New perspectives on the evolution of within-individual genome variation and germline/soma distinction

Alexander Suh[1,2], Anne-Marie Dion-Côté[3]

[1]School of Biological Sciences – Organisms and the Environment, University of East Anglia, NR4 7TU, Norwich, UK

[2]Department of Organismal Biology – Systematic Biology, Evolutionary Biology Centre (EBC), Science for Life Laboratory, Uppsala University, SE-752 36, Uppsala, Sweden.

[3]Département de Biologie, Université de Moncton, Moncton, NB, E1A 3E9, Canada.

Correspondence: A.Suh@uea.ac.uk, anne-marie.dion-cote@umoncton.ca

Abstract

Genomes can vary significantly even within the same individual. The underlying mechanisms are manifold, ranging from somatic mutation and recombination, development-associated ploidy changes and genetic bottlenecks, over to programmed DNA elimination during germline/soma differentiation. In this perspective piece, we briefly review recent developments in the study of within-individual genome variation in eukaryotes and prokaryotes. We highlight an SMBE 2020 virtual symposium entitled "*Within-individual genome variation and germline/soma distinction*" and the present Special Section of the same name in *Genome Biology and Evolution*, together

fostering cross-taxon synergies in the field to identify and tackle key open questions in the understanding of within-individual genome variation.

Significance

Genome variation within an individual organism can arise through a plethora of mechanisms. Here we provide a perspective on recent developments in the study of within-individual genome variation as highlighted through a virtual symposium and the present Special Section in *Genome Biology and Evolution*, ranging from polyploidy in bacteria, uniparental genome elimination in fishes, mitochondrial heteroplasmy in molluscs, to germline-restricted chromosomes in insects and songbirds. We outline key open questions that can be addressed through combination of diverse methods and diverse study systems.

Main text

1. Emerging appreciation of diverse forms of within-individual genome variation

The dynamic nature of organismal genomes is becoming increasingly appreciated. Perhaps the longest known form of within-individual genome variation is somatic mutation, specifically the movement of transposable elements in maize kernels whose observable phenotype led to the discovery of gene regulation by Barbara McClintock (McClintock 1950, 1956). For the sake of clarity, "germline" refers to the cells or nuclei bearing the genome to be transmitted to the next generation while the term "soma" applies to all other cells that may exhibit genome variation relative to each other, or to the germline. Despite these definitions, we emphasize that some organisms do not necessarily have a clear distinction between the germline and soma, and some

forms of within-individual genome variation occur in multicellular and unicellular eukaryotes, and even prokaryotes.

Somatic variation may occur through mutations (single-nucleotide changes, small-scale or large-scale structural changes) in individual cells or nuclei during development (Fig. 1A), and is perhaps best studied in the form of complex mutations in human cancer (Chang, et al. 2015; Voronina, et al. 2020), retrotransposition in the human brain (Jönsson, et al. 2020), and single-nucleotide changes in long-lived plants and fungi (Schmid-Siegert, et al. 2017; Hiltunen, et al. 2019; Schoen and Schultz 2019). Another type of somatic variation can arise through somatic recombination, such as in the V(D)J locus of human lymphocytes generating genetic variation for antibodies and T cell receptors (Schatz and Ji 2011). Rather than sequence changes, somatic variation can also arise from ploidy changes during development (Fig. 1B), with prominent examples being the giant polytene chromosomes in the salivary glands of insects (Stormo and Fox 2017) as well as hepatocytes in mammals (Neiman, et al. 2017). Lesser recognized examples are extreme ploidy changes in various groups of unicellular eukaryotes which contain more than one nucleus (Parfrey, et al. 2008) and even some prokaryotes (Angert 2021).

Organellar genomes add another dimension to within-individual genome variation in that different genotypes may coexist (heteroplasmy) and segregate differently during development (Fig. 1C) (Stewart and Larsson 2014; Breton, et al. 2015). Mitochondrial heteroplasmy of some bivalves might be particularly prone to such patterns due to their doubly uniparental inheritance, i.e., sex-specific transmission of otherwise coexisting maternal and paternal mitochondria

(Zouros, et al. 1994; Capt, et al. 2020; Stewart, et al. 2020), which contrasts sharply with the usually strictly maternal inheritance of animal mitochondria.

