

An update on the genetic predisposition of testicular germ cell tumors

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Testicular germ cell tumors (TGCTs) are the most common solid tumors in young males (15–45 years). Among all risk factors, various genetic abnormalities greatly influence the development and progression of TGCTs and are also associated with treatment and risk of recurrence (1,2). Therefore, understanding the genetic basis of TGCTs is a crucial point for their early prediction, diagnosis, prognosis as well as treatment, recurrence monitoring, and longterm outcome for patients. Despite the high heritability of TGCTs (1), no genes [like *BRCA1* and *BRCA2* in breast and prostate cancer (3)] with high-penetrance predisposition have been identified. Nevertheless, only one gene (*CHEK2*, a tumor suppressor gene associated with DNA break repair, cell cycle regulation, and apoptosis) has been identified with moderate penetrance (4).

CHEK2 mutations are closely associated with increased risk of different cancers. For example, the 1100delC mutation in CHEK2 is strongly correlated with the increased risk of breast, colorectal, kidney, papillary thyroid, prostate, and many other cancers (5). AlDubayan *et al.* (4) found pathogenic variants of CHEK2 to be associated with susceptibility to TGTCs. There, the authors identified 22 pathogenic germline DNA repair gene variants by conducting a multicenter case-control analysis of 205 TGCT patients and 27,173 controls. Remarkably, onethird of these variants were found in CHEK2, and TGCTs patients were more likely (four to six times) to have CHEK2 variants with germline loss-of-function [odds ratio (OR), 3.87; 95% confidence interval (CI): 1.65-8.86; nominal P=0.006; q=0.018] compared to the controls. It was also demonstrated that compared to men with the CHEK2 wildtype alleles (5.95 years; 95% CI: 1.48-10.42 years; P=0.009), men with the CHEK2 loss-of-function variants developed TGCTs 6 years earlier, suggesting that CHEK2 variants serve as high-risk drivers of susceptibility to TGCTs (4). Similarly, Paumard-Hernández et al. (6) performed exome sequencing of 71 family members (41 affected and 30 healthy) from 19 families, and subsequently evaluated candidate gene variants in an additional 391 patients with sporadic TGCTs and 1,170 controls to identify novel susceptibility genes responsible for TGCTs. The authors identified five statistically significant gene variants in their sample group. However, only three of these [p.Tyr2054Cys (DNAH7), p.Arg344AlafsTer10 (EXO5), p.Arg433Gln (PLEC)] were detected in a second independent analysis and most likely result in increased susceptibility to TGCTs (6). Furthermore, other research groups have also attempted to identify prominent high penetrance genes that are

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associated with predisposition to TGCTs (7). However, these studies detected only a few common genetic variations with low to moderate penetrance.

Most recently Pyle et al. (8) performed exome sequencing and gene burden analysis of men (n=293) with familial or bilateral high-risk TGCTs from 228 unique families compared to cancer-free controls (n=3,157). Using multilevel deep genomic analysis, the authors found numerous new specific variants associated with the risk of TGCTs. For example, a variant p.Glu124Gln in PIM1 (a proto-oncogene that promotes and maintains tumorigenesis of various cancers) was identified in 19 individuals [1.5% minor allele frequency in high-risk TGCTs individuals and 0.19% in unaffected controls; OR, 8.3, 95% CI: 3.24-21.3; P<0.001; genome aggregation database (gnomAD) population frequency 0.18%], reflecting the association with the risk of TGCTs. Besides, the authors found protein loss-of-function (pLoF) variants for 462 genes nominally associated with TGCTs. However, it appears that only ten genes, including ZP4, NIN, and QRSL1 with pLoF variants had the most significant association with TGCTs risk. On top, several other variants (including nonsynonymous) in different genes (BCLAF1, SPRR3, TNFRSF10C, FRG1, LILRA4, and STOML3) were also identified and nominally associated with TGCTs risk.

