least one somatic mutation was identified, and the number of somatic variants detected ranged up to 482 mutations per sample (median, 23). Patients underwent allogeneic hematopoietic stem cell transplants from related or unrelated donors, and pretreatment included myeloablative or reduced-intensity conditioning regimens. For sequencing post-transplant samples, the authors employed an error-corrected sequencing approach using unique molecular identifiers along with coverage depths greater than 30,000 to maximize sensitivity. The probes were custom designed to target all the somatic single-nucleotide variants detected in the pretransplant samples. In 30-day post-transplant samples, 32 of the 86 patients had at least one mutation present, defined as a maximum variant allele frequency of at least 0.5 percent, and the presence of such a mutation was associated with a higher risk of disease progression at one year post-transplant. The worst outcomes were seen in patients with a post-transplant mutation who had received a reduced-intensity conditioning regimen. In a multivariate analysis that included age, Revised International Prognostic Scoring System score, type of MDS, *TP53* mutation status, and conditioning regimen, the presence of at least one post-transplant mutation was an independent prognostic factor associated with worse progression-free survival. Although such a sequencing assay design is highly sensitive, it is not practical to perform whole exome sequencing and create custom probe sets to monitor individual patients. Therefore, the authors examined whether a gene panel of 40 genes sequenced using the same error-corrected sequencing approach would be similarly effective for monitoring. Although trackable somatic mutations could be identified in only 68 patients, the associations with progression-free survival were similar. Therefore, such a panel could be used to monitor patients undergoing transplant for MDS in whom a trackable mutation could be identified. Overall, this study demonstrates that mutations associated with MDS not only can be used to monitor a patient for residual or recurrent disease but also can serve as an important prognostic factor to determine risk of progression in the post-transplant setting.

Duncavage EJ, Jacoby MA, Chang GS, et al. Mutation clearance after transplantation for myelodysplastic syndrome. *N Engl J Med.* 2018;379(11):1028–1041.

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