Uniparental genome elimination, i.e., the elimination of either the maternal or paternal chromosome set during development (Fig. 1D) (Gardner and Ross 2014), may not necessarily lead to within-individual genome variation if elimination only happens during meiosis. However, in some arthropods with paternal genome elimination such as predatory mites, the paternal chromosomes are not silenced but eliminated from the soma (Nelson-Rees, et al. 1980). A form of uniparental genome elimination also exists in some hybrid lineages undergoing hybridogenesis such as *Pelophylax* frogs (Chmielewska et al. 2018), in which a chromosome complement from one parental species is eliminated without recombination during meiosis (reviewed in Lamatsch and Stöck 2009; Dalziel, et al. 2020). Fertilization of the haploid oocytes by one of the parental species regenerates diploidy in offspring, which are thus effectively hemiclonal (Lavanchy and Schwander 2019).

An especially peculiar form of within-individual genome variation is caused by programmed DNA elimination during development (Fig. 1E-F). The resulting, often significant, germline/soma genome differences have been observed in a wide range of animals and ciliates, (Wang and Davis 2014; Smith, et al. 2021), two taxa with an early distinction between germline and soma (germline and somatic cells in animals; micronucleus and macronucleus in ciliates). As a detailed review is beyond the scope of this perspective piece, we point the reader to comprehensive reviews of programmed DNA elimination across ciliates (Chalker and Yao 2011; Bracht, et al. 2013; Noto and Mochizuki 2018) and vertebrates (Smith, et al. 2021). During

programmed genome rearrangement or chromatin diminution (Fig. 1E), specific regions of chromosomes are eliminated from the differentiating macronucleus in ciliates, as well as from differentiating somatic cells of some nematodes, copepods, and other animals, leading to extensive genome rearrangements in these organisms (Wang and Davis 2014). Recent genomic and transcriptomic data in ciliates, nematodes, and have revealed that eliminated sequences include both germline-expressed genes and repetitive sequences in varying proportions depending on the study system (Wang, et al. 2012; Hamilton, et al. 2016; Wang, et al. 2017).

Another form of programmed DNA elimination entails the loss of entire chromosomes during germline/soma differentiation (Fig. 1F), which may either affect sex chromosomes as, for example, in a marsupial species (Close 1984; Wang and Davis 2014) or so-called germline-restricted chromosomes (GRCs) of hagfishes, songbirds, and some arthropods (Wang and Davis 2014; Smith, et al. 2021). In lampreys, entire chromosomes are eliminated from somatic cells (Timoshevskiy, et al. 2019) and pioneer transcriptomic studies have revealed that these contain germline-expressed genes and repetitive sequences (Smith et al. 2012; Bryant et al. 2016; Smith et al. 2018). Although some insects have numerous GRCs (Hodson and Ross 2021) and the zebra finch GRC is the largest chromosome of its karyotype (Pigozzi and Solari 1998), genomic and transcriptomic data of any GRCs have been restricted to a 19-kb intergenic region of zebra finch GRCs until recently (Itoh, et al. 2009). It is only recently that a wealth of sequencing data has provided first glimpses into the sequence content of GRCs of songbirds (Biederman, et al. 2018; Kinsella, et al. 2019; Torgasheva, et al. 2019; Pei, et al. 2021) and sciarid flies (Hodson, et al. 2021), revealing that GRCs contain many dozens to hundreds of genes, and that they may have existed for millions of years in these lineages (Kinsella, et al. 2019; Hodson, et al. 2021).

Taken together, the study of the diverse forms of within-individual genome variation is currently undergoing a transformation towards more diverse study systems across the tree of life.

