

7 References

- Abascal, F., Ezkurdia, I., Rodriguez-Rivas, J., Rodriguez, J.M., del Pozo, A., Vázquez, J., Valencia, A., and Tress, M.L. (2015). Alternatively Spliced Homologous Exons Have Ancient Origins and Are Highly Expressed at the Protein Level. *PLoS Comput. Biol.* **11**, e1004325.
- Aebersold, R., Agar, J.N., Amster, I.J., Baker, M.S., Bertozzi, C.R., Boja, E.S., Costello, C.E., Cravatt, B.F., Fenselau, C., Garcia, B.A., et al. (2018). How many human proteoforms are there? *Nat. Chem. Biol.* **14**, 206–214.
- Aebi, M., Hornig, H., Padgett, R.A., Reiser, J., and Weissmann, C. (1986). Sequence requirements for splicing of higher eukaryotic nuclear pre-mRNA. *Cell* **47**, 555–565.
- An, P., and Grabowski, P.J. (2007). Exon silencing by UAGG motifs in response to neuronal excitation. *PLoS Biol.* **5**, e36.
- Andersson, R., Enroth, S., Rada-Iglesias, A., Wadelius, C., and Komorowski, J. (2009). Nucleosomes are well positioned in exons and carry characteristic histone modifications. *Genome Res.* **19**, 1732–1741.
- Ares, M., Jr (2007). Sing the genome electric: excited cells adjust their splicing. *PLoS Biol.* **5**, e55.
- Artamonova, I.I., and Gelfand, M.S. (2007). Comparative genomics and evolution of alternative splicing: the pessimists' science. *Chem. Rev.* **107**, 3407–3430.
- Arzalluz-Luque, Á., and Conesa, A. (2018). Single-cell RNAseq for the study of isoforms-how is that possible? *Genome Biol.* **19**, 110.
- Ast, G. (2004). How did alternative splicing evolve? *Nat. Rev. Genet.* **5**, 773–782.
- Bacolla, A., and Wells, R.D. (2004). Non-B DNA conformations, genomic rearrangements, and human disease. *J. Biol. Chem.* **279**, 47411–47414.
- Bacolla, A., Tainer, J.A., Vasquez, K.M., and Cooper, D.N. (2016). Translocation and deletion breakpoints in cancer genomes are associated with potential non-B DNA-forming sequences. *Nucleic Acids Res.* **44**, 5673–5688.
- Baek, D., and Green, P. (2005). Sequence conservation, relative isoform frequencies, and nonsense-mediated decay in evolutionarily conserved alternative splicing. *Proc. Natl. Acad. Sci. U. S. A.* **102**, 12813–12818.
- Bang, I. (1910). Untersuchungen über die Guanylsäure. *Biochem. Z.* **26**, 293–311.
- Barash, Y., Calarco, J.A., Gao, W., Pan, Q., Wang, X., Shai, O., Blencowe, B.J., and Frey, B.J. (2010). Deciphering the splicing code. *Nature* **465**, 53–59.
- Barbosa-Morais, N.L., Irimia, M., Pan, Q., Xiong, H.Y., Gueroussov, S., Lee, L.J., Slobodeniuc, V., Kutter, C., Watt, S., Colak, R., et al. (2012). The evolutionary landscape of alternative splicing in vertebrate species. *Science* **338**, 1587–1593.
- Bartschat, S., and Samuelsson, T. (2010). U12 type introns were lost at multiple occasions during evolution. *BMC Genomics* **11**, 106.
- Bartys, N., Kierzek, R., and Lisowiec-Wachnicka, J. (2019). The regulation properties of RNA secondary structure in alternative splicing. *Biochim. Biophys. Acta Gene Regul. Mech.* **194401**.
- Beachy, P.A., Helfand, S.L., and Hogness, D.S. (1985). Segmental distribution of bithorax complex

proteins during *Drosophila* development. *Nature* 313, 545–551.

Behzadnia, N., Golas, M.M., Hartmuth, K., Sander, B., Kastner, B., Deckert, J., Dube, P., Will, C.L., Urlaub, H., Stark, H., et al. (2007). Composition and three-dimensional EM structure of double affinity-purified, human prespliceosomal A complexes. *The EMBO Journal* 26, 1737–1748.

Benhalevy, D., Gupta, S.K., Danan, C.H., Ghosal, S., Sun, H.-W., Kazemier, H.G., Paeschke, K., Hafner, M., and Juranek, S.A. (2017). The Human CCHC-type Zinc Finger Nucleic Acid-Binding Protein Binds G-Rich Elements in Target mRNA Coding Sequences and Promotes Translation. *Cell Reports* 18, 2979–2990.

Benson, D.A., Karsch-Mizrachi, I., Lipman, D.J., Ostell, J., and Wheeler, D.L. (2004). GenBank: update. *Nucleic Acids Res.* 32, D23–D26.

Bevilacqua, P.C., Ritchey, L.E., Su, Z., and Assmann, S.M. (2016a). Genome-Wide Analysis of RNA Secondary Structure. *Annu. Rev. Genet.* 50, 235–266.

Bevilacqua, P.C., Ritchey, L.E., Su, Z., and Assmann, S.M. (2016b). Genome-Wide Analysis of RNA Secondary Structure. *Annu. Rev. Genet.* 50, 235–266.

Bhattacharyya, D., Mirihana Arachchilage, G., and Basu, S. (2016). Metal Cations in G-Quadruplex Folding and Stability. *Front Chem* 4, 38.

Biffi, G., Tannahill, D., McCafferty, J., and Balasubramanian, S. (2013). Quantitative visualization of DNA G-quadruplex structures in human cells. *Nat. Chem.* 5, 182–186.

Biffi, G., Di Antonio, M., Tannahill, D., and Balasubramanian, S. (2014). Visualization and selective chemical targeting of RNA G-quadruplex structures in the cytoplasm of human cells. *Nat. Chem.* 6, 75–80.

Bitton, D.A., Rallis, C., Jeffares, D.C., Smith, G.C., Chen, Y.Y.C., Codlin, S., Marguerat, S., and Bähler, J. (2014). LaSSO, a strategy for genome-wide mapping of intronic lariats and branch points using RNA-seq. *Genome Res.* 24, 1169–1179.

Black, D.L. (1991). Does steric interference between splice sites block the splicing of a short c-src neuron-specific exon in non-neuronal cells? *Genes Dev.* 5, 389–402.

Blazquez, L., Emmett, W., Faraway, R., Pineda, J.M.B., Bajew, S., Gohr, A., Haberman, N., Sibley, C.R., Bradley, R.K., Irimia, M., et al. (2018). Exon Junction Complex Shapes the Transcriptome by Repressing Recursive Splicing. *Mol. Cell* 72, 496–509.e9.

Blencowe, B.J. (2017). The Relationship between Alternative Splicing and Proteomic Complexity. *Trends Biochem. Sci.* 42, 407–408.

Bochman, M.L., Paeschke, K., and Zakian, V.A. (2012). DNA secondary structures: stability and function of G-quadruplex structures. *Nat. Rev. Genet.* 13, 770–780.

Boehm, V., Britto-Borges, T., Steckelberg, A.-L., Singh, K.K., Gerbracht, J.V., Gueney, E., Blazquez, L., Altmüller, J., Dieterich, C., and Gehring, N.H. (2018). Exon Junction Complexes Suppress Spurious Splice Sites to Safeguard Transcriptome Integrity. *Mol. Cell* 72, 482–495.e7.

Bornstein, S.R., Ehrhart-Bornstein, M., Androutsellis-Theotokis, A., Eisenhofer, G., Vukicevic, V., Licinio, J., Wong, M.L., Calissano, P., Nisticò, G., Preziosi, P., et al. (2012). Chromaffin cells: the peripheral brain. *Mol. Psychiatry* 17, 354–358.

Brackenridge, S. (2003). Efficient use of a “dead-end” GA 5' splice site in the human fibroblast growth factor receptor genes. *The EMBO Journal* 22, 1620–1631.

Bradley, R.K., Merkin, J., Lambert, N.J., and Burge, C.B. (2012). Alternative splicing of RNA triplets is often regulated and accelerates proteome evolution. *PLoS Biol.* 10, e1001229.

- Braunschweig, U., Barbosa-Morais, N.L., Pan, Q., Nachman, E.N., Alipanahi, B., Gonatopoulos-Pournatzis, T., Frey, B., Irimia, M., and Blencowe, B.J. (2014). Widespread intron retention in mammals functionally tunes transcriptomes. *Genome Res.* 24, 1774–1786.
- Brinegar, A.E., Xia, Z., Loehr, J.A., Li, W., Rodney, G.G., and Cooper, T.A. (2017). Extensive alternative splicing transitions during postnatal skeletal muscle development are required for calcium handling functions.
- Brugge, J.S., Cotton, P.C., Queral, A.E., Barrett, J.N., Nonner, D., and Keane, R.W. (1985). Neurones express high levels of a structurally modified, activated form of pp60c-src. *Nature* 316, 554–557.
- Buljan, M., Chalancon, G., Eustermann, S., Wagner, G.P., Fuxreiter, M., Bateman, A., and Babu, M.M. (2012). Tissue-specific splicing of disordered segments that embed binding motifs rewires protein interaction networks. *Mol. Cell* 46, 871–883.
- Buratti, E., and Baralle, F.E. (2004). Influence of RNA secondary structure on the pre-mRNA splicing process. *Mol. Cell. Biol.* 24, 10505–10514.
- Buratti, E., Muro, A.F., Giombi, M., Gherbassi, D., Iaconcig, A., and Baralle, F.E. (2004). RNA folding affects the recruitment of SR proteins by mouse and human polypyrimidic enhancer elements in the fibronectin EDA exon. *Mol. Cell. Biol.* 24, 1387–1400.
- Burge, C.B., Tuschl, T., and Sharp, P.A. (1999). Splicing of precursors to mRNAs by the spliceosomes. *Cold Spring Harbor Monogr. Ser.* 37, 525–560.
- Burset, M. (2000). Analysis of canonical and non-canonical splice sites in mammalian genomes. *Nucleic Acids Research* 28, 4364–4375.
- Calarco, J.A., Superina, S., O'Hanlon, D., Gabut, M., Raj, B., Pan, Q., Skalska, U., Clarke, L., Gelinas, D., van der Kooy, D., et al. (2009). Regulation of vertebrate nervous system alternative splicing and development by an SR-related protein. *Cell* 138, 898–910.
- Capra, J.A., Paeschke, K., Singh, M., and Zakian, V.A. (2010). G-quadruplex DNA sequences are evolutionarily conserved and associated with distinct genomic features in *Saccharomyces cerevisiae*. *PLoS Comput. Biol.* 6, e1000861.
- Caputi, M., and Zahler, A.M. (2001). Determination of the RNA Binding Specificity of the Heterogeneous Nuclear Ribonucleoprotein (hnRNP) H/H'/F/2H9 Family. *J. Biol. Chem.* 276, 43850–43859.
- Carmel, I., Tal, S., Vig, I., and Ast, G. (2004). Comparative analysis detects dependencies among the 5' splice-site positions. *RNA* 10, 828–840.
- Catterall, W.A. (2011). Voltage-gated calcium channels. *Cold Spring Harb. Perspect. Biol.* 3, a003947.
- Cer, R.Z., Donohue, D.E., Mudunuri, U.S., Temiz, N.A., Loss, M.A., Starner, N.J., Halusa, G.N., Volfovsky, N., Yi, M., Luke, B.T., et al. (2013). Non-B DB v2.0: a database of predicted non-B DNA-forming motifs and its associated tools. *Nucleic Acids Res.* 41, D94–D100.
- Chakraborty, P., and Grosse, F. (2011). Human DHX9 helicase preferentially unwinds RNA-containing displacement loops (R-loops) and G-quadruplexes. *DNA Repair* 10, 654–665.
- Chambers, V.S., Marsico, G., Boutell, J.M., Di Antonio, M., Smith, G.P., and Balasubramanian, S. (2015). High-throughput sequencing of DNA G-quadruplex structures in the human genome. *Nat. Biotechnol.* 33, 877–881.
- Chan, W.H., Komada, M., Fukushima, T., Southard-Smith, E.M., Anderson, C.R., and Wakefield, M.J. (2019). RNA-seq of Isolated Chromaffin Cells Highlights the Role of Sex-Linked and Imprinted Genes in Adrenal Medulla Development. *Sci. Rep.* 9, 3929.
- Chang, H., Lim, J., Ha, M., and Kim, V.N. (2014). TAIL-seq: genome-wide determination of poly(A) tail

length and 3' end modifications. *Mol. Cell* 53, 1044–1052.

