Childhood cancer genome study reveals hidden variants

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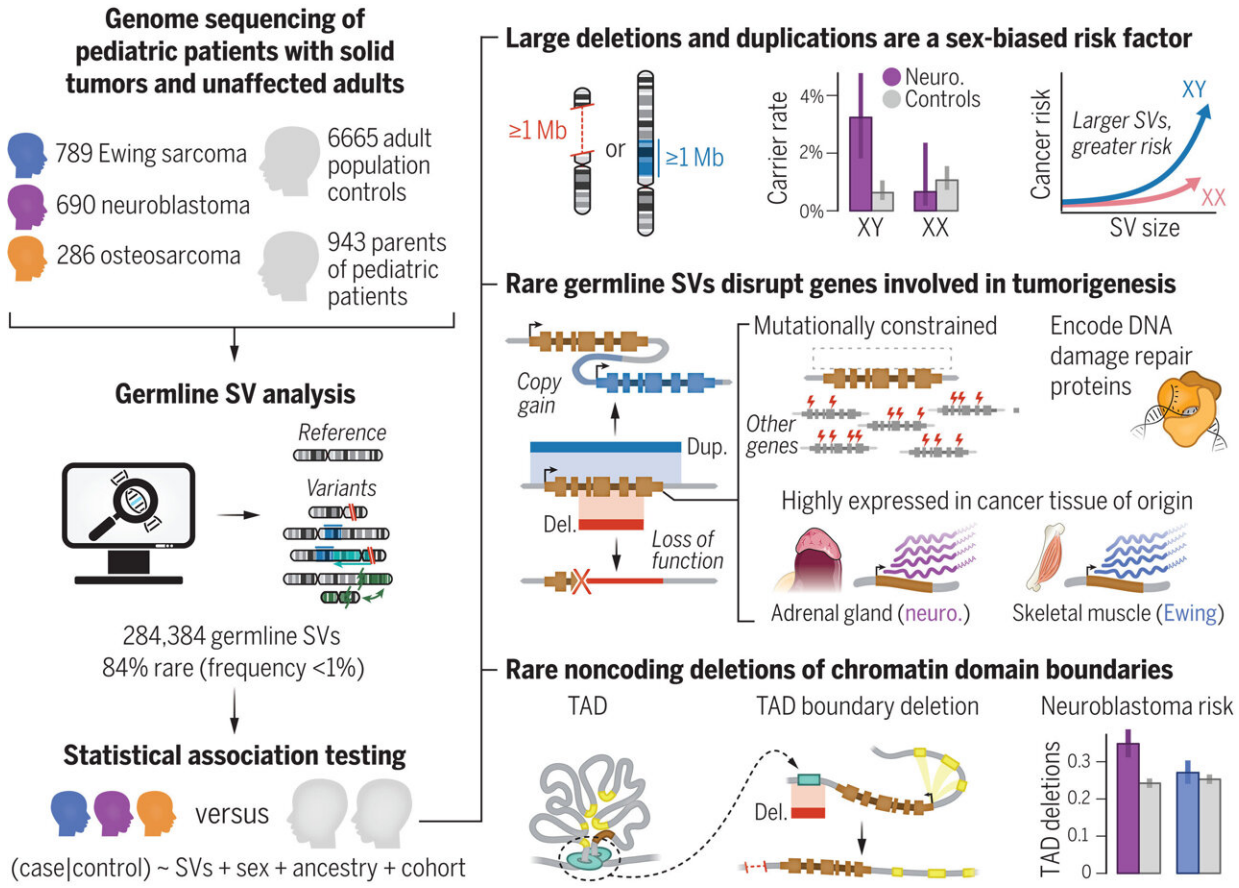

Rare germline SVs are risk factors for pediatric solid tumors. Credit: *Science* (2025). DOI: 10.1126/science.adq0071

Researchers at Dana-Farber Cancer Institute collaborated with multiple

institutions to pinpoint rare germline structural variants as risk factors for non-blood-related cancers in children, including tumors in various organs. Findings indicate that structural variations in both coding and noncoding regions of the genome contribute to childhood cancers such as neuroblastoma, Ewing sarcoma, and osteosarcoma.