2. An SMBE 2020 virtual symposium showcasing diversity of the field

Together with *Genome Biology and Evolution* editor-in-chief Laura A. Katz, we had initially planned a symposium to showcase the diversity of the present topic as part of the SMBE 2020 meeting, which was to be held in Québec City on June 28 to July 02, 2020, to foster exchange across study systems and career stages. After pandemic events led to a cancellation of the in-person meeting, we organized the symposium as a free-of-charge virtual event on June 29, 2020. The keynote speaker and the six speakers selected from submitted abstracts for the original in-person meeting all agreed to participate in the virtual symposium. We also solicited additional abstracts for virtual poster presentations on short notice, from which we selected six. Nearly 129 participants registered, representing 35 nationalities working in 24 countries.

The selection of talks and posters spanned the breadth of study systems and career stages among symposium participants. Laurence Hurst gave a 15-minute keynote talk entitled "*The human early embryo is a selection arena*", and 5-minute regular talks from submitted abstracts were given by Esther Angert on "*Challenges faced by highly polyploid bacteria with limits on chromosome inheritance*", Marie-Julie Favé on "*Multi-omics profiles of somatic mutations in immune cells from an aging human population*", Christina Hodson on "*Evolution of a germline restricted chromosome in the fungus gnat* Sciara coprophila", Mariangela Iannello on "*A naturally heteroplasmic clam shows the effects of genetic bottleneck on paternal mtDNA*",

Zuzana Majtanová on "*Chromosome dynamics of sexually-parasitic, unisexual carp gudgeons (*Hypseleotris*)*", and Jeramiah Smith on "*Programmed genome rearrangement in lamprey*". Subsequently, the six poster presenters gave 2-minute lightning talks about their posters further highlighting the diversity of study systems, followed by poster presentations in three virtual rooms which allowed participants to move freely between topics and discussions.

Peak attendance was around 120 participants and our impression was that the real-time virtual symposium with written chat function, combined with a permanent written discussion board, encouraged participants, and especially early-career researchers, to ask questions in a written manner on both platforms, allowing speakers to respond to questions in spoken and written form as time permitted. Taken together, we believe that the free-of-charge virtual format with shorter talks led to participation of researchers from across the world, at all career stages, and may have ultimately increased diversity in this symposium beyond what would have been possible at an in-person symposium.

3. A Special Section with new insights into within-individual genome variation

In this Special Section of *Genome Biology and Evolution*, we synthesized some of the key insights discussed at the virtual SMBE symposium. Four of the symposium speakers contribute a manuscript with their respective coauthors, and we believe that this selection of manuscripts highlights the diversity of study systems, methods, and concepts for tackling key questions of the field.

Angert (2021) reviews a phenomenon that many eukaryote biologists are probably not aware of – polyploidy in bacteria. Some firmicute bacteria are highly polyploid and produce intracellular offspring instead of binary fission, leading to some chromosome copies effectively having a somatic role by not being passed on to the offspring (Angert 2021).

Majtánová et al. (2021) show that hybrid carp gudgeons undergo uniparental genome elimination, effectively resulting in hybridogenesis. The authors also reveal that genome elimination occurs pre-meiotically during the juvenile stage, followed by the duplication of the other chromosome complement before meiosis entry (Majtánová, et al. 2021). This means that diploid somatic cells bear one copy of each parental species genome, whereas pre-meiotic germline cells bear two copies of one parental genome.

Iannello et al. (2021) investigate mitochondrial heteroplasmy in a bivalve species with doubly uniparental inheritance. Their results reveal pronounced differences in mitochondrial genotypes among different tissues, possibly as a result of a strong bottleneck early during development (Iannello, et al. 2021).

Hodson & Ross (2021) review the diversity of germline-restricted chromosomes in dipteran insects, showcasing the known distribution of GRCs among Sciaridae (dark-winged fungus gnats), Cecidomyiidae (gall gnats), and Chironomidae (non-biting midges). Depending on the taxon, these insects exhibit a single and up to dozens of GRCs with either paternal, maternal, or unbiased inheritance (Hodson and Ross 2021). The authors discuss the potential of genome

sequencing for a deeper understanding of GRCs and highlight key questions regarding the evolution of GRCs in dipteran insects.