Chen, L., Chen, J.-Y., Zhang, X., Gu, Y., Xiao, R., Shao, C., Tang, P., Qian, H., Luo, D., Li, H., et al. (2017). R-ChIP Using Inactive RNase H Reveals Dynamic Coupling of R-loops with Transcriptional Pausing at Gene Promoters. *Mol. Cell* 68, 745–757.e5.

Chernyavsky, A.I., Arredondo, J., Piser, T., Karlsson, E., and Grando, S.A. (2008). Differential Coupling of M1 Muscarinic and $\alpha 7$ Nicotinic Receptors to Inhibition of Pemphigus Acantholysis. *J. Biol. Chem.* 283, 3401–3408.

Cocquerelle, C., Mascrez, B., Hétuin, D., and Bailleul, B. (1993). Mis-splicing yields circular RNA molecules. *FASEB J.* 7, 155–160.

Cocquet, J., Chong, A., Zhang, G., and Veitia, R.A. (2006). Reverse transcriptase template switching and false alternative transcripts. *Genomics* 88, 127–131.

Coelho, M.B., and Smith, C.W.J. (2014). Regulation of Alternative Pre-mRNA Splicing. In *Spliceosomal Pre-mRNA Splicing: Methods and Protocols*, K.J. Hertel, ed. (Totowa, NJ: Humana Press), pp. 55–82.

Cogoi, S., and Xodo, L.E. (2006). G-quadruplex formation within the promoter of the KRAS proto-oncogene and its effect on transcription. *Nucleic Acids Res.* 34, 2536–2549.

Collett, J.W., and Steele, R.E. (1992). Identification and developmental expression of Src+ mRNAs in *Xenopus laevis*. *Dev. Biol.* 152, 194–198.

Coolidge, C.J., Seely, R.J., and Patton, J.G. (1997). Functional analysis of the polypyrimidine tract in pre-mRNA splicing. *Nucleic Acids Res.* 25, 888–896.

Cooper, T.A., and Ordahl, C.P. (1985). A single cardiac troponin T gene generates embryonic and adult isoforms via developmentally regulated alternate splicing. *J. Biol. Chem.* 260, 11140–11148.

Cooper, D.A., Cortés-López, M., and Miura, P. (2018). Genome-Wide circRNA Profiling from RNA-seq Data. In *Circular RNAs: Methods and Protocols*, C. Dieterich, and A. Papantonis, eds. (New York, NY: Springer New York), pp. 27–41.

Cox, J.S., and Walter, P. (1996). A novel mechanism for regulating activity of a transcription factor that controls the unfolded protein response. *Cell* 87, 391–404.

Crossley, M.P., Bocek, M., and Cimprich, K.A. (2019). R-Loops as Cellular Regulators and Genomic Threats. *Mol. Cell* 73, 398–411.

DeBoever, C., Ghia, E.M., Shepard, P.J., Rassenti, L., Barrett, C.L., Jepsen, K., Jamieson, C.H.M., Carson, D., Kipps, T.J., and Frazer, K.A. (2015). Transcriptome sequencing reveals potential mechanism of cryptic 3' splice site selection in SF3B1-mutated cancers. *PLoS Comput. Biol.* 11, e1004105.

De Conti, L., Baralle, M., and Buratti, E. (2013). Exon and intron definition in pre-mRNA splicing. *Wiley Interdiscip. Rev. RNA* 4, 49–60.

Desai, A., Hu, Z., French, C.E., Lloyd, J.P.B., and Brenner, S.E. (2020). Networks of Splice Factor Regulation by Unproductive Splicing Coupled With Nonsense Mediated mRNA Decay.

Dias Neto, E., Correa, R.G., Verjovski-Almeida, S., Briones, M.R., Nagai, M.A., da Silva, W., Jr, Zago, M.A., Bordin, S., Costa, F.F., Goldman, G.H., et al. (2000). Shotgun sequencing of the human transcriptome with ORF expressed sequence tags. *Proc. Natl. Acad. Sci. U. S. A.* 97, 3491–3496.

Didiot, M.-C., Tian, Z., Schaeffer, C., Subramanian, M., Mandel, J.-L., and Moine, H. (2008). The G-quartet containing FMRP binding site in FMR1 mRNA is a potent exonic splicing enhancer. *Nucleic Acids Res.* 36, 4902–4912.

- Di Tommaso, P., Chatzou, M., Floden, E.W., Barja, P.P., Palumbo, E., and Notredame, C. (2017). Nextflow enables reproducible computational workflows. *Nat. Biotechnol.* 35, 316–319.
- Dobin, A., Davis, C.A., Schlesinger, F., Drenkow, J., Zaleski, C., Jha, S., Batut, P., Chaisson, M., and Gingeras, T.R. (2013). STAR: ultrafast universal RNA-seq aligner. *Bioinformatics* 29, 15–21.
- Dominguez, C., Fisette, J.-F., Chabot, B., and Allain, F.H.-T. (2010). Structural basis of G-tract recognition and encaging by hnRNP F quasi-RRMs. *Nat. Struct. Mol. Biol.* 17, 853–861.
- Dominguez, D., Freese, P., Alexis, M.S., Su, A., Hochman, M., Palden, T., Bazile, C., Lambert, N.J., Van Nostrand, E.L., Pratt, G.A., et al. (2018). Sequence, Structure, and Context Preferences of Human RNA Binding Proteins. *Mol. Cell* 70, 854–867.e9.
- Dominski, Z., and Kole, R. (1991). Selection of splice sites in pre-mRNAs with short internal exons. *Mol. Cell. Biol.* 11, 6075–6083.
- Downie, J.M. (2017). Surveying the Genetic Risk Landscape Of Amyotrophic Lateral Sclerosis in The Era of Next-Generation Sequencing. The University of Utah.
- Du, X., Gertz, E.M., Wojtowicz, D., Zhabinskaya, D., Levens, D., Benham, C.J., Schäffer, A.A., and Przytycka, T.M. (2014). Potential non-B DNA regions in the human genome are associated with higher rates of nucleotide mutation and expression variation. *Nucleic Acids Res.* 42, 12367–12379.
- Duff, M.O., Olson, S., Wei, X., Garrett, S.C., Osman, A., Bolisetty, M., Plocik, A., Celniker, S.E., and Graveley, B.R. (2015). Genome-wide identification of zero nucleotide recursive splicing in *Drosophila*. *Nature* 521, 376–379.
- Dujardin, G., Lafaille, C., Petrillo, E., Buggiano, V., Gómez Acuña, L.I., Fiszbein, A., Godoy Herz, M.A., Nieto Moreno, N., Muñoz, M.J., Alló, M., et al. (2013). Transcriptional elongation and alternative splicing. *Biochim. Biophys. Acta* 1829, 134–140.
- Duquette, M.L., Handa, P., Vincent, J.A., Taylor, A.F., and Maizels, N. (2004). Intracellular transcription of G-rich DNAs induces formation of G-loops, novel structures containing G4 DNA. *Genes Dev.* 18, 1618–1629.
- Dye, M.J., Gromak, N., and Proudfoot, N.J. (2006). Exon tethering in transcription by RNA polymerase II. *Mol. Cell* 21, 849–859.
- Eddy, J., and Maizels, N. (2008). Conserved elements with potential to form polymorphic G-quadruplex structures in the first intron of human genes. *Nucleic Acids Res.* 36, 1321–1333.
- Ehlers, M.D., Tingley, W.G., and Huganir, R.L. (1995). Regulated subcellular distribution of the NR1 subunit of the NMDA receptor. *Science* 269, 1734–1737.
- Ehrmann, I., Crichton, J.H., Gazzara, M.R., James, K., Liu, Y., Grellscheid, S.N., Curk, T., de Rooij, D., Steyn, J.S., Cockell, S., et al. (2019). An ancient germ cell-specific RNA-binding protein protects the germline from cryptic splice site poisoning. *Elife* 8.
- Ellis, J.D., Barrios-Rodiles, M., Colak, R., Irimia, M., Kim, T., Calarco, J.A., Wang, X., Pan, Q., O'Hanlon, D., Kim, P.M., et al. (2012). Tissue-specific alternative splicing remodels protein-protein interaction networks. *Mol. Cell* 46, 884–892.
- ENCODE Project Consortium (2004). The ENCODE (ENCyclopedia Of DNA Elements) Project. *Science* 306, 636–640.
- Engström, P.G., Steijger, T., Sipos, B., Grant, G.R., Kahles, A., Rätsch, G., Goldman, N., Hubbard, T.J., Harrow, J., Guigó, R., et al. (2013). Systematic evaluation of spliced alignment programs for RNA-seq data. *Nat. Methods* 10, 1185–1191.
- Erkelenz, S., Theiss, S., Kaisers, W., Ptok, J., Walotka, L., Müller, L., Hillebrand, F., Brillen, A.-L., Sladek, M., and Schaal, H. (2018). Ranking noncanonical 5' splice site usage by genome-wide

- RNA-seq analysis and splicing reporter assays. *Genome Res.* 28, 1826–1840.
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P., Haw, R., Jassal, B., Korninger, F., May, B., et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res.* 46, D649–D655.
- Fay, M.M., Lyons, S.M., and Ivanov, P. (2017). RNA G-Quadruplexes in Biology: Principles and Molecular Mechanisms. *J. Mol. Biol.* 429, 2127–2147.
- Fiszbein, A., and Kornblihtt, A.R. (2017). Alternative splicing switches: Important players in cell differentiation. *Bioessays* 39.
- Florea, L., Hartzell, G., Zhang, Z., Rubin, G.M., and Miller, W. (1998). A computer program for aligning a cDNA sequence with a genomic DNA sequence. *Genome Res.* 8, 967–974.
- Forbes, S.A., Bindal, N., Bamford, S., Cole, C., Kok, C.Y., Beare, D., Jia, M., Shepherd, R., Leung, K., Menzies, A., et al. (2011). COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. *Nucleic Acids Res.* 39, D945–D950.
- Fox-Walsh, K.L., Dou, Y., Lam, B.J., Hung, S.-P., Baldi, P.F., and Hertel, K.J. (2005). The architecture of pre-mRNAs affects mechanisms of splice-site pairing. *Proc. Natl. Acad. Sci. U. S. A.* 102, 16176–16181.
- Frazee, A.C., Jaffe, A.E., Langmead, B., and Leek, J.T. (2015). Polyester: simulating RNA-seq datasets with differential transcript expression. *Bioinformatics* 31, 2778–2784.
- Furlanis, E., Traunmüller, L., Fucile, G., and Scheiffele, P. (2019). Landscape of ribosome-engaged transcript isoforms reveals extensive neuronal-cell-class-specific alternative splicing programs. *Nat. Neurosci.*
- Gaffney, D.J., McVicker, G., Pai, A.A., Fondufe-Mittendorf, Y.N., Lewellen, N., Michelini, K., Widom, J., Gilad, Y., and Pritchard, J.K. (2012). Controls of nucleosome positioning in the human genome. *PLoS Genet.* 8, e1003036.
- Gandal, M.J., Zhang, P., Hadjimichael, E., Walker, R.L., Chen, C., Liu, S., Won, H., van Bakel, H., Varghese, M., Wang, Y., et al. (2018). Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* 362.
- Garalde, D.R., Snell, E.A., Jachimowicz, D., Sipos, B., Lloyd, J.H., Bruce, M., Pantic, N., Admassu, T., James, P., Warland, A., et al. (2018). Highly parallel direct RNA sequencing on an array of nanopores. *Nat. Methods* 15, 201–206.
- Garber, M., Grabherr, M.G., Guttman, M., and Trapnell, C. (2011). Computational methods for transcriptome annotation and quantification using RNA-seq. *Nat. Methods* 8, 469–477.
- Garg, K., and Green, P. (2007). Differing patterns of selection in alternative and constitutive splice sites. *Genome Res.* 17, 1015–1022.
- Garrido-Martín, D., Palumbo, E., Guigó, R., and Breschi, A. (2018). ggsashimi: Sashimi plot revised for browser- and annotation-independent splicing visualization. *PLoS Comput. Biol.* 14, e1006360.
- Gaspard, N., Bouschet, T., Hourez, R., Dimidschstein, J., Naeije, G., van den Ameele, J., Espuny-Camacho, I., Herpoel, A., Passante, L., Schiffmann, S.N., et al. (2008). An intrinsic mechanism of corticogenesis from embryonic stem cells. *Nature* 455, 351–357.
- Gelfman, S., Burstein, D., Penn, O., Savchenko, A., Amit, M., Schwartz, S., Pupko, T., and Ast, G. (2012). Changes in exon-intron structure during vertebrate evolution affect the splicing pattern of exons. *Genome Res.* 22, 35–50.
- Gellert, M., Lipsett, M.N., and Davies, D.R. (1962). Helix formation by guanylic acid. *Proc. Natl. Acad.*

Sci. U. S. A. 48, 2013–2018.

