New research about human genetic diseases and human development

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The density of transposable (jumping) elements between sex chromosomes in primates may have important consequences for the studies of human genetic diseases, say Penn State University researchers.

Erika Kvikstad, a 2009 Penn State Ph.D. graduate in genetics, and Kateryna Makova, an associate professor of biology at Penn State, used a statistical regression method to study the genomes of the human, chimpanzee, macaque, and orangutan, concluding that there is a strong sex-chromosome bias in the distribution of transposable elements, and providing insights about whether these non-coding, but important, DNA elements integrate themselves specifically into the male germline or

female germline, or integrate themselves into the genome during the early stages of embryogenesis. Their study will be published in the May 2010 issue of the scientific journal Genome Research.

According to Kvikstad, now a postdoctoral scholar at the Université Claude Bernard Lyon 1 in Lyon, France, the team chose to study primates because of the importance of human evolution, human disease, and the "unique availability of a very detailed description of the human genome -- more so than any other mammalian genome." The strides made in sequencing the human and other primate genomes have made this research possible only in the last decade. Makova, one of the researchers who contributed to the analysis of the macaque and chimpanzee genomes, notes that the sequence of the orangutan genome used in the Penn State study has not yet been published. Makova received special permission to use the orangutan data set in her study.

The team looked specifically at the densities of transposable elements, which are snippets of DNA capable of moving about, replicating themselves, and inserting copies within the genome. The classes of transposable elements are further distinguished by being short or long interspersed nuclear elements -- SINEs and LINEs. Kvikstad and Makova looked at one SINE family -- Alu sequences, which are about 300 base pairs long, -- and one LINE family -- L1 sequences, which can be thousands of bases long.

"The transposable elements that we chose to study, Alus and L1s, are significant because they are abundant," says Kvikstad. "They comprise about a third of the primate genome. They are actively moving around in the genome via a copy-and-paste retrotransposition mechanism, so they can create new variation; for example, human diseases and cancers."

Even more importantly, Kvikstad points out, "These transposable elements are highly abundant on the sex chromosomes -- X and Y --

which means they could be evolving uniquely because of the unusual nature of sex-chromosome transmission. The Y is paternally inherited, so it resides in the male germline only; the X spends two-thirds of its time in the female germline and one-third in the male germline. If there are germline-specific differences in the activity of transposable elements, for example, we should see clues to these differences in their sex-chromosome distributions."

The team's findings surprised Kvikstad and Makova. "Even after we corrected for regional genomic effects, we still observed a very strong sex-chromosome bias in distributions of transposable elements," says Makova. "This finding clearly indicates that there are biases according to which elements integrate into the genome. There also are differences between these two classes of elements. Our study suggests that Alus probably integrate mostly in the male germline, while L1s integrate in both male and female germlines, or they might integrate in early embryogenesis."

This bias has implications for understanding and perhaps someday even preventing and treating genetic diseases. "For us to really understand how the genetic diseases occur, we need to know when the elements integrate -- at what point in human development this occurs," says Makova. "We are studying evolution mostly, but our results are relevant to genetic diseases caused by insertions of transposable elements in the genome. For instance, Alu insertions are known to cause some types of neurofibromatosis, hemophilia, breast cancer, Apert syndrome, cholinesterase deficiency, and complement deficiency."

When transposable elements were first discovered in the 1940s, many in the scientific community labeled them as "junk" DNA. Says Makova, "I don't think many people agree that they are 'junk' DNA any longer. Many of these elements have function. Alu elements frequently possess the regulatory elements. Both the Alu and L1 elements are often

involved in recombination, the phenomenon under which the genome can undergo rearrangement and reshuffling."

Kvikstad and Makova spent a year analyzing the primate data. Previously, together with Francesca Chiaromonte, associate professor of statistics at Penn State, they had worked together on a project looking at primate insertions and deletions of a much smaller size, under 30 base pairs. "We are the first team to look into this much detail at the distribution of transposable elements on human sex chromosomes," Makova says.

Kvikstad points out other important implications of this study. "In particular, we noted that gene density was not a significant predictor of either Alu or L1 element density, at any evolutionary time point," she says. "By contrast, density of conserved non-coding DNA or 'most conserved elements' was a strong negative predictor of L1 density -- so L1 elements are scarce in regions of the genome that might contain many of these potentially functional noncoding DNAs. This is an important distinction, since previous studies inferring the action of natural selection in shaping the densities of transposable elements relied on gene density as a proxy for natural selection. Our results suggest that the potentially functional DNA residing in these most-conserved elements may be an additional hallmark of natural selection."

More information: genome.cshlp.org/

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