New type of extra-chromosomal DNA discovered

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(PhysOrg.com) -- A team of scientists from the University of Virginia and University of North Carolina in the US have discovered a previously unidentified type of small circular DNA molecule occurring outside the chromosomes in mouse and human cells. The circular DNA is 200-400 base pairs in length and consists of non-repeating sequences. The new type of extra-chromosomal circular DNA (eccDNA) has been dubbed microDNA. Unlike other forms of eccDNA, in microDNA the sequences of base pairs are non-repetitive and are usually found associated with particular genes. This suggests they may be produced by micro-deletions of small sections of the chromosomal DNA.

Professor Anindya Dutta and colleagues pruified DNA taken from samples of mouse brain tissue and then digested away the linear DNA

(which consists of millions of base pairs) to leave only circular DNA pieces, which they then sequenced using ultra-high-throughput sequencing. Circles were identified by a new bioinformatics program.

They found the size of the circles was around the same length as the DNA on a nucleosome (a sub-unit of a chromosome). The small size of the circular DNA surprised them since extra-chromosomal DNA circles are larger. Their circular DNA was also dissimilar to the previously-known circles known as polydispersed DNA because the latter usually consist of repeating sequences of base pairs. Another interesting finding was that the circles are rich in the base pair GC (guanine-cytosine) with relatively little AT (adenine-thymine. The researchers repeated their experiments on other mouse tissues and on human cells.

The team also compared the circular DNA to the linear DNA originally digested away, and they were able to match the microDNA with micro-deletions on the linear DNA. This result suggests that the DNA found in tissue cells may exhibit more variation than previously thought, and the implication of this is that sequencing of the DNA in blood cells (which are the cells usually used for sequencing) may give misleading results if microdeletions have occurred in the DNA of other tissues but not in blood cells. Examples in which this might be important are in genetic seqencing for autism or schizophrenia, which could be caused by incorrect functioning of certain genes in brain tissue. Many cancers are also caused by incorrect functioning of genes; in this case tumor suppressor genes, and sequencing of blood cell DNA could also give misleading results.

The researchers suggest that microDNA might be formed during replication of DNA or during DNA repair processes, but more research will be needed to identify the exact processes involved. The team will next turn to investigating cancer genomes.

The paper was published in the journal *Science*.

More information: Extrachromosomal MicroDNAs and Chromosomal Microdeletions in Normal Tissues, *Science* DOI: 10.1126/science.1213307

Abstract

We have identified tens of thousands of short extrachromosomal circular DNAs (microDNA) in mouse tissues as well as mouse and human cell lines. These microDNAs are 200 to 400 bp long, derived from unique nonrepetitive sequence, and are enriched in the 5' untranslated regions of genes, exons, and CpG islands. Chromosomal loci that are enriched sources of microDNA in adult brain are somatically mosaic for microdeletions that appear to arise from the excision of microDNAs. Germline microdeletions identified by the “Thousand Genomes” project may also arise from the excision of microDNAs in the germline lineage. We have thus identified a new DNA entity in mammalian cells and provide evidence that their generation leaves behind deletions in different genomic loci.