Georgakopoulos-Soares, I., Morganella, S., Jain, N., Hemberg, M., and Nik-Zainal, S. (2018). Noncanonical secondary structures arising from non-B DNA motifs are determinants of mutagenesis. *Genome Res.* 28, 1264–1271.

Georgakopoulos-Soares, I., Parada, G.E., Wong, H.Y., Miska, E.A., Kwok, C.K., and Hemberg, M. Alternative splicing modulation by G-quadruplexes.

Georgakopoulos-Soares, I., Koh, G., Jiricny, J., Hemberg, M., and Nik-Zainal, S. Transcription-coupled repair and mismatch repair contribute towards preserving genome integrity at mononucleotide repeat tracts.

Ghosh, A., and Bansal, M. (2003). A glossary of DNA structures from A to Z. *Acta Crystallographica Section D Biological Crystallography* 59, 620–626.

Goecks, J., Nekrutenko, A., Taylor, J., and Galaxy Team (2010). Galaxy: a comprehensive approach for supporting accessible, reproducible, and transparent computational research in the life sciences. *Genome Biol.* 11, R86.

Gokce, O., Stanley, G.M., Treutlein, B., Neff, N.F., Camp, J.G., Malenka, R.C., Rothwell, P.E., Fuccillo, M.V., Südhof, T.C., and Quake, S.R. (2016). Cellular Taxonomy of the Mouse Striatum as Revealed by Single-Cell RNA-Seq. *Cell Rep.* 16, 1126–1137.

Gomez, D., Lemarteleur, T., Lacroix, L., Mailliet, P., Mergny, J.-L., and Riou, J.-F. (2004). Telomerase downregulation induced by the G-quadruplex ligand 12459 in A549 cells is mediated by hTERT RNA alternative splicing. *Nucleic Acids Res.* 32, 371–379.

Gonatopoulos-Pournatzis, T., and Blencowe, B.J. (2020). Microexons: at the nexus of nervous system development, behaviour and autism spectrum disorder. *Curr. Opin. Genet. Dev.* 65, 22–33.

Gonatopoulos-Pournatzis, T., Wu, M., Braunschweig, U., Roth, J., Han, H., Best, A.J., Raj, B., Aregger, M., O'Hanlon, D., Ellis, J.D., et al. (2018). Genome-wide CRISPR-Cas9 Interrogation of Splicing Networks Reveals a Mechanism for Recognition of Autism-Misregulated Neuronal Microexons. *Mol. Cell* 72, 510–524.e12.

Gonatopoulos-Pournatzis, T., Aregger, M., Brown, K.R., Farhangmehr, S., Braunschweig, U., Ward, H.N., Ha, K.C.H., Weiss, A., Billmann, M., Durbic, T., et al. (2020). Genetic interaction mapping and exon-resolution functional genomics with a hybrid Cas9-Cas12a platform. *Nat. Biotechnol.* 38, 638–648.

Graveley, B.R. (2001). Alternative splicing: increasing diversity in the proteomic world. *Trends Genet.* 17, 100–107.

Graveley, B.R. (2005). Mutually exclusive splicing of the insect Dscam pre-mRNA directed by competing intronic RNA secondary structures. *Cell* 123, 65–73.

Grüning, B., Dale, R., Sjödin, A., Chapman, B.A., Rowe, J., Tomkins-Tinch, C.H., Valieris, R., Köster, J., and Bioconda Team (2018). Bioconda: sustainable and comprehensive software distribution for the life sciences. *Nat. Methods* 15, 475–476.

GTEX Consortium (2013). The Genotype-Tissue Expression (GTEX) project. *Nat. Genet.* 45, 580–585.

GTEX Consortium (2015). Human genomics. The Genotype-Tissue Expression (GTEX) pilot analysis: multitissue gene regulation in humans. *Science* 348, 648–660.

Guiblet, W.M., Cremona, M.A., Cechova, M., Harris, R.S., Kejnovská, I., Kejnovsky, E., Eckert, K., Chiaromonte, F., and Makova, K.D. (2018). Long-read sequencing technology indicates genome-wide effects of non-B DNA on polymerization speed and error rate. *Genome Res.* 28, 1767–1778.

Guo, J.U., and Bartel, D.P. (2016). RNA G-quadruplexes are globally unfolded in eukaryotic cells and

depleted in bacteria. *Science* 353.

Guo, M., Lo, P.C., and Mount, S.M. (1993). Species-specific signals for the splicing of a short Drosophila intron *in vitro*. *Mol. Cell. Biol.* 13, 1104–1118.

Guth, S., Martínez, C., Gaur, R.K., and Valcárcel, J. (1999). Evidence for substrate-specific requirement of the splicing factor U2AF(35) and for its function after polypyrimidine tract recognition by U2AF(65). *Mol. Cell. Biol.* 19, 8263–8271.

Han, K., Yeo, G., An, P., Burge, C.B., and Grabowski, P.J. (2005). A combinatorial code for splicing silencing: UAGG and GGGG motifs. *PLoS Biol.* 3, e158.

Hänsel-Hertsch, R., Beraldi, D., Lensing, S.V., Marsico, G., Zyner, K., Parry, A., Di Antonio, M., Pike, J., Kimura, H., Narita, M., et al. (2016). G-quadruplex structures mark human regulatory chromatin. *Nat. Genet.* 48, 1267–1272.

Hänsel-Hertsch, R., Di Antonio, M., and Balasubramanian, S. (2017). DNA G-quadruplexes in the human genome: detection, functions and therapeutic potential. *Nat. Rev. Mol. Cell Biol.* 18, 279–284.

Harrow, J., Denoeud, F., Frankish, A., Reymond, A., Chen, C.-K., Chrast, J., Lagarde, J., Gilbert, J.G.R., Storey, R., Swarbreck, D., et al. (2006). GENCODE: producing a reference annotation for ENCODE. *Genome Biol.* 7 *Suppl 1*, S4.1–9.

Hastings, M.L., and Krainer, A.R. (2001). Pre-mRNA splicing in the new millennium. *Curr. Opin. Cell Biol.* 13, 302–309.

Hermey, G., Blüthgen, N., and Kuhl, D. (2017). Neuronal activity-regulated alternative mRNA splicing. *Int. J. Biochem. Cell Biol.* 91, 184–193.

Hinrichs, A.S., Karolchik, D., Baertsch, R., Barber, G.P., Bejerano, G., Clawson, H., Diekhans, M., Furey, T.S., Harte, R.A., Hsu, F., et al. (2006). The UCSC genome browser database: update 2006. *Nucleic Acids Res.* 34, D590–D598.

Hodges, C., Bintu, L., Lubkowska, L., Kashlev, M., and Bustamante, C. (2009). Nucleosomal fluctuations govern the transcription dynamics of RNA polymerase II. *Science* 325, 626–628.

Hollander, D., Naftelberg, S., Lev-Maor, G., Kornblith, A.R., and Ast, G. (2016). How Are Short Exons Flanked by Long Introns Defined and Committed to Splicing? *Trends Genet.* 32, 596–606.

Hood, L., and Galas, D. (2003). The digital code of DNA. *Nature* 421, 444–448.

Houseley, J., and Tollervey, D. (2010). Apparent non-canonical trans-splicing is generated by reverse transcriptase *in vitro*. *PLoS One* 5, e12271.

Howe, K.J., and Ares, M., Jr (1997). Intron self-complementarity enforces exon inclusion in a yeast pre-mRNA. *Proc. Natl. Acad. Sci. U. S. A.* 94, 12467–12472.

Hsu, F., Kent, W.J., Clawson, H., Kuhn, R.M., Diekhans, M., and Haussler, D. (2006). The UCSC Known Genes. *Bioinformatics* 22, 1036–1046.

Huang, H., Zhang, J., Harvey, S.E., Hu, X., and Cheng, C. (2017). RNA G-quadruplex secondary structure promotes alternative splicing via the RNA-binding protein hnRNPf. *Genes Dev.* 31, 2296–2309.

Hubbard, T., Barker, D., Birney, E., Cameron, G., Chen, Y., Clark, L., Cox, T., Cuff, J., Curwen, V., Down, T., et al. (2002). The Ensembl genome database project. *Nucleic Acids Res.* 30, 38–41.

Huntsman, M.M., Tran, B.-V., Potkin, S.G., Bunney, W.E., and Jones, E.G. (1998). Altered ratios of alternatively spliced long and short $\gamma 2$ subunit mRNAs of the γ -amino butyrate type A receptor in prefrontal cortex of schizophrenics. *Proc. Natl. Acad. Sci. U. S. A.* 95, 15066–15071.

- Huppert, J.L., and Balasubramanian, S. (2007). G-quadruplexes in promoters throughout the human genome. *Nucleic Acids Res.* 35, 406–413.
- Hurley, L.H., Von Hoff, D.D., Siddiqui-Jain, A., and Yang, D. (2006). Drug targeting of the c-MYC promoter to repress gene expression via a G-quadruplex silencer element. *Semin. Oncol.* 33, 498–512.
- Iqbal, Z., Willemsen, M.H., Papon, M.-A., Musante, L., Benevento, M., Hu, H., Venselaar, H., Wissink-Lindhout, W.M., Vulto-van Silfhout, A.T., Vissers, L.E.L.M., et al. (2015). Homozygous SLC6A17 mutations cause autosomal-recessive intellectual disability with progressive tremor, speech impairment, and behavioral problems. *Am. J. Hum. Genet.* 96, 386–396.
- Irimia, M., Weatheritt, R.J., Ellis, J.D., Parikshak, N.N., Gonatopoulos-Pournatzis, T., Babor, M., Quesnel-Vallières, M., Tapial, J., Raj, B., O'Hanlon, D., et al. (2014). A highly conserved program of neuronal microexons is misregulated in autistic brains. *Cell* 159, 1511–1523.
- Jackson, I.J. (1991). A reappraisal of non-consensus mRNA splice sites. *Nucleic Acids Res.* 19, 3795–3798.
- Jeck, W.R., Sorrentino, J.A., Wang, K., Slevin, M.K., Burd, C.E., Liu, J., Marzluff, W.F., and Sharpless, N.E. (2013). Circular RNAs are abundant, conserved, and associated with ALU repeats. *RNA* 19, 141–157.
- Jiang, M., Anderson, J., Gillespie, J., and Mayne, M. (2008). uShuffle: a useful tool for shuffling biological sequences while preserving the k-let counts. *BMC Bioinformatics* 9, 192.
- Jin, Y., Yang, Y., and Zhang, P. (2011). New insights into RNA secondary structure in the alternative splicing of pre-mRNAs. *RNA Biol.* 8, 450–457.
- Kadener, S. (2001). Antagonistic effects of T-Ag and VP16 reveal a role for RNA pol II elongation on alternative splicing. *The EMBO Journal* 20, 5759–5768.
- Kahles, A., Lehmann, K.-V., Toussaint, N.C., Hüser, M., Stark, S.G., Sachsenberg, T., Stegle, O., Kohlbacher, O., Sander, C., Cancer Genome Atlas Research Network, et al. (2018). Comprehensive Analysis of Alternative Splicing Across Tumors from 8,705 Patients. *Cancer Cell* 34, 211–224.e6.
- Kamiguchi, H., and Lemmon, V. (1998). A neuronal form of the cell adhesion molecule L1 contains a tyrosine-based signal required for sorting to the axonal growth cone. *J. Neurosci.* 18, 3749–3756.
- Kamiguchi, H., Long, K.E., Pendergast, M., Schaefer, A.W., Rapoport, I., Kirchhausen, T., and Lemmon, V. (1998). The neural cell adhesion molecule L1 interacts with the AP-2 adaptor and is endocytosed via the clathrin-mediated pathway. *J. Neurosci.* 18, 5311–5321.
- Karolchik, D., Baertsch, R., Diekhans, M., Furey, T.S., Hinrichs, A., Lu, Y.T., Roskin, K.M., Schwartz, M., Sugnet, C.W., Thomas, D.J., et al. (2003). The UCSC Genome Browser Database. *Nucleic Acids Res.* 31, 51–54.
- Kaushik, M., Kaushik, S., Roy, K., Singh, A., Mahendru, S., Kumar, M., Chaudhary, S., Ahmed, S., and Kukreti, S. (2016). A bouquet of DNA structures: Emerging diversity. *Biochem Biophys Rep* 5, 388–395.
- Keenan, S., Wetherill, S.J., Ugbode, C.I., Chawla, S., Brackenbury, W.J., and Evans, G.J.O. (2017). Inhibition of N1-Src kinase by a specific SH3 peptide ligand reveals a role for N1-Src in neurite elongation by L1-CAM. *Sci. Rep.* 7, 43106.
- Keren, H., Lev-Maor, G., and Ast, G. (2010). Alternative splicing and evolution: diversification, exon definition and function. *Nat. Rev. Genet.* 11, 345–355.
- Kikin, O., D'Antonio, L., and Bagga, P.S. (2006). QGRS Mapper: a web-based server for predicting G-quadruplexes in nucleotide sequences. *Nucleic Acids Res.* 34, W676–W682.

