DNA: Too Much--or Too Little--Can Be a Bad Thing

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PHILADELPHIA, PENNSYLVANIA--There's more variety to DNA than you might think: Deletions or additions of genetic material between individuals, called copy number variations (CNVs), are a common source of genetic diversity. Now, preliminary work reported here today at the American Society of Human Genetics meeting suggests that men who have more CNVs than average may be more likely to sire children with the eye cancer retinoblastoma. The research reflects growing enthusiasm among geneticists for CNVs, a type of genetic variation that hadn't gotten much attention until recently but that's now being linked to a number of diseases.

All youngsters who develop retinoblastoma in both eyes inherited a defective gene that caused the disease. But in 80% of these cases, neither parent carries the mutation. Somehow it arose in the father's sperm. No one knows how this happens, but researchers have speculated that some fathers may be more susceptible to DNA damage than others. At the University of Pennsylvania (U Penn) and the Children's Hospital of Philadelphia, researchers have spent about 7 years collecting cases of this rare cancer and gathering DNA from children and their parents. They are also inquiring about a range of environmental exposures that may have affected fathers, but that information isn't yet available.

The genetic findings, however, are slowly coming together. At the meeting, geneticist Elizabeth Chao, a postdoctoral fellow at U Penn working with geneticist Arupa Ganguly, described DNA taken from 169 fathers whose children developed the disease. They identified 37 CNVs they considered large--greater than 500,000 DNA bases--and in general found that the fathers had more CNVs than controls, about eight on average versus three. Twenty-one dads had no detectable CNVs at all, but Chao suspects this may be due to the technology used, which has difficulty picking up very small stretches of DNA that are duplicated or deleted.

Particularly interesting were CNVs in genes that protect against DNA damage, such as the breast cancer gene *BRCA2*. Chao doesn't know whether these CNVs are inherited by the fathers from their own parents or whether they accumulate with age. And it's too early to say how or even whether CNVs contribute to the risk of a mutated retinoblastoma gene. One possibility, says Chao, is that high numbers of CNVs somehow cause DNA damage by making dads less able to protect themselves from environmental insults such as radiation. Another explanation is that the CNVs are just "markers of a less stable genome," suggesting that these men are more vulnerable to DNA damage generally. The fathers aren't at higher risk of cancer themselves, Chao adds.

Although these dads are healthy, the findings are similar to those in other diseases tied to high

CNV levels. For example, take Li-Fraumeni syndrome, a genetic condition that leads to a number of cancers. In work published in August in the *Proceedings of the National Academy of Sciences* and presented today, researchers from the Hospital for Sick Children in Toronto, Canada, studied 11 families with Li-Fraumeni syndrome and reported that those affected had an average of 12 CNVs in their genome, compared with three in controls. Other work described an increased burden of CNVs in schizophrenia, particularly in DNA that's part of a gene.

The retinoblastoma work is "very preliminary," says geneticist Stephen Scherer of the Hospital for Sick Children, who participated in the Li-Fraumeni study. In general, CNV data are "getting much better," but the work is still challenging because different technologies yield different copy-number variants. "It's really, really tricky" both to accurately identify CNVs and to determine their relevance to disease, he says. Still, says Scherer, identifications of large, rare CNVs are likely to be accurate, and the approach is offering new hope in pinpointing DNA that's driving disease.

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