Finally, Asalone et al. (2021) present a transcriptomic-based pipeline that they modified to detect germline-restricted sequences in zebra finch. This method relies on aligning whole genome sequencing reads to a germline genome assembly to detect germline-specific sequences based on read depth. Their approach identifies several newly identified germline-restricted contigs, 51 of which they validated by qPCR.

4. Next steps towards elucidating the evolution of within-individual genome variation

This Special Section highlights the diversity of within-individual genome variation both in terms of study systems and methods, and that the field is further progressing thanks to the development of cost-efficient or sample-efficient methods for high-throughput data generation. In particular, we anticipate that the continuous improvement of sequencing read length and quality (Sedlazeck, et al. 2018) will further increase the resolution for detecting different types of somatic variation, ranging from single-nucleotide variants to large-scale structural variants. Similarly, the development of ultra-low-input libraries for long-read sequencing (Kingan, et al. 2019) promises the opportunity of studying within-individual genome variation in organisms with small bodies and/or tissues. However, there is a disconnect between signal/noise in sequencing data and actual chromosome structure which may remain for some genomic regions until accurate megabase-scale reads are available (Peona, et al. 2018), and we therefore emphasize the importance of validating complex genomic results with molecular cytogenetic methods (Deakin, et al. 2019).

Which forms of within-individual genome variation are stochastic vs. fulfill a biological function remains elusive (Box 1), as well as what biological function that might be. The latter is exemplified by the phenomenon of programmed DNA elimination which has been proposed to either be a means to limit selfish genetic elements to the germline or to minimize antagonistic pleiotropy of genes that are beneficial for the germline but deleterious for the soma (Smith et al. 2012; Wang and Davis 2014; Smith 2017). Comparisons of closely related species are necessary to solve such "chicken or egg" problems, as well as developmental and functional genomics of key candidate genes across different developmental stages. To conclude, the time may have come for agnostic "fishing expeditions" to test whether within-individual genome variation, especially in the form of massive germline/soma genome differences, are the odd exception or the overlooked rule across the Tree of Life.

Acknowledgements

We thank *Genome Biology and Evolution* editors-in-chief Laura A. Katz and Adam Eyre-Walker for inviting us to prepare this Special Section and perspective piece. We are grateful to all presenters and participants for the valuable interactions at the SMBE 2020 virtual symposium, and to the Special Section authors for contributing their manuscripts. We also wish to thank Simone Fouché, Augustin Chen, Francisco J. Ruiz-Ruano, and four reviewers for their constructive feedback on an earlier version of this manuscript. A.S. was supported by the Swedish Research Council Vetenskapsrådet (2016-05139, 2020-04436) and the Swedish Research Council Formas (2017-01597). A.M.D.C. was supported by the National Sciences and Engineering Research Council of Canada (RGPIN-2019-05744).

References

Angert ER. 2021. Challenges faced by highly polyploid bacteria with limits on DNA inheritance. Genome Biol Evol in press.

Biederman MK, Nelson MM, Asalone KC, Pedersen AL, Saldanha CJ, Bracht JR. 2018. Discovery of the first germline-restricted gene by subtractive transcriptomic analysis in the zebra finch, *Taeniopygia guttata*. Curr Biol 28:1620-1627.

Bracht John R, Fang W, Goldman Aaron D, Dolzhenko E, Stein Elizabeth M, Landweber Laura F. 2013. Genomes on the edge: programmed genome instability in ciliates. Cell 152:406-416.

Breton S, Stewart DT, Bonen L. 2015. Atypical mitochondrial inheritance patterns in eukaryotes. Genome 58:423-431.

Bryant SA, Herdy JR, Amemiya CT, Smith JJ. 2016. Characterization of somatically-eliminated genes during development of the sea lamprey (*Petromyzon marinus*). Mol Biol Evol 33:2337-2344.

Capt C, Bouvet K, Guerra D, Robicheau BM, Stewart DT, Pante E, Breton S. 2020. Unorthodox features in two venerid bivalves with doubly uniparental inheritance of mitochondria. Sci Rep 10:1087.