- Kim, D., Langmead, B., and Salzberg, S.L. (2015). HISAT: a fast spliced aligner with low memory requirements. *Nat. Methods* **12**, 357–360.
- Kim, D., Langmead, B., and Salzberg, S. (2017). HISAT2: graph-based alignment of next-generation sequencing reads to a population of genomes.
- Kim, E., Magen, A., and Ast, G. (2007). Different levels of alternative splicing among eukaryotes. *Nucleic Acids Res.* **35**, 125–131.
- Kim, E., Goren, A., and Ast, G. (2008). Alternative splicing: current perspectives. *Bioessays* **30**, 38–47.
- Köster, J., and Rahmann, S. (2012). Snakemake—a scalable bioinformatics workflow engine. *Bioinformatics* **28**, 2520–2522.
- Kouzine, F., Wojtowicz, D., Baranello, L., Yamane, A., Nelson, S., Resch, W., Kieffer-Kwon, K.-R., Benham, C.J., Casellas, R., Przytycka, T.M., et al. (2017). Permanganate/S1 Nuclease Footprinting Reveals Non-B DNA Structures with Regulatory Potential across a Mammalian Genome. *Cell Syst* **4**, 344–356.e7.
- Královicová, J., and Vorechovsky, I. (2006). Position-dependent repression and promotion of DQB1 intron 3 splicing by GGGG motifs. *J. Immunol.* **176**, 2381–2388.
- Kwok, C.K., and Merrick, C.J. (2017). G-Quadruplexes: Prediction, Characterization, and Biological Application. *Trends Biotechnol.* **35**, 997–1013.
- Kwok, C.K., Marsico, G., Sahakyan, A.B., Chambers, V.S., and Balasubramanian, S. (2016). rG4-seq reveals widespread formation of G-quadruplex structures in the human transcriptome. *Nat. Methods* **13**, 841–844.
- Kwok, C.K., Marsico, G., and Balasubramanian, S. (2018). Detecting RNA G-Quadruplexes (rG4s) in the Transcriptome. *Cold Spring Harb. Perspect. Biol.* **10**.
- Lagarde, J., Uszczynska-Ratajczak, B., Santoyo-Lopez, J., Gonzalez, J.M., Tapanari, E., Mudge, J.M., Steward, C.A., Wilming, L., Tanzer, A., Howald, C., et al. (2016). Extension of human lncRNA transcripts by RACE coupled with long-read high-throughput sequencing (RACE-Seq). *Nat. Commun.* **7**, 12339.
- Lam, E.Y.N., Beraldí, D., Tannahill, D., and Balasubramanian, S. (2013). G-quadruplex structures are stable and detectable in human genomic DNA. *Nat. Commun.* **4**, 1796.
- Lambert, N., Robertson, A., Jangi, M., McGeary, S., Sharp, P.A., and Burge, C.B. (2014). RNA Bind-n-Seq: quantitative assessment of the sequence and structural binding specificity of RNA binding proteins. *Mol. Cell* **54**, 887–900.
- Lambowitz, A.M., and Zimmerly, S. (2011). Group II introns: mobile ribozymes that invade DNA. *Cold Spring Harb. Perspect. Biol.* **3**, a003616.
- Langmead, B., Trapnell, C., Pop, M., and Salzberg, S.L. (2009). Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. *Genome Biol.* **10**, R25.
- Lareau, L.F., Green, R.E., Bhatnagar, R.S., and Brenner, S.E. (2004). The evolving roles of alternative splicing. *Curr. Opin. Struct. Biol.* **14**, 273–282.
- Lareau, L.F., Inada, M., Green, R.E., Wengrod, J.C., and Brenner, S.E. (2007). Unproductive splicing of SR genes associated with highly conserved and ultraconserved DNA elements. *Nature* **446**, 926–929.
- Larsonneur, E., Mercier, J., Wiart, N., Floch, E.L., Delhomme, O., and Meyer, V. (2018). Evaluating Workflow Management Systems: A Bioinformatics Use Case. In 2018 IEEE International Conference

on Bioinformatics and Biomedicine (BIBM), pp. 2773–2775.

Lau, E., Han, Y., Williams, D.R., Thomas, C.T., Shrestha, R., Wu, J.C., and Lam, M.P.Y. (2019). Splice-Junction-Based Mapping of Alternative Isoforms in the Human Proteome. *Cell Rep.* **29**, 3751–3765.e5.

Lee, M.S., and Ji, Q.C. (2017). Protein Analysis using Mass Spectrometry: Accelerating Protein Biotherapeutics from Lab to Patient (John Wiley & Sons).

Lee, Y., and Rio, D.C. (2015). Mechanisms and Regulation of Alternative Pre-mRNA Splicing. *Annu. Rev. Biochem.* **84**, 291–323.

Lee, C.-Y., McNerney, C., Ma, K., Zhao, W., Wang, A., and Myong, S. (2020). R-loop induced G-quadruplex in non-template promotes transcription by successive R-loop formation. *Nat. Commun.* **11**, 3392.

Lee, J.-A., Xing, Y., Nguyen, D., Xie, J., Lee, C.J., and Black, D.L. (2007). Depolarization and CaM kinase IV modulate NMDA receptor splicing through two essential RNA elements. *PLoS Biol.* **5**, e40.

Lee, J.-A., Tang, Z.-Z., and Black, D.L. (2009). An inducible change in Fox-1/A2BP1 splicing modulates the alternative splicing of downstream neuronal target exons. *Genes Dev.* **23**, 2284–2293.

Le Hir, H., Saulière, J., and Wang, Z. (2016). The exon junction complex as a node of post-transcriptional networks. *Nat. Rev. Mol. Cell Biol.* **17**, 41–54.

Leipzig, J. (2017). A review of bioinformatic pipeline frameworks. *Brief. Bioinform.* **18**, 530–536.

Leung, D.W., and Amarasinghe, G.K. (2016). When your cap matters: structural insights into self vs non-self recognition of 5' RNA by immunomodulatory host proteins. *Curr. Opin. Struct. Biol.* **36**, 133–141.

Leung, M.K.K., Xiong, H.Y., Lee, L.J., and Frey, B.J. (2014). Deep learning of the tissue-regulated splicing code. *Bioinformatics* **30**, i121–i129.

Levine, A., and Durbin, R. (2001). A computational scan for U12-dependent introns in the human genome sequence. *Nucleic Acids Res.* **29**, 4006–4013.

Lev-Maor, G., Ram, O., Kim, E., Sela, N., Goren, A., Levanon, E.Y., and Ast, G. (2008). Intronic Alus influence alternative splicing. *PLoS Genet.* **4**, e1000204.

Levy, J.B., Dorai, T., Wang, L.H., and Brugge, J.S. (1987). The structurally distinct form of pp60c-src detected in neuronal cells is encoded by a unique c-src mRNA. *Mol. Cell. Biol.* **7**, 4142–4145.

Lewis, B.P., Green, R.E., and Brenner, S.E. (2003). Evidence for the widespread coupling of alternative splicing and nonsense-mediated mRNA decay in humans. *Proc. Natl. Acad. Sci. U. S. A.* **100**, 189–192.

Lewis, C.J.T., Pan, T., and Kalsotra, A. (2017a). RNA modifications and structures cooperate to guide RNA-protein interactions. *Nat. Rev. Mol. Cell Biol.* **18**, 202–210.

Lewis, P.A., Bradley, I.C., Pizzey, A.R., Isaacs, H.V., and Evans, G.J.O. (2017b). N1-Src Kinase Is Required for Primary Neurogenesis in Xenopus tropicalis. *J. Neurosci.* **37**, 8477–8485.

Li, H., and Durbin, R. (2009). Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754–1760.

Li, X., and Manley, J.L. (2005). Inactivation of the SR protein splicing factor ASF/SF2 results in genomic instability. *Cell* **122**, 365–378.

Li, H., Liu, G., Yu, J., Cao, W., Lobo, V.G., and Xie, J. (2009). In vivo selection of kinase-responsive

- RNA elements controlling alternative splicing. *J. Biol. Chem.* **284**, 16191–16201.
- Li, Y., Li, C., Li, S., Peng, Q., An, N.A., He, A., and Li, C.-Y. (2018). Human exonization through differential nucleosome occupancy. *Proc. Natl. Acad. Sci. U. S. A.* **115**, 8817–8822.
- Li, Y.I., Sanchez-Pulido, L., Haerty, W., and Ponting, C.P. (2015). RBFOX and PTBP1 proteins regulate the alternative splicing of micro-exons in human brain transcripts. *Genome Res.* **25**, 1–13.
- Lim, L.P., and Burge, C.B. (2001). A computational analysis of sequence features involved in recognition of short introns. *Proc. Natl. Acad. Sci. U. S. A.* **98**, 11193–11198.
- Lim, Y., Han, I., Kwon, H.J., and Oh, E.-S. (2002). Trichostatin A-induced detransformation correlates with decreased focal adhesion kinase phosphorylation at tyrosine 861 in ras-transformed fibroblasts. *J. Biol. Chem.* **277**, 12735–12740.
- Lin, C.-F., Mount, S.M., Jarmołowski, A., and Makałowski, W. (2010). Evolutionary dynamics of U12-type spliceosomal introns. *BMC Evol. Biol.* **10**, 47.
- Lin, C.-L., Taggart, A.J., Lim, K.H., Cygan, K.J., Ferraris, L., Creton, R., Huang, Y.-T., and Fairbrother, W.G. (2016). RNA structure replaces the need for U2AF2 in splicing. *Genome Res.* **26**, 12–23.
- Liu, G., Razanau, A., Hai, Y., Yu, J., Sohail, M., Lobo, V.G., Chu, J., Kung, S.K.P., and Xie, J. (2012). A conserved serine of heterogeneous nuclear ribonucleoprotein L (hnRNP L) mediates depolarization-regulated alternative splicing of potassium channels. *J. Biol. Chem.* **287**, 22709–22716.
- Liu, Y., González-Porta, M., Santos, S., Brazma, A., Marioni, J.C., Aebersold, R., Venkitaraman, A.R., and Wickramasinghe, V.O. (2017). Impact of Alternative Splicing on the Human Proteome. *Cell Rep.* **20**, 1229–1241.
- Louie, A.L., Aigner, S., Bergalet, J., Zhou, B., and Su, A. (2018). A large-scale binding and functional map of human RNA binding proteins. *bioRxiv*.
- Lovci, M.T., Ghanem, D., Marr, H., Arnold, J., Gee, S., Parra, M., Liang, T.Y., Stark, T.J., Gehman, L.T., Hoon, S., et al. (2013). Rbfox proteins regulate alternative mRNA splicing through evolutionarily conserved RNA bridges. *Nat. Struct. Mol. Biol.* **20**, 1434–1442.
- Luco, R.F., Allo, M., Schor, I.E., Kornblihtt, A.R., and Misteli, T. (2011). Epigenetics in alternative pre-mRNA splicing. *Cell* **144**, 16–26.
- Lukacsovich, D., Winterer, J., Que, L., Luo, W., Lukacsovich, T., and Földy, C. (2019). Single-Cell RNA-Seq Reveals Developmental Origins and Ontogenetic Stability of Neurexin Alternative Splicing Profiles. *Cell Rep.* **27**, 3752–3759.e4.
- Lunter, G., and Goodson, M. (2011). Stampy: a statistical algorithm for sensitive and fast mapping of Illumina sequence reads. *Genome Res.* **21**, 936–939.
- Lykke-Andersen, S., and Jensen, T.H. (2015). Nonsense-mediated mRNA decay: an intricate machinery that shapes transcriptomes. *Nat. Rev. Mol. Cell Biol.* **16**, 665–677.
- Mader, R.M., Schmidt, W.M., Sedivy, R., Rizovski, B., Braun, J., Kalipciyan, M., Exner, M., Steger, G.G., and Mueller, M.W. (2001). Reverse transcriptase template switching during reverse transcriptase-polymerase chain reaction: artificial generation of deletions in ribonucleotide reductase mRNA. *J. Lab. Clin. Med.* **137**, 422–428.
- Maizels, N., and Gray, L.T. (2013). The G4 genome. *PLoS Genet.* **9**, e1003468.
- Marcel, V., Tran, P.L.T., Sagne, C., Martel-Planche, G., Vaslin, L., Teulade-Fichou, M.-P., Hall, J., Mergny, J.-L., Hainaut, P., and Van Dyck, E. (2011). G-quadruplex structures in TP53 intron 3: role in alternative splicing and in production of p53 mRNA isoforms. *Carcinogenesis* **32**, 271–278.
- Marcucci, R., Baralle, F.E., and Romano, M. (2007). Complex splicing control of the human