Variant enrichment analysis was then performed to uncover the associations with both pLoF and nonsynonymous variants within previously reported pathways or TGCT predisposition. However, no enrichment of variants in genes associated with sex and germ cell development was found. Moreover, no significant association of nonsynonymous coding variants with TGCTs genome-wide association studies (GWASs) regions was discovered. Subsequently, an unbiased network analysis predicted possible pathways for the predisposition of TGCTs related to coding variants. Genes with non-synonymous variants were associated with initiation of DNA replication, DNAdependent DNA replication, and mitotic cell cycle control pathways, while genes with pLoF variants were associated with cytoskeleton-dependent cytokinesis and cell division pathways. Then, all significant variants (both pLoF and non-synonymous) were cross-analyzed with the latest GWAS-to-function variants and three signaling pathways such as mitosis/cell cycle, co-translational protein targeting (including to the membrane and nonsense-mediated decay) and sexual differentiation were identified, which are closely related to TGCT susceptibility.

Finally, several known pathogenic candidate gene

variants associated with TGCTs were reanalyzed and the highest number of variants (n=8), including the previously reported c.1100delC and p.S428F were identified in *CHEK2*. In addition, the c.136delA variant was also detected in *KIAA0586*. Additional gene-specific analysis revealed that the most common variant (p.Phe508del) in *CFTR* was found in 3.4% of probands and 2.9% of the unaffected cohort (P=0.69) in comparison to 1.2% of the general European population.

Indeed, the study included the largest sample cohort in the analysis to identify genes with high penetrance predisposition to TGCTs. Although a number of new genes with variants have been identified, none of them exhibit high penetrance predisposition, leaving the longawaited challenges in determining the absolute genetic risk of TGCTs unresolved. At different levels of analysis, the authors identified a broader association between coding genomic variants, TGCTs predisposition, pathways of mitosis, cell-cycle control, and co-translational protein targeting, as well as an association with sex differentiation. The authors hypothesize, that there is no gene with high-penetrance predisposition in TGCTs (8). However, extending such an approach to include samples from different regions of origin might allow to identify genes with high penetrance predisposition associated with TGCTs risk. Further, in parallel the research focus could be extended to the study of epigenetic alterations, such as DNA methylation, histone modification, and chromatin accessibility. In fact, such alterations have been identified as a risk factor in other cancers (9,10). Nonetheless, the authors provide a promising polygenic etiology, implying a role in cancer-predisposition polygenic risk score for familial TGCTs and identify new candidate genes (e.g., CFTR, PIM1, and CRBN). This represents the starting point to unveiling the underlying mechanisms to understand the etiology of TGCTs as well as identify targets for personalized clinical treatment.

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References

- Martin FC, Conduit C, Loveland KL, et al. Genetics of testicular cancer: a review. Curr Opin Urol 2022;32:481-7.
- 2. Nakhaei-Rad S, Soleimani Z, Vahedi S, et al. Testicular germ cell tumors: Genomic alternations and RAS-

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- Barnes DR, Silvestri V, Leslie G, et al. Breast and Prostate Cancer Risks for Male BRCA1 and BRCA2 Pathogenic Variant Carriers Using Polygenic Risk Scores. J Natl Cancer Inst 2022;114:109-22.
- AlDubayan SH, Pyle LC, Gamulin M, et al. Association of Inherited Pathogenic Variants in Checkpoint Kinase 2 (CHEK2) With Susceptibility to Testicular Germ Cell Tumors. JAMA Oncol 2019;5:514-22.
- Stolarova L, Kleiblova P, Janatova M, et al. CHEK2 Germline Variants in Cancer Predisposition: Stalemate Rather than Checkmate. Cells 2020;9:2675.
- Paumard-Hernández B, Calvete O, Inglada Pérez L, et al. Whole exome sequencing identifies PLEC, EXO5 and DNAH7 as novel susceptibility genes in testicular cancer. Int J Cancer 2018;143:1954-62.
- Loveday C, Law P, Litchfield K, et al. Large-scale Analysis Demonstrates Familial Testicular Cancer to have Polygenic Aetiology. Eur Urol 2018;74:248-52.
- Pyle LC, Kim J, Bradfield J, et al. Germline Exome Sequencing for Men with Testicular Germ Cell Tumor Reveals Coding Defects in Chromosomal Segregation and Protein-targeting Genes. Eur Urol 2023. [Epub ahead of print]. doi: 10.1016/j.eururo.2023.05.008.
- 9. Cheng Y, He C, Wang M, et al. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduct Target Ther 2019;4:62.
- Lu Y, Chan YT, Tan HY, et al. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. Mol Cancer 2020;19:79.

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