Chalker DL, Yao M-C. 2011. DNA elimination in ciliates: transposon domestication and genome surveillance. Annu Rev Genet 45:227-246.

Chang MT, Asthana S, Gao SP, Lee BH, Chapman JS, Kandoth C, Gao J, Socci ND, Solit DB, Olshen AB, et al. 2015. Identifying recurrent mutations in cancer reveals widespread lineage diversity and mutational specificity. Nat Biotech advance online publication.

Chmielewska M, Dedukh D, Haczkiewicz K, Rozenblut-Kościsty B, Kaźmierczak M, Kolenda K, Serwa E, Pietras-Lebioda A, Krasikova A, Ogielska M. 2018. The Programmed DNA Elimination and Formation of Micronuclei in Germ Line Cells of the Natural Hybridogenetic Water Frog Pelophylax Esculentus. Scientific Reports 8 (1): 7870.

Close R. 1984. Rates of sex chromosome loss during development in different tissues of the bandicoots *Perameles nasuta* and *Isoodon macrourus* (Marsupialia: Peramelidae). Australian Journal of Biological Sciences 37:53-62.

Dalziel AC, Tirbhowan S, Drapeau HF, Power C, Jonah LS, Gbotsyo YA, Dion-Côté A-M. 2020. Using asexual vertebrates to study genome evolution and animal physiology: Banded (*Fundulus diaphanus*) x Common Killifish (*F. heteroclitus*) hybrid lineages as a model system. Evolutionary Applications 13:1214-1239.

Deakin JE, Potter S, O'Neill R, Ruiz-Herrera A, Cioffi MB, Eldridge MDB, Fukui K, Marshall Graves JA, Griffin D, Grutzner F, et al. 2019. Chromosomics: Bridging the gap between genomes and chromosomes. Genes 10:627.

Gardner A, Ross L. 2014. Mating ecology explains patterns of genome elimination. Ecol Lett 17:1602-1612.

Hamilton EP, Kapusta A, Huvos PE, Bidwell SL, Zafar N, Tang H, Hadjithomas M, Krishnakumar V, Badger JH, Caler EV, et al. 2016. Structure of the germline genome of *Tetrahymena thermophila* and relationship to the massively rearranged somatic genome. eLife 5:e19090.

Hiltunen M, Grudzinska-Sterno M, Wallerman O, Ryberg M, Johannesson H. 2019. Maintenance of high genome integrity over vegetative growth in the fairy-ring mushroom *Marasmius oreades*. Curr Biol 29:2758-2765.e2756.

Hodson CN, Jaron KS, Gerbi S, Ross L. 2021. Evolution of gene-rich germline restricted chromosomes in black-winged fungus gnats through introgression (Diptera: Sciaridae). bioRxiv:2021.2002.2008.430288.

