

**Research**

<b>Delayed DNA replication in haploid human embryonic stem cells</b> Matthew M. Edwards, Michael V. Zuccaro, Ido Sagi, Qiliang Ding, Dan Vershkov, Nissim Benvenisty, Dieter Egli, and Amnon Koren	2155
<b>Decoding the function of bivalent chromatin in development and cancer</b> Dhirendra Kumar, Senthilkumar Cinghu, Andrew J. Oldfield, Pengyi Yang, and Raja Jothi	2170 <sup>OA</sup>
<b>Epstein–Barr virus nuclear antigen 2 extensively rewires the human chromatin landscape at autoimmune risk loci</b> Ted Hong, Sreeja Parameswaran, Omer A. Donmez, Daniel Miller, Carmy Forney, Michael Lape, Mariana Saint Just Ribeiro, Jun Liang, Lee E. Edsall, Albert F. Magnusen, William Miller, Iouri Chepelev, John B. Harley, Bo Zhao, Leah C. Kottyan, and Matthew T. Weirauch	2185 <sup>OA</sup>
<b>A multi-enhancer <i>RET</i> regulatory code is disrupted in Hirschsprung disease</b> Sumantra Chatterjee, Kameko M. Karasaki, Lauren E. Fries, Ashish Kapoor, and Aravinda Chakravarti	2199
<b>Individualized VDJ recombination predisposes the available Ig sequence space</b> Andrei Slabodkin, Maria Chernigovskaya, Ivana Mikocziova, Rahmad Akbar, Lonneke Scheffer, Milena Pavlović, Habib Bashour, Igor Snapkov, Brij Bhushan Mehta, Cédric R. Weber, Jose Gutierrez-Marcos, Ludvig M. Sollid, Ingrid Hobæk Haff, Geir Kjetil Sandve, Philippe A. Robert, and Victor Greiff	2209 <sup>OA</sup>
<b>Mutagenesis of human genomes by endogenous mobile elements on a population scale</b> Nelson T. Chuang, Eugene J. Gardner, Diane M. Terry, Jonathan Crabtree, Anup A. Mahurkar, Guillermo L. Rivell, Charles C. Hong, James A. Perry, and Scott E. Devine	2225
<b><i>Alu</i> insertion variants alter gene transcript levels</b> Lindsay M. Payer, Jared P. Steranka, Maria S. Kryatova, Giacomo Grillo, Mathieu Lupien, Pedro P. Rocha, and Kathleen H. Burns	2236
<b>Structural variants are a major source of gene expression differences in humans and often affect multiple nearby genes</b> Alexandra J. Scott, Colby Chiang, and Ira M. Hall	2249 <sup>OA</sup>
<b>Human and rat skeletal muscle single-nuclei multi-omic integrative analyses nominate causal cell types, regulatory elements, and SNPs for complex traits</b> Peter Orchard, Nandini Manickam, Christa Ventresca, Swarooparani Vadlamudi, Arushi Varshney, Vivek Rai, Jeremy Kaplan, Claudia Lalancette, Karen L. Mohlke, Katherine Gallagher, Charles F. Burant, and Stephen C.J. Parker	2258

(continued)

<b>Evolutionary rewiring of the wheat transcriptional regulatory network by lineage-specific transposable elements</b>	<b>2276</b>
Yuyun Zhang, Zijuan Li, Yu'e Zhang, Kande Lin, Yuan Peng, Luhuan Ye, Yili Zhuang, Meiyue Wang, Yilin Xie, Jingyu Guo, Wan Teng, Yiping Tong, Wenli Zhang, Yongbiao Xue, Zhaobo Lang, and Yijing Zhang	
<b>Transcriptional activity and epigenetic regulation of transposable elements in the symbiotic fungus <i>Rhizophagus irregularis</i></b>	<b>2290<sup>OA</sup></b>
Alexandra Dallaire, Bethan F. Manley, Maya Wilkens, Iliana Bista, Clement Quan, Edouard Evangelisti, Charles R. Bradshaw, Navin B. Ramakrishna, Sebastian Schornack, Falk Butter, Uta Paszkowski, and Eric A. Miska	
<b>Intergenic ORFs as elementary structural modules of de novo gene birth and protein evolution</b>	<b>2303</b>
Chris Papadopoulos, Isabelle Callebaut, Jean-Christophe Gelly, Isabelle Hatin, Olivier Namy, Maxime Renard, Olivier Lespinet, and Anne Lopes	
<b>Different trajectories of polyploidization shape the genomic landscape of the <i>Brettanomyces bruxellensis</i> yeast species</b>	<b>2316<sup>OA</sup></b>
Chris Eberlein, Omar Abou Saada, Anne Friedrich, Warren Albertin, and Joseph Schacherer	
<b>Methods</b>	
<b>Genome-wide cancer-specific chromatin accessibility patterns derived from archival processed xenograft tumors</b>	<b>2327</b>
Shelsa S. Marcel, Austin L. Quimby, Melodie P. Noel, Oscar C. Jaimes, Marjan Mehrab-Mohseni, Suud A. Ashur, Brian Velasco, James K. Tsuruta, Sandeep K. Kasoji, Charlene M. Santos, Paul A. Dayton, Joel S. Parker, Ian J. Davis, and Samantha G. Pattenden	
<b>Quantifying full-length circular RNAs in cancer</b>	<b>2340</b>
Ken Hung-On Yu, Christina Huan Shi, Bo Wang, Savio Ho-Chit Chow, Grace Tin-Yun Chung, Raymond Wai-Ming Lung, Ke-En Tan, Yat-Yuen Lim, Anna Chi-Man Tsang, Kwok-Wai Lo, and Kevin Y. Yip	
<b>Global quantification exposes abundant low-level off-target activity by base editors</b>	<b>2354</b>
Ilana Buchumenski, Shalom Hillel Roth, Eli Kopel, Efrat Katsman, Ariel Feiglin, Erez Y. Levanon, and Eli Eisenberg	
<b>Reviewer Index</b>	<b>2362</b>

<sup>OA</sup>Open Access paper



**Cover** According to Greek mythology, the Phoenix is an immortal bird that regenerates periodically. Similarly, the birth and death of transposable elements (TEs) in the genome occur throughout eukaryotes and contribute to complex genome evolution. More than 85% of the wheat genome is composed of TEs, which participate in host transcriptional regulation via embedded transcription factor binding sites (TFBSs) that can be captured from the host genome. A significant proportion of wheat TFBSs comes from degraded TEs, which may be further captured and used by other TEs in the next regulatory innovation cycle, increasing the adaptability of the host. This is analogous to the rebirth of the Phoenix after suffering. In the illustration, the Phoenix on the DNA double helix represents TE-embedded TFBSs. Its tail is reminiscent of wheat. The insertion and degeneration of TEs next to the wheat-specific stress-responsive genes (mountain) rewire the regulatory network related to the evolution and adaptation of the wheat genome. (Cover illustration by Yuanyuan Wu, yyandesign@outlook.com. [For details, see Zhang et al., pp. 2276–2289.]