- Thrombopoietin gene by intronic G runs. *Nucleic Acids Res.* 35, 132–142.
- Marnef, A., Cohen, S., and Legube, G. (2017). Transcription-Coupled DNA Double-Strand Break Repair: Active Genes Need Special Care. *J. Mol. Biol.* 429, 1277–1288.
- Marsico, G., Chambers, V.S., Sahakyan, A.B., McCauley, P., Boutell, J.M., Di Antonio, M., and Balasubramanian, S. (2019a). Whole genome experimental maps of DNA G-quadruplexes in multiple species. *Nucleic Acids Research* 47, 3862–3874.
- Marsico, G., Chambers, V.S., Sahakyan, A.B., McCauley, P., Boutell, J.M., Di Antonio, M., and Balasubramanian, S. (2019b). Whole genome experimental maps of DNA G-quadruplexes in multiple species. *Nucleic Acids Res.*
- Martinez, R., Mathey-Prevot, B., Bernards, A., and Baltimore, D. (1987). Neuronal pp60c-src contains a six-amino acid insertion relative to its non-neuronal counterpart. *Science* 237, 411–415.
- de la Mata, M., Alonso, C.R., Kadener, S., Fededa, J.P., Blaustein, M., Pelisch, F., Cramer, P., Bentley, D., and Kornblith, A.R. (2003). A slow RNA polymerase II affects alternative splicing in vivo. *Mol. Cell* 12, 525–532.
- Matera, A.G., and Wang, Z. (2014). A day in the life of the spliceosome. *Nat. Rev. Mol. Cell Biol.* 15, 108–121.
- Matlin, A.J., Clark, F., and Smith, C.W.J. (2005). Understanding alternative splicing: towards a cellular code. *Nat. Rev. Mol. Cell Biol.* 6, 386–398.
- Mauger, D.M., Lin, C., and Garcia-Blanco, M.A. (2008). hnRNP H and hnRNP F complex with Fox2 to silence fibroblast growth factor receptor 2 exon IIIc. *Mol. Cell. Biol.* 28, 5403–5419.
- McCullough, A.J., and Berget, S.M. (1997). G triplets located throughout a class of small vertebrate introns enforce intron borders and regulate splice site selection. *Mol. Cell. Biol.* 17, 4562–4571.
- McCullough, A.J., and Berget, S.M. (2000). An intronic splicing enhancer binds U1 snRNPs to enhance splicing and select 5' splice sites. *Mol. Cell. Biol.* 20, 9225–9235.
- McGlincy, N.J., and Smith, C.W.J. (2008). Alternative splicing resulting in nonsense-mediated mRNA decay: what is the meaning of nonsense? *Trends Biochem. Sci.* 33, 385–393.
- McManus, C.J., and Graveley, B.R. (2011). RNA structure and the mechanisms of alternative splicing. *Curr. Opin. Genet. Dev.* 21, 373–379.
- McNally, L.M., Yee, L., and McNally, M.T. (2006). Heterogeneous nuclear ribonucleoprotein H is required for optimal U11 small nuclear ribonucleoprotein binding to a retroviral RNA-processing control element: implications for U12-dependent RNA splicing. *J. Biol. Chem.* 281, 2478–2488.
- Melé, M., Ferreira, P.G., Reverter, F., DeLuca, D.S., Monlong, J., Sammeth, M., Young, T.R., Goldmann, J.M., Pervouchine, D.D., Sullivan, T.J., et al. (2015). Human genomics. The human transcriptome across tissues and individuals. *Science* 348, 660–665.
- Merrill, R.A., Plum, L.A., Kaiser, M.E., and Clagett-Dame, M. (2002). A mammalian homolog of unc-53 is regulated by all-trans retinoic acid in neuroblastoma cells and embryos. *Proc. Natl. Acad. Sci. U. S. A.* 99, 3422–3427.
- Metzakopian, E., Bouhali, K., Alvarez-Saavedra, M., Whitsett, J.A., Picketts, D.J., and Ang, S.-L. (2015). Genome-wide characterisation of Foxa1 binding sites reveals several mechanisms for regulating neuronal differentiation in midbrain dopamine cells. *Development* 142, 1315–1324.
- Miriami, E., Margalit, H., and Sperling, R. (2003). Conserved sequence elements associated with exon skipping. *Nucleic Acids Res.* 31, 1974–1983.
- Miyoshi, D., Nakao, A., and Sugimoto, N. (2003). Structural transition from antiparallel to parallel

G-quadruplex of d(G4T4G4) induced by Ca²⁺. *Nucleic Acids Res.* 31, 1156–1163.

Montell, C., Fisher, E.F., Caruthers, M.H., and Berk, A.J. (1982). Resolving the functions of overlapping viral genes by site-specific mutagenesis at a mRNA splice site. *Nature* 295, 380–384.

Morgan, M., Much, C., DiGiacomo, M., Azzi, C., Ivanova, I., Vitsios, D.M., Pistolic, J., Collier, P., Moreira, P.N., Benes, V., et al. (2017). mRNA 3' uridylation and poly(A) tail length sculpt the mammalian maternal transcriptome. *Nature* 548, 347–351.

Mortazavi, A., Williams, B.A., McCue, K., Schaeffer, L., and Wold, B. (2008). Mapping and quantifying mammalian transcriptomes by RNA-Seq. *Nat. Methods* 5, 621–628.

Moss, S.J., Doherty, C.A., and Huganir, R.L. (1992). Identification of the cAMP-dependent protein kinase and protein kinase C phosphorylation sites within the major intracellular domains of the beta 1, gamma 2S, and *J. Biol. Chem.*

Mount, S.M., Burks, C., Hertz, G., Stormo, G.D., White, O., and Fields, C. (1992). Splicing signals in *Drosophila*: intron size, information content, and consensus sequences. *Nucleic Acids Res.* 20, 4255–4262.

Müllner, D., and Others (2013). fastcluster: Fast hierarchical, agglomerative clustering routines for R and Python. *J. Stat. Softw.* 53, 1–18.

Murtagh, F., and Legendre, P. (2014). Ward's Hierarchical Agglomerative Clustering Method: Which Algorithms Implement Ward's Criterion? *J. Classification* 31, 274–295.

Nahkuri, S., Taft, R.J., and Mattick, J.S. (2009). Nucleosomes are preferentially positioned at exons in somatic and sperm cells. *Cell Cycle* 8, 3420–3424.

Nakagaki-Silva, E.E., Gooding, C., Llorian, M., Jacob, A.G., Richards, F., Buckroyd, A., Sinha, S., and Smith, C.W. (2019). Identification of RBPMs as a mammalian smooth muscle master splicing regulator via proximity of its gene with super-enhancers. *Elife* 8.

Nasiri, A.H., Wurm, J.P., Immer, C., and Weickmann, A.K. (2016). An intermolecular G-quadruplex as the basis for GTP recognition in the class V–GTP aptamer. *RNA*.

Nguyen, H.D., Zou, L., and Graubert, T.A. (2019). Targeting R-loop-associated ATR response in myelodysplastic syndrome. *Oncotarget* 10, 2581–2582.

Ni, J.Z., Grate, L., Donohue, J.P., Preston, C., Nobida, N., O'Brien, G., Shiue, L., Clark, T.A., Blume, J.E., and Ares, M., Jr (2007). Ultraconserved elements are associated with homeostatic control of splicing regulators by alternative splicing and nonsense-mediated decay. *Genes Dev.* 21, 708–718.

Nickless, A., Bailis, J.M., and You, Z. (2017). Control of gene expression through the nonsense-mediated RNA decay pathway. *Cell Biosci.* 7, 26.

Nieto Moreno, N., Giono, L.E., Cambindo Botto, A.E., Muñoz, M.J., and Kornblihtt, A.R. (2015). Chromatin, DNA structure and alternative splicing. *FEBS Lett.* 589, 3370–3378.

Nogués, G., Kadener, S., Cramer, P., Bentley, D., and Kornblihtt, A.R. (2002). Transcriptional Activators Differ in Their Abilities to Control Alternative Splicing. *J. Biol. Chem.* 277, 43110–43114.

Novikova, O., and Belfort, M. (2017). Mobile Group II Introns as Ancestral Eukaryotic Elements. *Trends Genet.* 33, 773–783.

Ohnishi, T., Shirane, M., and Nakayama, K.I. (2017). SRRM4-dependent neuron-specific alternative splicing of protrudin transcripts regulates neurite outgrowth. *Sci. Rep.* 7, 41130.

Okazaki, Y., Furuno, M., Kasukawa, T., Adachi, J., Bono, H., Kondo, S., Nikaido, I., Osato, N., Saito, R., Suzuki, H., et al. (2002). Analysis of the mouse transcriptome based on functional annotation of

- 60,770 full-length cDNAs. *Nature* **420**, 563–573.
- Padgett, R.A. (2012). New connections between splicing and human disease. *Trends Genet.* **28**, 147–154.
- Paeschke, K., Capra, J.A., and Zakian, V.A. (2011). DNA replication through G-quadruplex motifs is promoted by the *Saccharomyces cerevisiae* Pif1 DNA helicase. *Cell* **145**, 678–691.
- Pai, A.A., Paggi, J.M., Yan, P., Adelman, K., and Burge, C.B. (2018). Numerous recursive sites contribute to accuracy of splicing in long introns in flies. *PLoS Genet.* **14**, e1007588.
- Pan, Q. (2006). Quantitative microarray profiling provides evidence against widespread coupling of alternative splicing with nonsense-mediated mRNA decay to control gene expression. *Genes & Development* **20**, 153–158.
- Pan, Q., Shai, O., Lee, L.J., Frey, B.J., and Blencowe, B.J. (2008). Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. *Nat. Genet.* **40**, 1413–1415.
- Pannunzio, N.R., and Lieber, M.R. (2018). Concept of DNA Lesion Longevity and Chromosomal Translocations. *Trends Biochem. Sci.* **43**, 490–498.
- Paoletti, P., Bellone, C., and Zhou, Q. (2013). NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease. *Nat. Rev. Neurosci.* **14**, 383–400.
- Papasaikas, P., and Valcárcel, J. (2016). The Spliceosome: The Ultimate RNA Chaperone and Sculptor. *Trends Biochem. Sci.* **41**, 33–45.
- Parada, G.E., Munita, R., Cerda, C.A., and Gysling, K. (2014). A comprehensive survey of non-canonical splice sites in the human transcriptome. *Nucleic Acids Res.* **42**, 10564–10578.
- Park, J., and Belden, W.J. (2018). Long non-coding RNAs have age-dependent diurnal expression that coincides with age-related changes in genome-wide facultative heterochromatin. *BMC Genomics* **19**, 777.
- Parras, A., Anta, H., Santos-Galindo, M., Swarup, V., Elorza, A., Nieto-González, J.L., Picó, S., Hernández, I.H., Díaz-Hernández, J.I., Belloc, E., et al. (2018). Autism-like phenotype and risk gene mRNA deadenylation by CPEB4 mis-splicing. *Nature* **560**, 441–446.
- Patel, A.A., and Steitz, J.A. (2003). Splicing double: insights from the second spliceosome. *Nat. Rev. Mol. Cell Biol.* **4**, 960–970.
- Pertea, M., Shumate, A., Pertea, G., Varabyou, A., Breitwieser, F.P., Chang, Y.-C., Madugundu, A.K., Pandey, A., and Salzberg, S.L. (2018). CHESS: a new human gene catalog curated from thousands of large-scale RNA sequencing experiments reveals extensive transcriptional noise. *Genome Biol.* **19**, 208.
- Pickrell, J.K., Pai, A.A., Gilad, Y., and Pritchard, J.K. (2010). Noisy splicing drives mRNA isoform diversity in human cells. *PLoS Genet.* **6**, e1001236.
- Pineda, J.M.B., and Bradley, R.K. (2018). Most human introns are recognized via multiple and tissue-specific branchpoints. *Genes Dev.* **32**, 577–591.
- Pipes, L., Li, S., Bozinoski, M., Palermo, R., Peng, X., Blood, P., Kelly, S., Weiss, J.M., Thierry-Mieg, J., Thierry-Mieg, D., et al. (2013). The non-human primate reference transcriptome resource (NHPTR) for comparative functional genomics. *Nucleic Acids Res.* **41**, D906–D914.
- Placek, K., Baer, G.M., Elman, L., McCluskey, L., Hennessy, L., Ferraro, P.M., Lee, E.B., Lee, V.M.Y., Trojanowski, J.Q., Van Deerlin, V.M., et al. (2019). UNC13A polymorphism contributes to frontotemporal disease in sporadic amyotrophic lateral sclerosis. *Neurobiol. Aging* **73**, 190–199.