Hodson CN, Ross L. 2021. Evolutionary perspectives on germline restricted chromosomes in flies (Diptera). Genome Biol Evol in press.
Iannello M, Bettinazzi S, Breton S, Ghiselli F, Milani L. 2021. A naturally heteroplasmic clam provides clues about the effects of genetic bottleneck on paternal mtDNA. Genome Biol Evol.
Itoh Y, Kampf K, Pigozzi MI, Arnold AP. (Itoh2009 co-authors). 2009. Molecular cloning and characterization of the germline-restricted chromosome sequence in the zebra finch. Chromosoma 118:527-536.
Jönsson ME, Garza R, Johansson PA, Jakobsson J. 2020. Transposable elements: a common feature of neurodevelopmental and neurodegenerative disorders. Trends Genet 36:610-623.
Kingan SB, Heaton H, Cudini J, Lambert CC, Baybayan P, Galvin BD, Durbin R, Korlach J, Lawniczak MKN. 2019. A high-quality de novo genome assembly from a single mosquito using PacBio sequencing. Genes 10:62.
Kinsella CM, Ruiz-Ruano FJ, Dion-Côté A-M, Charles AJ, Gossmann TI, Kappei JCD, Hemmings N, Simons MJP, Camacho JPM, Forstmeier W, et al. 2019. Programmed DNA elimination of germline development genes in songbirds. Nat Commun 10:5468.
Lamatsch DK, Stöck M. 2009. Sperm-Dependent Parthenogenesis and Hybridogenesis in Teleost Fishes. In: Schön I, Martens K, Dijk P, editors. Lost Sex: The Evolutionary Biology of Parthenogenesis. Dordrecht: Springer Netherlands. p. 399-432.
Lavanchy G, Schwander T. 2019. Hybridogenesis. Curr Biol 29:R9-R11.
Majtánová Z, Dedukh D, Choleva L, Adams M, Ráb P, Unmack PJ, Ezaz T. 2021. Uniparental genome elimination in Australian carp gudgeons. Genome Biol Evol.
McClintock B. 1956. Controlling elements and the gene. Cold Spring Harb Symp Quant Biol 21:197-216.
McClintock B. 1950. The origin and behavior of mutable loci in maize. Proceedings of the National Academy of Sciences 36:344-355.
Neiman M, Beaton MJ, Hessen DO, Jeyasingh PD, Weider LJ. 2017. Endopolyploidy as a potential driver of animal ecology and evolution. Biological Reviews 92:234-247.
Nelson-Rees WA, Hoy MA, Roush RT. 1980. Heterochromatinization, chromatin elimination and haploidization in the parahaploid mite Metaseiulus occidentalis (Nesbitt) (Acarina: Phytoseiidae). Chromosoma 77:263-276.
Noto T, Mochizuki K. 2018. Small RNA-mediated trans-nuclear and trans-element communications in *Tetrahymena* DNA elimination. Curr Biol 28:1938-1949.e1935.
Parfrey LW, Lahr DJG, Katz LA. 2008. The dynamic nature of eukaryotic genomes. Mol Biol Evol 25:787-794.
Pei Y, Forstmeier W, Ruiz-Ruano FJ, Mueller JC, Cabrero J, Camacho JPM, Alche JD, Franke A, Hoeppner M, Boerno S, et al. 2021. Occasional paternal inheritance of the germline-restricted chromosome in songbirds. bioRxiv:2021.2001.2028.428604.
Peona V, Weissensteiner MH, Suh A. 2018. How complete are 'complete' genome assemblies? – An avian perspective. Mol Ecol Resour 18:1188-1195.
Pigozzi MI, Solari AJ. 1998. Germ cell restriction and regular transmission of an accessory chromosome that mimics a sex body in the zebra finch, *Taeniopygia guttata*. Chromosome Res 6:105-113.
Schatz DG, Ji Y. 2011. Recombination centres and the orchestration of V(D)J recombination. Nature Reviews Immunology 11:251-263.
Schmid-Siegert E, Sarkar N, Iseli C, Calderon S, Gouhier-Darimont C, Chrast J, Cattaneo P, Schütz F, Farinelli L, Pagni M, et al. 2017. Low number of fixed somatic mutations in a long-lived oak tree. Nature Plants 3:926-929.
Schoen DJ, Schultz ST. 2019. Somatic Mutation and Evolution in Plants. Annu Rev Ecol Evol Syst 50:49-73.

