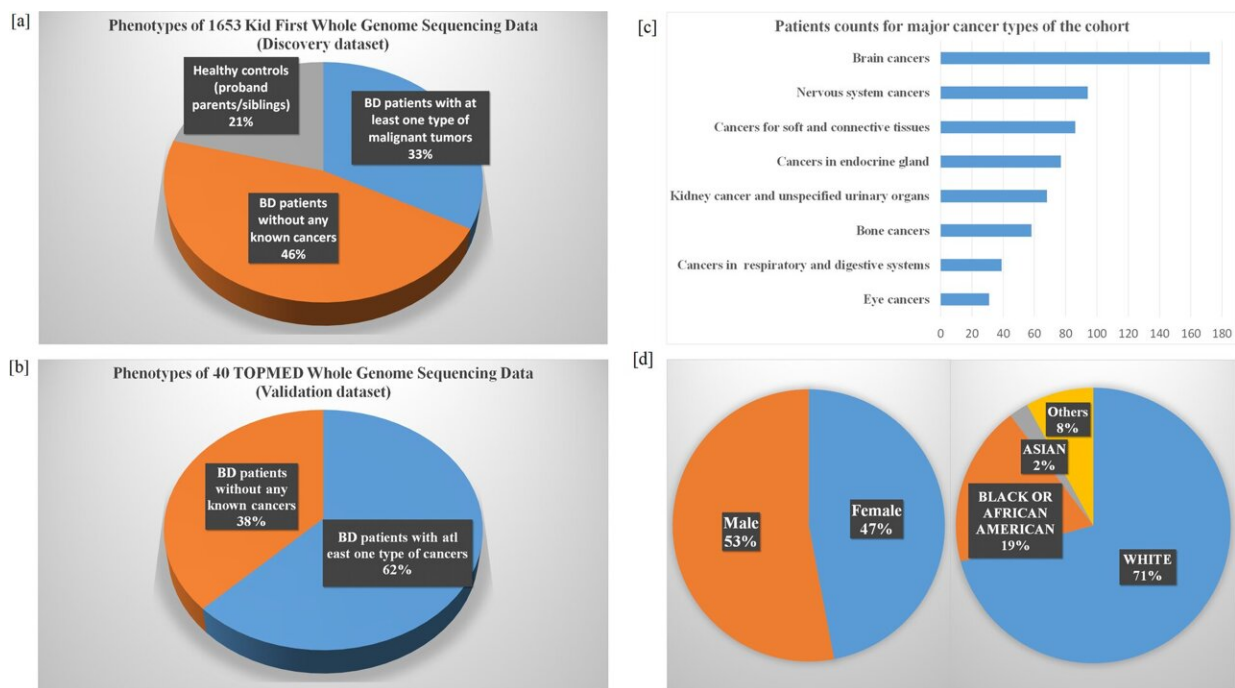


Researchers identify potential genetic variants linked to increased cancer risk in children with birth defects

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Demographic information of the cohort. a Phenotype information of the discovery cohort; b Phenotype information of the validation cohort; c Number of patients with cancers; d Gender and ethnicity distribution of the cohort. Credit: *Biomarker Research* (2022). DOI: 10.1186/s40364-022-00431-y

Researchers from Children's Hospital of Philadelphia (CHOP) have identified several genetic variants associated with increased risk of

cancer in children with non-chromosomal birth defects, such as congenital heart disease and defects of the central nervous system. While the risk of developing cancer is not as high as children with chromosomal birth defects, it is significantly higher than children with no birth defects at all, and the findings may provide a basis for early detection in these understudied patients.

The findings were recently published in the journal *Biomarker Research*.

Children with birth defects are more likely to develop cancer, and that increased risk of cancer persists into adulthood. Prior studies have demonstrated that [children](#) with chromosomal birth defects, such as Down syndrome and Klinefelter syndrome, are more than 11 times more likely to be diagnosed with cancer than children without any birth defects. However, children with non-chromosomal birth defects are up to 2.5 times more likely to be diagnosed with cancer than those without birth defects. With birth defects of any kind occurring in 1 in every 33 births in the United States each year, that increased risk affects a significant number of children.

The underlying genetics of non-chromosomal birth defects have not been studied in great detail. Researchers at the Center for Applied Genomics (CAG) at CHOP wanted to determine which [molecular mechanisms](#) were at play and potentially identify genetic clues that could lead to early identification of cancer in these patients.

"We assembled one of the largest pediatric oncology and birth defects projects in children as part of the Gabriella Miller Kids First program project, which helps to uncover new insights into childhood cancer and structural birth defects," said Hakon Hakonarson, MD, Ph.D., director of the CAG at CHOP and senior author of the study. "With this partnership, we sought to identify functional molecular pathways based on mutations we identified as part of this study."

In this study, researchers used data obtained from whole genome sequencing of blood samples from 1,653 individuals without chromosomal abnormalities that were acquired from the Kids First Data Resource Center. These samples included 541 birth defect probands—the first person in a family to receive genetic counseling or testing for hereditary risk of a disease—with at least one type of malignant tumor, 767 birth defect probands without malignant tumors, and 345 healthy family members who are parents or siblings of the aforementioned probands. Additionally, once variants were identified, whole genome sequencing data from 40 birth defect probands from outside the data resource center, including 25 patients with at least one type of cancer, were used to further validate the study.

The study identified thousands of variants of interest, including 119 genes with at least two variants in coding regions—regions of the gene that will eventually be transcribed and translated into proteins to carry out essential functions—and 478 genes with at least 20 variants in their non-coding regions. Five genes in particular—AXIN2, BMP1, CR1, ERBB2, and RYR1—are associated with birth defects and increased risk of cancer. Additionally, the researchers built a deep learning model to assess the variants of interest identified in the Kids First cohort when compared with the 40 validation samples and found that they had achieved approximately 75% accuracy, with even greater accuracy for variants that were associated with non-coding regions.

Further detailed analysis of this data could identify genes and noncoding mutations that not only result in specific [birth](#) defects, but also identify which types of cancer they are more prone to and whether the risk is more pronounced in childhood or adulthood.

"While more research is needed to delve into the variants of interest we identified, this study represents a critical step toward the earlier detection of [cancer](#) children with non-chromosomal [birth defects](#),"

Hakonarson said.

More information: Yichuan Liu et al, Identification of risk variants related to malignant tumors in children with birth defects by whole genome sequencing, *Biomarker Research* (2022). [DOI: 10.1186/s40364-022-00431-y](https://doi.org/10.1186/s40364-022-00431-y)

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