- Popp, M.W.-L., and Maquat, L.E. (2013). Organizing principles of mammalian nonsense-mediated mRNA decay. *Annu. Rev. Genet.* **47**, 139–165.
- Porter, R.S., Jaamour, F., and Iwase, S. (2018). Neuron-specific alternative splicing of transcriptional machineries: Implications for neurodevelopmental disorders. *Mol. Cell. Neurosci.* **87**, 35–45.
- Pruitt, K.D., Brown, G.R., Hiatt, S.M., Thibaud-Nissen, F., Astashyn, A., Ermolaeva, O., Farrell, C.M., Hart, J., Landrum, M.J., McGarvey, K.M., et al. (2014). RefSeq: an update on mammalian reference sequences. *Nucleic Acids Res.* **42**, D756–D763.
- PsychENCODE Consortium, Akbarian, S., Liu, C., Knowles, J.A., Vaccarino, F.M., Farnham, P.J., Crawford, G.E., Jaffe, A.E., Pinto, D., Dracheva, S., et al. (2015). The PsychENCODE project. *Nat. Neurosci.* **18**, 1707–1712.
- Pucker, B., and Brockington, S.F. (2018). Genome-wide analyses supported by RNA-Seq reveal non-canonical splice sites in plant genomes. *BMC Genomics* **19**, 980.
- Pulido, R., Krueger, N.X., Serra-Pagès, C., Saito, H., and Streuli, M. (1995a). Molecular Characterization of the Human Transmembrane Protein-tyrosine Phosphatase δ: EVIDENCE FOR TISSUE-SPECIFIC EXPRESSION OF ALTERNATIVE HUMAN TRANSMEMBRANE PROTEIN-TYROSINE PHOSPHATASE δ ISOFORMS. *J. Biol. Chem.* **270**, 6722–6728.
- Pulido, R., Serra-Pagès, C., Tang, M., and Streuli, M. (1995b). The LAR/PTP delta/PTP sigma subfamily of transmembrane protein-tyrosine-phosphatases: multiple human LAR, PTP delta, and PTP sigma isoforms are expressed in a tissue-specific manner and associate with the LAR-interacting protein LIP-1. *Proc. Natl. Acad. Sci. U. S. A.* **92**, 11686–11690.
- Qiu, J., McQueen, J., Bilican, B., Dando, O., Magnani, D., Punovuori, K., Selvaraj, B.T., Livesey, M., Hagh, G., Heron, S., et al. (2016). Evidence for evolutionary divergence of activity-dependent gene expression in developing neurons. *Elife* **5**.
- Quesnel-Vallières, M., Irimia, M., Cordes, S.P., and Blencowe, B.J. (2015). Essential roles for the splicing regulator nSR100/SRRM4 during nervous system development. *Genes Dev.* **29**, 746–759.
- Quesnel-Vallières, M., Dargaei, Z., Irimia, M., Gonatopoulos-Pournatzis, T., Ip, J.Y., Wu, M., Sterne-Weiler, T., Nakagawa, S., Woodin, M.A., Blencowe, B.J., et al. (2016). Misregulation of an Activity-Dependent Splicing Network as a Common Mechanism Underlying Autism Spectrum Disorders. *Mol. Cell* **64**, 1023–1034.
- Raj, B., O'Hanlon, D., Vessey, J.P., Pan, Q., Ray, D., Buckley, N.J., Miller, F.D., and Blencowe, B.J. (2011). Cross-regulation between an alternative splicing activator and a transcription repressor controls neurogenesis. *Mol. Cell* **43**, 843–850.
- Raj, B., Irimia, M., Braunschweig, U., Sterne-Weiler, T., O'Hanlon, D., Lin, Z.-Y., Chen, G.I., Easton, L.E., Ule, J., Gingras, A.-C., et al. (2014). A global regulatory mechanism for activating an exon network required for neurogenesis. *Mol. Cell* **56**, 90–103.
- Ratcliffe, C.D.H., Siddiqui, N., Coelho, P.P., Laterre, N., Cookey, T.N., Sonenberg, N., and Park, M. (2019). HGF-induced migration depends on the PI(3,4,5)P3-binding microexon-spliced variant of the Arf6 exchange factor cytohesin-1. *J. Cell Biol.* **218**, 285–298.
- Ribeiro, M.M., Teixeira, G.S., Martins, L., Marques, M.R., de Souza, A.P., and Line, S.R.P. (2015). G-quadruplex formation enhances splicing efficiency of PAX9 intron 1. *Hum. Genet.* **134**, 37–44.
- Rissland, O.S., and Norbury, C.J. (2009). Decapping is preceded by 3' uridylation in a novel pathway of bulk mRNA turnover. *Nat. Struct. Mol. Biol.* **16**, 616–623.
- Robberson, B.L., Cote, G.J., and Berget, S.M. (1990). Exon definition may facilitate splice site selection in RNAs with multiple exons. *Mol. Cell. Biol.* **10**, 84–94.
- Roweis, S.T. (1998). EM Algorithms for PCA and SPCA. In *Advances in Neural Information*

- Processing Systems 10, M.I. Jordan, M.J. Kearns, and S.A. Solla, eds. (MIT Press), pp. 626–632.
- Roy, S.W., and Irimia, M. (2008). When good transcripts go bad: artifactual RT-PCR “splicing” and genome analysis. *Bioessays* 30, 601–605.
- Rumbaugh, G., Prybylowski, K., Wang, J.F., and Vicini, S. (2000). Exon 5 and spermine regulate deactivation of NMDA receptor subtypes. *J. Neurophysiol.* 83, 1300–1306.
- Runfola, V., Sebastian, S., Dilworth, F.J., and Gabellini, D. (2015). Rbfox proteins regulate tissue-specific alternative splicing of Mef2D required for muscle differentiation. *J. Cell Sci.* 128, 631–637.
- Ruskin, B., Zamore, P.D., and Green, M.R. (1988). A factor, U2AF, is required for U2 snRNP binding and splicing complex assembly. *Cell* 52, 207–219.
- Rybak-Wolf, A., Stottmeister, C., Glažar, P., Jens, M., Pino, N., Giusti, S., Hanan, M., Behm, M., Bartok, O., Ashwal-Fluss, R., et al. (2015). Circular RNAs in the Mammalian Brain Are Highly Abundant, Conserved, and Dynamically Expressed. *Mol. Cell* 58, 870–885.
- Saito, Y., Yuan, Y., Zucker-Scharff, I., Fak, J.J., Jereb, S., Tajima, Y., Licatalosi, D.D., and Darnell, R.B. (2019). Differential NOVA2-Mediated Splicing in Excitatory and Inhibitory Neurons Regulates Cortical Development and Cerebellar Function. *Neuron* 101, 707–720.e5.
- Sakharkar, M.K., Chow, V.T.K., and Kangueane, P. (2004). Distributions of exons and introns in the human genome. *In Silico Biol.* 4, 387–393.
- Saltzman, A.L., Kim, Y.K., Pan, Q., Fagnani, M.M., Maquat, L.E., and Blencowe, B.J. (2008). Regulation of multiple core spliceosomal proteins by alternative splicing-coupled nonsense-mediated mRNA decay. *Mol. Cell. Biol.* 28, 4320–4330.
- Samatanga, B., Dominguez, C., Jelesarov, I., and Allain, F.H.-T. (2013). The high kinetic stability of a G-quadruplex limits hnRNP F qRRM3 binding to G-tract RNA. *Nucleic Acids Res.* 41, 2505–2516.
- Santoni, M.J., Barthels, D., Vopper, G., Boned, A., Goridis, C., and Wille, W. (1989). Differential exon usage involving an unusual splicing mechanism generates at least eight types of NCAM cDNA in mouse brain. *EMBO J.* 8, 385–392.
- Santos-Pereira, J.M., and Aguilera, A. (2015). R loops: new modulators of genome dynamics and function. *Nat. Rev. Genet.* 16, 583–597.
- Sasaki-Haraguchi, N., Shimada, M.K., Taniguchi, I., Ohno, M., and Mayeda, A. (2012). Mechanistic insights into human pre-mRNA splicing of human ultra-short introns: potential unusual mechanism identifies G-rich introns. *Biochem. Biophys. Res. Commun.* 423, 289–294.
- Schellenberg, M.J., Ritchie, D.B., and MacMillan, A.M. (2008). Pre-mRNA splicing: a complex picture in higher definition. *Trends Biochem. Sci.* 33, 243–246.
- Schor, I.E., Rascovan, N., Pelisch, F., Alló, M., and Kornblith, A.R. (2009). Neuronal cell depolarization induces intragenic chromatin modifications affecting NCAM alternative splicing. *Proc. Natl. Acad. Sci. U. S. A.* 106, 4325–4330.
- Schwartz, S., Meshorer, E., and Ast, G. (2009). Chromatin organization marks exon-intron structure. *Nat. Struct. Mol. Biol.* 16, 990–995.
- Scott, D.B., Blanpied, T.A., Swanson, G.T., Zhang, C., and Ehlers, M.D. (2001). An NMDA receptor ER retention signal regulated by phosphorylation and alternative splicing. *J. Neurosci.* 21, 3063–3072.
- Scotti, M.M., and Swanson, M.S. (2016). RNA mis-splicing in disease. *Nat. Rev. Genet.* 17, 19–32.
- Semlow, D.R., and Staley, J.P. (2012). Staying on message: ensuring fidelity in pre-mRNA splicing.

Trends Biochem. Sci. 37, 263–273.

SEQC/MAQC-III Consortium (2014). A comprehensive assessment of RNA-seq accuracy, reproducibility and information content by the Sequencing Quality Control Consortium. *Nat. Biotechnol.* 32, 903–914.

Shapiro, M.B., and Senapathy, P. (1987). RNA splice junctions of different classes of eukaryotes: sequence statistics and functional implications in gene expression. *Nucleic Acids Res.* 15, 7155–7174.

Sharma, A., and Lou, H. (2011). Depolarization-mediated regulation of alternative splicing. *Front. Neurosci.* 5, 141.

Shendure, J., and Ji, H. (2008). Next-generation DNA sequencing. *Nat. Biotechnol.* 26, 1135–1145.

Shepard, P.J., and Hertel, K.J. (2008). Conserved RNA secondary structures promote alternative splicing. *RNA* 14, 1463–1469.

Sheth, N., Roca, X., Hastings, M.L., Roeder, T., Krainer, A.R., and Sachidanandam, R. (2006). Comprehensive splice-site analysis using comparative genomics. *Nucleic Acids Res.* 34, 3955–3967.

Shimada, M.K., Sasaki-Haraguchi, N., and Mayeda, A. (2015). Identification and Validation of Evolutionarily Conserved Unusually Short Pre-mRNA Introns in the Human Genome. *Int. J. Mol. Sci.* 16, 10376–10388.

Shrestha, P., Xiao, S., Dhakal, S., Tan, Z., and Mao, H. (2014). Nascent RNA transcripts facilitate the formation of G-quadruplexes. *Nucleic Acids Res.* 42, 7236–7246.

Shtukmaster, S., Schier, M.C., Huber, K., Krispin, S., Kalcheim, C., and Unsicker, K. (2013). Sympathetic neurons and chromaffin cells share a common progenitor in the neural crest in vivo. *Neural Dev.* 8, 12.

Sibley, C.R., Emmett, W., Blazquez, L., Faro, A., Haberman, N., Briese, M., Trabzuni, D., Ryten, M., Weale, M.E., Hardy, J., et al. (2015). Recursive splicing in long vertebrate genes. *Nature* 521, 371–375.

Sibley, C.R., Blazquez, L., and Ule, J. (2016). Lessons from non-canonical splicing. *Nat. Rev. Genet.* 17, 407–421.