Sedlazeck FJ, Lee H, Darby CA, Schatz MC. 2018. Piercing the dark matter: bioinformatics of long-range sequencing and mapping. Nat Rev Genet 19:329-346.
Smith JJ. 2017. Large-scale programmed genome rearrangements in vertebrates. In: Li X-Q, editor. Somatic Genome Variation in Animals, Plants, and Microorganisms. Hoboken, NJ: Wiley-Blackwell. p. 45-54.
Smith Jeramiah J, Baker C, Eichler Evan E, Amemiya Chris T. 2012. Genetic consequences of programmed genome rearrangement. Curr Biol 22:1524-1529.
Smith JJ, Timoshevskaya N, Ye C, Holt C, Keinath MC, Parker HJ, Cook ME, Hess JE, Narum SR, Lamanna F, et al. 2018. The sea lamprey germline genome provides insights into programmed genome rearrangement and vertebrate evolution. Nat Genet 50:270-277.
Smith JJ, Timoshevskiy VA, Saraceno C. 2021. Programmed DNA elimination in vertebrates. Annu Rev Anim Biosci 9:null.
Stewart DT, Breton S, Chase EE, Robicheau BM, Bettinazzi S, Pante E, Youssef N, Garrido-Ramos MA. 2020. An Unusual Evolutionary Strategy: The Origins, Genetic Repertoire, and Implications of Doubly Uniparental Inheritance of Mitochondrial DNA in Bivalves. In: Pontarotti P, editor. Evolutionary Biology—A Transdisciplinary Approach. Cham: Springer International Publishing. p. 301-323.
Stewart JB, Larsson N-G. 2014. Keeping mtDNA in shape between generations. PLoS Genet 10:e1004670.
Stormo BM, Fox DT. 2017. Polyteny: still a giant player in chromosome research. Chromosome Res 25:201-214.
Timoshevskiy VA, Timoshevskaya NY, Smith JJ. 2019. Germline-specific repetitive elements in programmatically eliminated chromosomes of the sea lamprey (*Petromyzon marinus*). Genes 10:832.
Torgasheva AA, Malinovskaya LP, Zadesenets KS, Karamysheva TV, Kizilova EA, Akberdina EA, Pristyazhnyuk IE, Shnaider EP, Volodkina VA, Saifitdinova AF, et al. 2019. Germline-restricted chromosome (GRC) is widespread among songbirds. Proc Natl Acad Sci USA 116:11845-11850.
Voronina N, Wong JKL, Hübschmann D, Hlevnjak M, Uhrig S, Heilig CE, Horak P, Kreutzfeldt S, Mock A, Stenzinger A, et al. 2020. The landscape of chromothripsis across adult cancer types. Nat Commun 11:2320.
Wang J, Davis RE. 2014. Programmed DNA elimination in multicellular organisms. Curr Opin Genet Dev 27:26-34.
Wang J, Gao S, Mostovoy Y, Kang Y, Zagoskin M, Sun Y, Zhang B, White LK, Easton A, Nutman TB, et al. 2017. Comparative genome analysis of programmed DNA elimination in nematodes. Genome Res 27:2001-2014.
Wang J, Mitreva M, Berriman M, Thorne A, Magrini V, Koutsovoulos G, Kumar S, Blaxter Mark L, Davis Richard E. 2012. Silencing of germline-expressed genes by DNA elimination in somatic cells. Dev Cell 23:1072-1080.
Zouros E, Oberhauser Ball A, Saavedra C, Freeman KR. 1994. An unusual type of mitochondrial DNA inheritance in the blue mussel Mytilus. Proc Natl Acad Sci USA 91:7463-7467.

