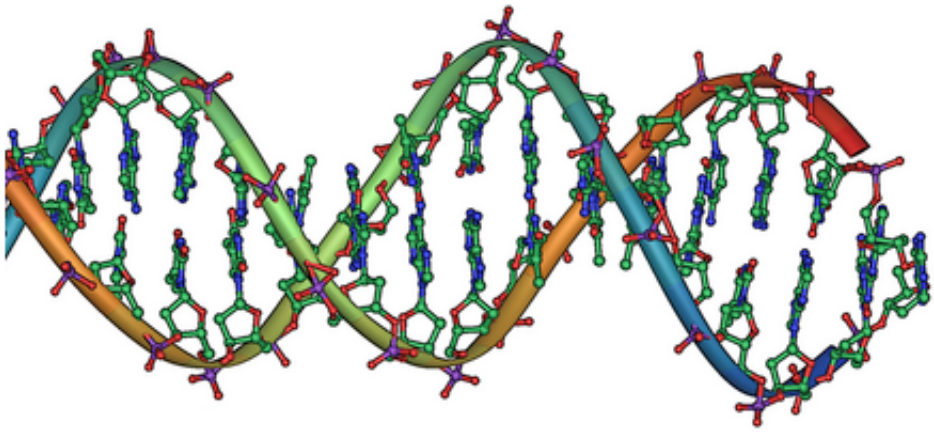
Study examines association of genetic variants with cognitive impairment

May 26 2015



DNA double helix. Credit: public domain

Individually rare but collectively common intermediate-size copy number variations may be negatively associated with educational attainment, according to a study in the May 26 issue of *JAMA*. Copy number variations (CNVs) are regions of the genome that differ in the number of segments of DNA.

The Database of Genomic Variants catalogs approximately 2.4 million DNA CNVs. Some of them have been previously implicated as causal of

a wide variety of traits and conditions. According to background information in the article large (defined as larger than 500 kb), recurrent CNVs have been particularly associated with developmental delay and intellectual disability (characterized by limited intellectual functioning and impaired adaptive behavior in everyday life) in symptomatic individuals ascertained in clinical settings.

Alexandre Reymond, Ph.D., and Katrin Männik, Ph.D., of the University of Lausanne, Switzerland, and colleagues used the population biobank of Estonia, which contains samples from 52,000 participants to explore the consequences of CNVs in a presumptively healthy population. General practitioners examined participants and filled out a questionnaire of health- and lifestyle-related questions, as well as reported diagnoses. For example, information was available regarding attained level of education for participants. Copy number variant analysis was conducted on a random sample of 7,877 individuals and genotype-phenotype associations with education and disease traits were evaluated. Phenotype is a characteristic of an individual that is the result of the interaction of the person's genetic makeup (genotype) and his or her environment.

Of the 7,877 in the Estonian cohort, the researchers identified 56 carriers of recurrent large CNVs associated with known syndromes. Many of these individuals had phenotypic features similar to symptomatic individuals ascertained in previous clinical studies.

A genome-wide evaluation of rare intermediate size CNVs (frequency ? 0.05 percent; ? 250 kb) identified 831 carriers (10.5 percent) in the tested population sample. This group of carriers had increased prevalence of intellectual disability and decreased education attainment. Eleven of 216 (5.1 percent) of carriers of a deletion of at least 250 kb and 5.9 percent of carriers of a duplication of at least l Mb had an intellectual disability compared with 1.7 percent in the Estonian cohort

without detected CNVs.

Of the deletion carriers, 33.5 percent did not graduate from high school while 39.1 percent of duplication carriers did not graduate high school compared to 25.3 percent in the Estonian population at large. These evidences for an association between rare intermediate size CNVs and lower educational attainment were further supported by analyses of cohorts including an intellectually high-functioning group of Estonians and 3 geographically distinct populations in the United Kingdom, the United States and Italy.

"Replication of these findings in additional population groups is warranted given the potential implications of this observation for genomics research, clinical care, and public health."

"The results reported by Mannik et al indicate that individually rare but collectively common intermediate-size CNVs contribute to the variance in educational attainment," writes James R. Lupski, M.D., Ph.D., D.Sc., of the Baylor College of Medicine, Houston, in an accompanying editorial.

"This phenotype is an objectively quantifiable trait that could trigger ordering of a genomic study capable of detecting CNV used in clinical care. With the recognition of a potentially causal mutation in an individual, tailored behavioral and educational interventions could be initiated with patients and family that could improve educational outcomes. Although changing a person's genome is not possible, identifying those with CNVs related to cognitive phenotypes could provide an opportunity to help them reach their fullest potential."

More information: DOI: 10.1001/jama.2015.4845
DOI: 10.1001/jama.2015.4846