Siddiqui-Jain, A., Grand, C.L., Bearss, D.J., and Hurley, L.H. (2002). Direct evidence for a G-quadruplex in a promoter region and its targeting with a small molecule to repress c-MYC transcription. *Proc. Natl. Acad. Sci. U. S. A.* 99, 11593–11598.

Singh, R.K., and Cooper, T.A. (2012). Pre-mRNA splicing in disease and therapeutics. *Trends Mol. Med.* 18, 472–482.

Sloan, C.A., Chan, E.T., Davidson, J.M., Malladi, V.S., Strattan, J.S., Hitz, B.C., Gabdank, I., Narayanan, A.K., Ho, M., Lee, B.T., et al. (2016). ENCODE data at the ENCODE portal. *Nucleic Acids Res.* 44, D726–D732.

Small, S.J., Haines, S.L., and Akeson, R.A. (1988). Polypeptide variation in an N-CAM extracellular immunoglobulin-like fold is developmentally regulated through alternative splicing. *Neuron* 1, 1007–1017.

Smith, C.W., and Valcárcel, J. (2000). Alternative pre-mRNA splicing: the logic of combinatorial control. *Trends Biochem. Sci.* 25, 381–388.

Spies, N., Nielsen, C.B., Padgett, R.A., and Burge, C.B. (2009). Biased chromatin signatures around polyadenylation sites and exons. *Mol. Cell* 36, 245–254.

Stacklies, W., Redestig, H., Scholz, M., Walther, D., and Selbig, J. (2007). pcaMethods—a

- bioconductor package providing PCA methods for incomplete data. *Bioinformatics* 23, 1164–1167.
- Stamm, S., Zhang, M.Q., Marr, T.G., and Helfman, D.M. (1994). A sequence compilation and comparison of exons that are alternatively spliced in neurons. *Nucleic Acids Res.* 22, 1515–1526.
- Standley, S., Roche, K.W., McCallum, J., Sans, N., and Wenthold, R.J. (2000). PDZ domain suppression of an ER retention signal in NMDA receptor NR1 splice variants. *Neuron* 28, 887–898.
- Stark, R., Grzelak, M., and Hadfield, J. (2019). RNA sequencing: the teenage years. *Nat. Rev. Genet.*
- Stepankiw, N., Raghavan, M., Fogarty, E.A., Grimson, A., and Pleiss, J.A. (2015). Widespread alternative and aberrant splicing revealed by lariat sequencing. *Nucleic Acids Res.* 43, 8488–8501.
- Sterner, D.A., Carlo, T., and Berget, S.M. (1996). Architectural limits on split genes. *Proc. Natl. Acad. Sci. U. S. A.* 93, 15081–15085.
- Sterne-Weiler, T., Weatheritt, R.J., Best, A.J., Ha, K.C.H., and Blencowe, B.J. (2018). Efficient and Accurate Quantitative Profiling of Alternative Splicing Patterns of Any Complexity on a Laptop. *Mol. Cell* 72, 187–200.e6.
- Strausberg, R.L., Feingold, E.A., Grouse, L.H., Derge, J.G., Klausner, R.D., Collins, F.S., Wagner, L., Shenmen, C.M., Schuler, G.D., Altschul, S.F., et al. (2002). Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. *Proc. Natl. Acad. Sci. U. S. A.* 99, 16899–16903.
- Strobel, E.J., Yu, A.M., and Lucks, J.B. (2018). High-throughput determination of RNA structures. *Nat. Rev. Genet.* 19, 615–634.
- Su, C.-H., D, D., and Tarn, W.-Y. (2018). Alternative Splicing in Neurogenesis and Brain Development. *Front Mol Biosci* 5, 12.
- Südhof, T.C. (2017). Synaptic Neurexin Complexes: A Molecular Code for the Logic of Neural Circuits. *Cell* 171, 745–769.
- Szafranski, K., Schindler, S., Taudien, S., Hiller, M., Huse, K., Jahn, N., Schreiber, S., Backofen, R., and Platzer, M. (2007). Violating the splicing rules: TG dinucleotides function as alternative 3' splice sites in U2-dependent introns. *Genome Biol.* 8, R154.
- Szklarczyk, D., Morris, J.H., Cook, H., Kuhn, M., Wyder, S., Simonovic, M., Santos, A., Doncheva, N.T., Roth, A., Bork, P., et al. (2017). The STRING database in 2017: quality-controlled protein-protein association networks, made broadly accessible. *Nucleic Acids Res.* 45, D362–D368.
- Takahashi, H., and Craig, A.M. (2013). Protein tyrosine phosphatases PTP δ , PTP σ , and LAR: presynaptic hubs for synapse organization. *Trends Neurosci.* 36, 522–534.
- Talerico, M., and Berget, S.M. (1994). Intron definition in splicing of small *Drosophila* introns. *Mol. Cell. Biol.* 14, 3434–3445.
- Taliaferro, J.M., Lambert, N.J., Sudmant, P.H., Dominguez, D., Merkin, J.J., Alexis, M.S., Bazile, C., and Burge, C.B. (2016). RNA Sequence Context Effects Measured *In Vitro* Predict *In Vivo* Protein Binding and Regulation. *Mol. Cell* 64, 294–306.
- Tapias, J., Ha, K.C.H., Sterne-Weiler, T., Gohr, A., Braunschweig, U., Hermoso-Pulido, A., Quesnel-Vallières, M., Permanyer, J., Sodaie, R., Marquez, Y., et al. (2017). An atlas of alternative splicing profiles and functional associations reveals new regulatory programs and genes that simultaneously express multiple major isoforms. *Genome Res.* 27, 1759–1768.
- Tarn, W.Y., and Steitz, J.A. (1996). A novel spliceosome containing U11, U12, and U5 snRNPs excises a minor class (AT-AC) intron *in vitro*. *Cell* 84, 801–811.
- Tasic, B., Menon, V., Nguyen, T.N., Kim, T.K., Jarsky, T., Yao, Z., Levi, B., Gray, L.T., Sorensen,

- S.A., Dolbeare, T., et al. (2016). Adult mouse cortical cell taxonomy revealed by single cell transcriptomics. *Nat. Neurosci.* **19**, 335–346.
- Tasic, B., Yao, Z., Graybuck, L.T., Smith, K.A., Nguyen, T.N., Bertagnolli, D., Goldy, J., Garren, E., Economo, M.N., Viswanathan, S., et al. (2018). Shared and distinct transcriptomic cell types across neocortical areas. *Nature* **563**, 72–78.
- Thakurela, S., Garding, A., Jung, J., Schübeler, D., Burger, L., and Tiwari, V.K. (2013). Gene regulation and priming by topoisomerase IIa in embryonic stem cells. *Nat. Commun.* **4**, 2478.
- Thanaraj, T.A., and Clark, F. (2001). Human GC-AG alternative intron isoforms with weak donor sites show enhanced consensus at acceptor exon positions. *Nucleic Acids Res.* **29**, 2581–2593.
- Thomas, J.D., Polaski, J.T., Feng, Q., De Neef, E.J., Hoppe, E.R., McSharry, M.V., Pangallo, J., Gabel, A.M., Belleville, A.E., Watson, J., et al. (2020). RNA isoform screens uncover the essentiality and tumor-suppressor activity of ultraconserved poison exons. *Nat. Genet.* **52**, 84–94.
- Tian, B., and Manley, J.L. (2017). Alternative polyadenylation of mRNA precursors. *Nat. Rev. Mol. Cell Biol.* **18**, 18–30.
- Tilgner, H., Nikolaou, C., Althammer, S., Sammeth, M., Beato, M., Valcárcel, J., and Guigó, R. (2009). Nucleosome positioning as a determinant of exon recognition. *Nat. Struct. Mol. Biol.* **16**, 996–1001.
- Tillo, D., and Hughes, T.R. (2009). G+C content dominates intrinsic nucleosome occupancy. *BMC Bioinformatics* **10**, 442.
- Tipping, M.E., and Bishop, C.M. (1999). Probabilistic Principal Component Analysis. *J. R. Stat. Soc. Series B Stat. Methodol.* **61**, 611–622.
- Torres-Méndez, A., Bonnal, S., Marquez, Y., Roth, J., Iglesias, M., Permanyer, J., Almudí, I., O'Hanlon, D., Guitart, T., Soller, M., et al. (2019). A novel protein domain in an ancestral splicing factor drove the evolution of neural microexons. *Nat Ecol Evol* **3**, 691–701.
- Trapnell, C., Pachter, L., and Salzberg, S.L. (2009). TopHat: discovering splice junctions with RNA-Seq. *Bioinformatics* **25**, 1105–1111.
- Traynelis, S.F., Hartley, M., and Heinemann, S.F. (1995). Control of proton sensitivity of the NMDA receptor by RNA splicing and polyamines. *Science* **268**, 873–876.
- Traynelis, S.F., Burgess, M.F., Zheng, F., Lyuboslavsky, P., and Powers, J.L. (1998). Control of voltage-independent zinc inhibition of NMDA receptors by the NR1 subunit. *J. Neurosci.* **18**, 6163–6175.
- Tress, M.L., Abascal, F., and Valencia, A. (2017a). Alternative Splicing May Not Be the Key to Proteome Complexity. *Trends in Biochemical Sciences* **42**, 98–110.
- Tress, M.L., Abascal, F., and Valencia, A. (2017b). Most Alternative Isoforms Are Not Functionally Important. *Trends Biochem. Sci.* **42**, 408–410.
- Trotman, J.B., and Schoenberg, D.R. (2019). A recap of RNA recapping. *Wiley Interdiscip. Rev. RNA* **10**, e1504.
- Tsai, Z.T.-Y., Chu, W.-Y., Cheng, J.-H., and Tsai, H.-K. (2014). Associations between intronic non-B DNA structures and exon skipping. *Nucleic Acids Res.* **42**, 739–747.
- Turimella, S.L., Bedner, P., Skubal, M., Vangoor, V.R., Kaczmarczyk, L., Karl, K., Zoidl, G., Gieselmann, V., Seifert, G., Steinhäuser, C., et al. (2015). Characterization of cytoplasmic polyadenylation element binding 2 protein expression and its RNA binding activity. *Hippocampus* **25**, 630–642.
- Ustianenko, D., Weyn-Vanhentenryck, S.M., and Zhang, C. (2017). Microexons: discovery, regulation,

and function. Wiley Interdiscip. Rev. RNA 8.

Uzilov, A.V., and Underwood, J.G. (2016). High-Throughput Nuclease Probing of RNA Structures Using FragSeq. RNA Structure Determination 105–134.

Vance, K.M., Hansen, K.B., and Traynelis, S.F. (2012). GluN1 splice variant control of GluN1/GluN2D NMDA receptors. J. Physiol. 590, 3857–3875.

Van Nostrand, E.L., Pratt, G.A., Shishkin, A.A., Gelboin-Burkhart, C., Fang, M.Y., Sundararaman, B., Blue, S.M., Nguyen, T.B., Surka, C., Elkins, K., et al. (2016). Robust transcriptome-wide discovery of RNA-binding protein binding sites with enhanced CLIP (eCLIP). Nat. Methods 13, 508–514.

Varizhuk, A.M., Sekridova, A.V., Tankevich, M.V., Podgorsky, V.S., Smirnov, I.P., and Pozmogova, G.E. (2017). Conformational polymorphysm of G-rich fragments of DNA Alu-repeats. II. The putative role of G-quadruplex structures in genomic rearrangements. Biochemistry (Moscow), Supplement Series B: Biomedical Chemistry 11, 146–153.

Verma, B., Akinyi, M.V., Norppa, A.J., and Frilander, M.J. (2018). Minor spliceosome and disease. Semin. Cell Dev. Biol. 79, 103–112.

Vogler, C., Spalek, K., Aerni, A., Demougin, P., Müller, A., Huynh, K.-D., Papassotiropoulos, A., and de Quervain, D.J.-F. (2009). CPEB3 is associated with human episodic memory. Front. Behav. Neurosci. 3, 4.

Voineagu, I., Wang, X., Johnston, P., Lowe, J.K., Tian, Y., Horvath, S., Mill, J., Cantor, R.M., Blencowe, B.J., and Geschwind, D.H. (2011). Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature 474, 380–384.

Volfovsky, N., Haas, B.J., and Salzberg, S.L. (2003). Computational discovery of internal micro-exons. Genome Res. 13, 1216–1221.

Vuong, C.K., Black, D.L., and Zheng, S. (2016). The neurogenetics of alternative splicing. Nat. Rev. Neurosci. 17, 265–281.