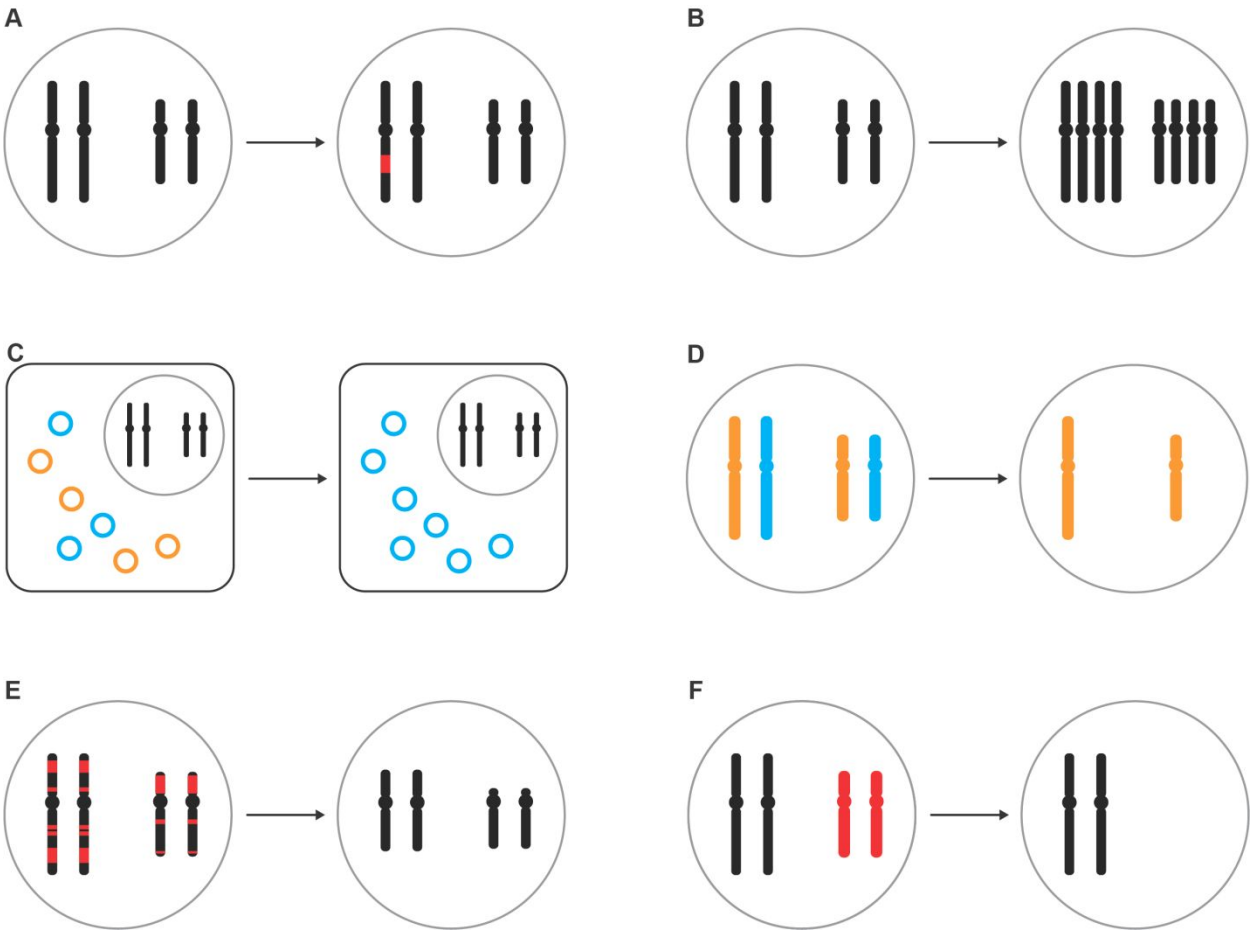

Figure 1: The diversity of within-individual genome variation. The patterns to the left of each arrow reflect the individual's genome as inherited from the parental generation and to be transmitted to the offspring ("germline"), while the patterns to the right of each arrow illustrate genome variation in some cells or nuclei of the individual ("soma"), although further variation may exist within germline and soma, respectively. (A) Somatic variation (red) generated by somatic mutation or somatic recombination. (B) Somatic variation generated by ploidy change. (C) Within-individual mitochondrial heteroplasmy (orange vs. blue). (D) Uniparental genome elimination of either maternal or paternal chromosomes (orange vs. blue). (E) Programmed DNA elimination of chromosome fragments (red; also known as programmed genome rearrangement or chromatin diminution) from the somatic genome. (F) Programmed DNA elimination of entire chromosomes (red; e.g., germline-restricted chromosomes) from the somatic genome. Shown are schematic illustrations of a karyotype with metacentric chromosomes inside a nucleus (grey circle), though some of these mechanisms may also apply to holocentric chromosomes of eukaryotes or circular chromosomes of prokaryotes. Note that some of these forms of variation may also arise during meiosis, leading to within-germline genome variation.

Box 1: Key questions for the study of within-individual genome variation and germline/soma distinction.

1. How common are the different forms of within-individual genome variation across the tree of life?
2. What are the beneficial, neutral, or deleterious effects of the different forms of within-individual genome variation?
3. Are there currently unknown forms of germline/soma, within-soma, or within-germline genome variation that await discovery with new sequencing technologies?