Solid tumors constitute about one-third of new childhood cancer diagnoses worldwide. Prior studies have focused on the genetic drivers of these tumors but have lacked comparable insight into the earliest germline risk factors. Recognized predisposition genes currently account for only 10 to 15% of childhood cancer cases, leaving most heritable factors uncharacterized.

Early identification of pathogenic genetic alterations in children is vital. Genetic screenings that account for structural variants have not yet been widely implemented, limiting the understanding of contributors to early tumorigenesis and slowing the rate at which research might develop targeted treatment interventions.

In the study, "Rare germline structural variants increase risk for pediatric solid tumors," published in *Science*, researchers analyzed high-coverage germline whole-genome sequencing data from 1,765 patients with neuroblastoma, Ewing sarcoma, or osteosarcoma, plus 943 unaffected parents and 6,665 unrelated adult controls, looking for hidden causal gene variants.

The GATK-SV pipeline was used to detect large deletions, duplications, inversions, translocations, and more complex rearrangements. A category-wide association framework was applied to systematically assess coding and noncoding structural variants in patient genomes relative to controls.

Researchers identified 84 extensive chromosomal abnormalities. These

ultra-rare deletions or duplications exceeding 1 million nucleotides were observed far more often in male pediatric patients and were linked to a substantially higher risk for childhood cancer compared with adult controls.

Intriguingly, abnormalities were predominantly (82%) inherited from unaffected parents. Most did not overlap known cancer-related genes or established pathogenic loci, suggesting an indirect elevation of cancer risk where the specific gene variant is only one part of the disease mechanism.

Rates of de novo germline variations were not substantially elevated in pediatric patients compared with adult controls but were distinguished by larger average size and greater disruption of protein-coding regions.

Complex structural rearrangements were notable in critical gene sets linked to DNA damage repair, mutational constraint, and tissue-specific expression. Events predicted to alter chromatin domain boundaries were strongly associated with neuroblastoma risk.

With a current scientific consensus of a 350% increased risk of childhood cancer if it has occurred elsewhere in the family, only 10–15% of cases can be attributed to known pathogenic inherited variants.

Estimates based on the findings suggest that rare germline structural variants may explain up to 5.6% of heritability in certain child tumors. The study authors suggest the findings support the integration of germline SVs into clinical practice and research efforts related to pediatric solid tumor predisposition.

A perspective article on the study, "Inherited genome instability: Germline structural variants are a risk factor for pediatric extracranial

solid tumors," also published in *Science*, suggests that a mechanism to consider is the overall instability of the genome in children.

Childhood tumors often harbor defects in DNA damage repair pathway genes, consistent with inherited genomic traits predisposed to higher mutation rates.

In the pediatric environment, where cell proliferation is naturally heightened for growth and development, cancer formation can be accelerated. Consequently, children may require fewer overall mutations than adults to drive tumorigenesis.

During critical growth periods, more active cell division occurs, which could accelerate the acquisition of mutations that can go unrepaired. Perhaps worse, non-pathogenic rare variants may be repaired incorrectly, leading to pathology.

Misrepair due to a faulty repair pathway can be worse because a mutation only happens once (and then replicates onward from a single cell), whereas a misrepair can occur continually in many progenitor cells, leading to more widespread replication.

Based on the study's findings, it may be time to consider the use of therapies that inhibit DNA damage repair pathways as a targeted approach against pediatric extracranial solid tumors.

More information: Riaz Gillani et al, Rare germline structural variants increase risk for pediatric solid tumors, *Science* (2025). DOI: 10.1126/science.adq0071

Jayne Y. Hehir-Kwa et al, Inherited genome instability, *Science* (2025). DOI: 10.1126/science.adu6125