Wahl, M.C., Will, C.L., and Lührmann, R. (2009). The spliceosome: design principles of a dynamic RNP machine. Cell 136, 701–718.

Wamsley, B., Jaglin, X.H., Favuzzi, E., Quattrocolo, G., Nigro, M.J., Yusuf, N., Khodadadi-Jamayran, A., Rudy, B., and Fishell, G. (2018). Rbfox1 Mediates Cell-type-Specific Splicing in Cortical Interneurons. Neuron 100, 846–859.e7.

Wang, G., and Peng, B. (2019). Script of Scripts: A pragmatic workflow system for daily computational research. PLoS Comput. Biol. 15, e1006843.

Wang, G., and Vasquez, K.M. (2017). Effects of Replication and Transcription on DNA Structure-Related Genetic Instability. Genes 8.

Wang, E.T., Sandberg, R., Luo, S., Khrebtukova, I., Zhang, L., Mayr, C., Kingsmore, S.F., Schroth, G.P., and Burge, C.B. (2008). Alternative isoform regulation in human tissue transcriptomes. Nature 456, 470–476.

Wang, J., Yin, G., Menon, P., Pang, J., Smolock, E.M., Yan, C., and Berk, B.C. (2010a). Phosphorylation of G protein-coupled receptor kinase 2-interacting protein 1 tyrosine 392 is required for phospholipase C-gamma activation and podosome formation in vascular smooth muscle cells. Arterioscler. Thromb. Vasc. Biol. 30, 1976–1982.

Wang, K., Singh, D., Zeng, Z., Coleman, S.J., Huang, Y., Savich, G.L., He, X., Mieczkowski, P., Grimm, S.A., Perou, C.M., et al. (2010b). MapSplice: accurate mapping of RNA-seq reads for splice junction discovery. Nucleic Acids Res. 38, e178.

Wang, X., Codreanu, S.G., Wen, B., Li, K., Chambers, M.C., Liebler, D.C., and Zhang, B. (2018).

Detection of Proteome Diversity Resulted from Alternative Splicing is Limited by Trypsin Cleavage Specificity. *Mol. Cell. Proteomics* 17, 422–430.

Wang, Z., Gerstein, M., and Snyder, M. (2009). RNA-Seq: a revolutionary tool for transcriptomics. *Nat. Rev. Genet.* 10, 57–63.

Warf, M.B., and Berglund, J.A. (2010). Role of RNA structure in regulating pre-mRNA splicing. *Trends Biochem. Sci.* 35, 169–178.

Watson, J.D., and Crick, F.H. (1953). Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid. *Nature* 171, 737–738.

Wei, C.M., Gershowitz, A., and Moss, B. (1975). Methylated nucleotides block 5' terminus of HeLa cell messenger RNA. *Cell* 4, 379–386.

Weischenfeldt, J., Waage, J., Tian, G., Zhao, J., Damgaard, I., Jakobsen, J.S., Kristiansen, K., Krogh, A., Wang, J., and Porse, B.T. (2012). Mammalian tissues defective in nonsense-mediated mRNA decay display highly aberrant splicing patterns. *Genome Biol.* 13, R35.

Weitzmann, M.N., Woodford, K.J., and Usdin, K. (1996). The development and use of a DNA polymerase arrest assay for the evaluation of parameters affecting intrastrand tetraplex formation. *J. Biol. Chem.* 271, 20958–20964.

Weldon, C., Dacanay, J.G., Gokhale, V., Boddually, P.V.L., Behm-Ansmant, I., Burley, G.A., Branst, C., Hurley, L.H., Dominguez, C., and Eperon, I.C. (2018). Specific G-quadruplex ligands modulate the alternative splicing of Bcl-X. *Nucleic Acids Res.* 46, 886–896.

Wells, S.E., Hillner, P.E., Vale, R.D., and Sachs, A.B. (1998). Circularization of mRNA by eukaryotic translation initiation factors. *Mol. Cell* 2, 135–140.

Weyn-Vanhentenryck, S.M., Feng, H., Ustianenko, D., Duffié, R., Yan, Q., Jacko, M., Martinez, J.C., Goodwin, M., Zhang, X., Hengst, U., et al. (2018). Precise temporal regulation of alternative splicing during neural development. *Nat. Commun.* 9, 2189.

Whiting, P., McKernan, R.M., and Iversen, L.L. (1990). Another mechanism for creating diversity in gamma-aminobutyrate type A receptors: RNA splicing directs expression of two forms of gamma 2 phosphorylation site. *Proc. Natl. Acad. Sci. U. S. A.* 87, 9966–9970.

Wiestler, O.D., and Walter, G. (1988). Developmental expression of two forms of pp60c-src in mouse brain. *Mol. Cell. Biol.* 8, 502–504.

Wilusz, C.J., Wormington, M., and Peltz, S.W. (2001). The cap-to-tail guide to mRNA turnover. *Nat. Rev. Mol. Cell Biol.* 2, 237–246.

Wolstencroft, K., Haines, R., Fellows, D., Williams, A., Withers, D., Owen, S., Soiland-Reyes, S., Dunlop, I., Nenadic, A., Fisher, P., et al. (2013). The Taverna workflow suite: designing and executing workflows of Web Services on the desktop, web or in the cloud. *Nucleic Acids Res.* 41, W557–W561.

Won, S.Y., and Kim, H.M. (2018). Structural Basis for LAR-RPTP-Mediated Synaptogenesis. *Mol. Cells* 41, 622–630.

Wright, J.C., Mudge, J., Weisser, H., Barzine, M.P., Gonzalez, J.M., Brazma, A., Choudhary, J.S., and Harrow, J. (2016). Improving GENCODE reference gene annotation using a high-stringency proteogenomics workflow. *Nat. Commun.* 7, 11778.

Wu, T.D., and Nacu, S. (2010). Fast and SNP-tolerant detection of complex variants and splicing in short reads. *Bioinformatics* 26, 873–881.

Wu, T.D., and Watanabe, C.K. (2005). GMAP: a genomic mapping and alignment program for mRNA and EST sequences. *Bioinformatics* 21, 1859–1875.

- Wu, J., Anczuków, O., Krainer, A.R., Zhang, M.Q., and Zhang, C. (2013). OLego: fast and sensitive mapping of spliced mRNA-Seq reads using small seeds. *Nucleic Acids Res.* **41**, 5149–5163.
- Xiao, X., Wang, Z., Jang, M., Nutiu, R., Wang, E.T., and Burge, C.B. (2009). Splice site strength-dependent activity and genetic buffering by poly-G runs. *Nat. Struct. Mol. Biol.* **16**, 1094–1100.
- Xie, J. (2008). Control of alternative pre-mRNA splicing by Ca(++) signals. *Biochim. Biophys. Acta* **1779**, 438–452.
- Xie, J., and Black, D.L. (2001). A CaMK IV responsive RNA element mediates depolarization-induced alternative splicing of ion channels. *Nature* **410**, 936–939.
- Xie, J., Jan, C., Stoilov, P., Park, J., and Black, D.L. (2005). A consensus CaMK IV-responsive RNA sequence mediates regulation of alternative exons in neurons. *RNA* **11**, 1825–1834.
- Xiong, H.Y., Alipanahi, B., Lee, L.J., Bretschneider, H., Merico, D., Yuen, R.K.C., Hua, Y., Gueroussov, S., Najafabadi, H.S., Hughes, T.R., et al. (2015). RNA splicing. The human splicing code reveals new insights into the genetic determinants of disease. *Science* **347**, 1254806.
- Yamagata, A., Yoshida, T., Sato, Y., Goto-Ito, S., Uemura, T., Maeda, A., Shiroshima, T., Iwasawa-Okamoto, S., Mori, H., Mishina, M., et al. (2015a). Mechanisms of splicing-dependent trans-synaptic adhesion by PTPδ-IL1RAPL1/IL-1RAcP for synaptic differentiation. *Nat. Commun.* **6**, 6926.
- Yamagata, A., Sato, Y., Goto-Ito, S., Uemura, T., Maeda, A., Shiroshima, T., Yoshida, T., and Fukai, S. (2015b). Structure of Slitrk2-PTPδ complex reveals mechanisms for splicing-dependent trans-synaptic adhesion. *Sci. Rep.* **5**, 9686.
- Yang, D., and Hurley, L.H. (2006). Structure of the biologically relevant G-quadruplex in the c-MYC promoter. *Nucleosides Nucleotides Nucleic Acids* **25**, 951–968.
- Yang, X., Coulombe-Huntington, J., Kang, S., Sheykman, G.M., Hao, T., Richardson, A., Sun, S., Yang, F., Shen, Y.A., Murray, R.R., et al. (2016). Widespread Expansion of Protein Interaction Capabilities by Alternative Splicing. *Cell* **164**, 805–817.
- Yang, Y., Zhan, L., Zhang, W., Sun, F., Wang, W., Tian, N., Bi, J., Wang, H., Shi, D., Jiang, Y., et al. (2011). RNA secondary structure in mutually exclusive splicing. *Nat. Struct. Mol. Biol.* **18**, 159–168.
- Yates, F. (1934). Contingency tables involving small numbers and the χ^2 test. Supplement to the Journal of the Royal Statistical Society **1**, 217–235.
- Yee, B.A., Pratt, G.A., Graveley, B.R., Van Nostrand, E.L., and Yeo, G.W. (2019). RBP-Maps enables robust generation of splicing regulatory maps. *RNA* **25**, 193–204.
- Yeo, G., Holste, D., Kreiman, G., and Burge, C.B. (2004a). Variation in alternative splicing across human tissues. *Genome Biol.* **5**, R74.
- Yeo, G., Hoon, S., Venkatesh, B., and Burge, C.B. (2004b). Variation in sequence and organization of splicing regulatory elements in vertebrate genes. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 15700–15705.
- You, X., Vlatkovic, I., Babic, A., Will, T., Epstein, I., Tushev, G., Akbalik, G., Wang, M., Glock, C., Quedenau, C., et al. (2015). Neural circular RNAs are derived from synaptic genes and regulated by development and plasticity. *Nat. Neurosci.* **18**, 603–610.
- Zaia, K.A., and Reimer, R.J. (2009). Synaptic Vesicle Protein NTT4/XT1 (SLC6A17) Catalyzes Na⁺-coupled Neutral Amino Acid Transport. *Journal of Biological Chemistry* **284**, 8439–8448.
- Zarnack, K., König, J., Tajnik, M., Martincorena, I., Eustermann, S., Stévant, I., Reyes, A., Anders, S., Luscombe, N.M., and Ule, J. (2013). Direct competition between hnRNP C and U2AF65 protects the

- transcriptome from the exonization of Alu elements. *Cell* **152**, 453–466.
- Zeng, X., Lin, W., Guo, M., and Zou, Q. (2017). A comprehensive overview and evaluation of circular RNA detection tools. *PLoS Comput. Biol.* **13**, e1005420.
- Zhang, X.H.-F., and Chasin, L.A. (2006). Comparison of multiple vertebrate genomes reveals the birth and evolution of human exons. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 13427–13432.
- Zhang, D.-H., Fujimoto, T., Saxena, S., Yu, H.-Q., Miyoshi, D., and Sugimoto, N. (2010). Monomorphic RNA G-quadruplex and polymorphic DNA G-quadruplex structures responding to cellular environmental factors. *Biochemistry* **49**, 4554–4563.
- Zhang, J., Harvey, S.E., and Cheng, C. (2019a). A high-throughput screen identifies small molecule modulators of alternative splicing by targeting RNA G-quadruplexes. *Nucleic Acids Res.* **47**, 3667–3679.
- Zhang, X., Chen, M.H., Wu, X., Kodani, A., Fan, J., Doan, R., Ozawa, M., Ma, J., Yoshida, N., Reiter, J.F., et al. (2016). Cell-Type-Specific Alternative Splicing Governs Cell Fate in the Developing Cerebral Cortex. *Cell* **166**, 1147–1162.e15.
- Zhang, Z., Pan, Z., Ying, Y., Xie, Z., Adhikari, S., Phillips, J., Carstens, R.P., Black, D.L., Wu, Y., and Xing, Y. (2019b). Deep-learning augmented RNA-seq analysis of transcript splicing. *Nat. Methods* **16**, 307–310.
- Zhao, J., Bacolla, A., Wang, G., and Vasquez, K.M. (2010). Non-B DNA structure-induced genetic instability and evolution. *Cell. Mol. Life Sci.* **67**, 43–62.
- Zheng, S. (2016). Alternative splicing and nonsense-mediated mRNA decay enforce neural specific gene expression. *International Journal of Developmental Neuroscience* **55**, 102–108.