Molecular Pathology Abstracts

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Effect of inherited *TP53* mutations on children with B-cell ALL

TP53 has been referred to as the "guardian of the genome" because it plays a central role in regulation of the cell cycle, DNA repair, and apoptosis, and because somatic mutations in *TP53* are frequently identified in many tumor types. Li-Fraumeni syndrome (LFS), caused by inherited pathogenic variants in *TP53*, is a rare disorder that segregates in an autosomal dominant fashion. Approximately half of people with LFS develop cancer by age 30 and have a lifetime risk of 75 percent (men) to 100 percent (women), with the most common malignancies occurring in the breast, bone, brain, and blood. Germline pathogenic *TP53* variants have been implicated in hypodiploid acute lymphoblastic leukemia (ALL) in children. Hypodiploidy (loss of several chromosomes) and masked hypodiploidy (doubling of hypodiploid chromosomes leading to multiple chromosomes with loss of heterozygosity) are associated with poor prognosis and outcome in ALL patients. The authors performed a comprehensive screening of *TP53* germline variation in children enrolled in nationwide frontline ALL trials to identify the risk conferred by *TP53* variants to leukemia and to evaluate the association of these variants with clinical features and outcomes. *TP53* targeted sequencing was performed in 3,801 children with newly diagnosed B-cell ALL who were enrolled in two consecutive Children's Oncology Group frontline clinical trials. The study's control group was derived from the Exome Aggregation Consortium (EXAC) data set of whole exome sequencing-based variants of 60,706 people. Each *TP53* variant was manually curated and classified as pathogenic or variant of unknown significance (VUS) using experimentally validated p53 transcriptional activity data, bioinformatics predictions, and the prevalence of the variant in the EXAC control cohort. The authors identified 49 rare non-silent *TP53* coding variants in 77 of the 3,801 children sequenced (population frequency, less than 0.5 percent), of which 22 were classified as pathogenic and 27 as VUS. Of the entire cohort, 26 (0.7 percent) children had a predicted pathogenic variant and 51 (1.3 percent) had a VUS in the *TP53* gene. When comparing the clinical characteristics of ALL, 17 of the 26 (65.4 percent) patients with pathogenic *TP53* mutations exhibited hypodiploidy, a much higher proportion than children with VUS (3.9 percent) or wild-type (1.2 percent) genotypes, although no statistical measure was provided. Furthermore, pathogenic *TP53* variants were strongly associated with poorer prognosis after adjusting for treatment protocols. When comparing the types of events between the ALL *TP53* variant groups, those with pathogenic *TP53* variants had a statistically significantly higher incidence of second cancers compared to the VUS/wild-type *TP53* group (36 versus four percent; $P = 1.2 \times 10\text{-}7$). This trend was even more pronounced in the hypodiploid ALL subgroup (50 versus five percent; $P = .01$). The authors concluded that this study highlights the association between inherited pathogenic variants and cancer susceptibility and prognosis, as well as the downstream implications of such variants to treatment options—for example, avoidance of irradiation therapy—and risk for second cancers.

Qian M, Cao X, Devidas M, et al. *TP53* germline variations influence the predisposition and prognosis of B-cell acute lymphoblastic leukemia in children. *J Clin Oncol.* 2018;36(6):591–599.

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Use of genetic tests to detect cause of cardiomyopathy in

underrepresented minorities

Cardiomyopathy is a collective group of disorders affecting the heart muscle, and numerous genes have been implicated in familial forms of the disease. The genes targeted for analysis by clinical laboratories are derived from research, such as family linkage or association studies and functional studies to demonstrate altered gene function. With the advent of multiple gene panels, the classification of variants as pathogenic, likely pathogenic, variant of unknown significance, likely benign, or benign relies heavily on large population databases to determine if the observed variant is a polymorphism (more likely to be benign) or a very rare variant (more likely to be disease causing). Cardiomyopathy, in particular, has a high rate of missense variants, making it difficult to distinguish between benign and pathogenic, especially without additional functional or family segregation studies. Although efforts have been made to increase ethnic diversity in study populations, most genetic studies historically have involved subjects of European ancestry. The authors conducted a study to determine if a person's racial/ethnic group influences the ability to detect an underlying genetic cause for cardiomyopathy. They looked at more than 7,400 probands referred for genetic testing and collectively grouped as underrepresented minorities (URM) people who self-reported as black, Hispanic, Native American, Alaska Native, Hawaiian, or other South Pacific Islander. Those of mixed, unspecified, or other races/ethnicities were not included in the analysis. Of the 5,729 people analyzed, 4,539 were white, 348 Asian, and 842 URM. The authors found a statistically significant reduction in the positive detection rate of pathogenic/likely pathogenic variants for cardiomyopathy in the URM group when compared with the white group (18.4 versus 29 percent; $P<.001$). The rate of inconclusive results, defined by the reporting of variants of unknown significance, was higher for the URM group compared with the white group (39.8 versus 24.6 percent; $P<.001$). The authors point out that an inconclusive result, reported as a variant of unknown significance, can lead to confusion and improper use of the results for clinical decision-making. Although the study had several limitations, the results highlight several caveats when interpreting genetic test results in URM populations. The observation of both a lower positive detection rate and a higher rate of inconclusive results may arise because the content on gene panels is highly influenced by research studies conducted on populations of European ancestry, and genes unique to URM may not be represented on these panels. Furthermore, the higher rate of inconclusive results for URM demonstrates that these tests may have more limited utility in these populations. Although great strides have been made to include more URM groups in research and clinical practice, this study indicates that gaps still exist and improvements are needed.

Landry LG, Rehm HL. Association of racial/ethnic categories with the ability of genetic tests to detect a cause of cardiomyopathy. *JAMA Cardiol.* 2018:e1–e5. doi:10.1001/jamacardio.2017.5333.

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