Mendel's laws of heredity on his 200th birthday: What have we learned by considering exceptions?

Jason B. Wolf[1,*], Anne C. Ferguson-Smith[2] & Alexander Lorenz[3]

[1]Department of Biology & Biochemistry and The Milner Centre for Evolution, University of Bath, Bath, UK
[2] Department of Genetics, University of Cambridge, UK
[3]Institute of Medical Sciences (IMS), University of Aberdeen, Aberdeen, UK

*Correspondence should be addressed to Jason B. Wolf (E-mail: j.b.wolf@bath.ac.uk)

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Discovery in science is often driven forward more by exceptions than by rules. In the field of genetics, the basic 'rules' are often taught in the form of Mendel's laws of heredity (Bateson, 1909). Formally, these laws are given as the 'law of dominance', the 'law of segregation', and the 'law of independent assortment', which are all ultimately components of an underlying assumption of particulate diploid inheritance. We now recognise that these laws are manifestations of the formation of gametes through meiosis and inheritance of allelic variants at autosomal loci. Although these laws were developed in the absence of any understanding of their causal basis, they nonetheless hold (at least loosely speaking) quite broadly. Consequently, they provided a key foundation for the development of the field of genetics for much of the 20th century. However, recent decades have seen an explosion in discoveries that violate even the broad rules of quasi-Mendelian inheritance, which has driven the field of genetics forward by leaps and bounds. The more we learn, the more we realise that these 'exceptions' can play key roles in shaping patterns of inheritance and can have important impacts on evolutionary processes. Hence, while the cliché may be that the exceptions prove the rule, when it comes to inheritance, it is becoming obvious that the exceptions complement the rule, and that, together, the rules and their exceptions combine to form a unified framework for understanding the basis of variation in nature.

Violations of Mendel's laws can generically be referred to as 'non-Mendelian inheritance'. However, from that broad perspective, nearly all inheritance systems would show non-Mendelian inheritance (at least to some degree). To hold exactly, Mendel's laws impose strict requirements: a locus has to contain two allelic variants that have discrete effects on categorical (or at least discrete and countable) traits, and they must show complete dominance. These strict conditions are rarely met in real systems (Hou *et al.*, 2016), both because allelic effects do not adhere to the strict law of dominance and because many traits of interest show continuous variation. Mendel recognised many of the exceptions related to effects of alleles, such as the presence of incomplete dominance, pleiotropy, and epistasis (see (Fairbanks, 2022), this volume), and Fisher (1918) reconciled the assumption of Mendelian inheritance with continuous variation. Hence, from this perspective, a large array of scenarios that show non-Mendelian inheritance are actually consistent with the conceptual foundation of Mendel's perspective based on elemental inheritance. Therefore, it is outside of this 'quasi-Mendelian inheritance' space (i.e., scenarios that do not challenge the underlying logical basis to the laws) that the field has been really pushing forward our understanding of genetics. By delving into this realm, the field has strived to capture, characterise, and dissect the broad array of inheritance mechanisms and phenomena that together determine patterns of inheritance. This is a direct continuation of the work that Mendel contributed towards understanding the basis of natural variation, which persists as one of the fundamental problems in genetics (and the core of the fields covered by *Heredity*). Moreover, Mendel took an interest in Darwin's writings (and his views on inheritance in particular) and was interested in evolutionary processes such as hybridization (Fairbanks, 2022) and how the shuffling of traits from one generation to the next creates diversity in a long-term evolutionary timeframe (see (van Dijk and Ellis, 2022), this volume), important topics such as this

continue to be very active areas of research in evolutionary genetics.

There is a diverse assortment of phenomena that can lead to violations of quasi-Mendelian inheritance, so rather than attempting a comprehensive overview of this problem here, we provide an outline of the basic classes of scenarios that cause non-Mendelian inheritance. The contributions in this special issue cover a range of these non-Mendelian phenomena, which we hope will encourage further research and conversations into processes that shape diversity in nature. The simplest scenarios essentially build on Mendel's own recognition that there can be phenomena that complicate (what we would call) the genotype-phenotype relationship (but where the system otherwise conforms to the basic logic of the Mendelian model). In addition to the phenomena recognised by Mendel that are mentioned above (epistasis, pleiotropy, and incomplete dominance), linkage disequilibrium can lead to the violation of the law of independent assortment. This possibility was recognized soon after the 'rediscovery' of Mendel's work and is easily reconciled with his conception of inheritance (Bateson *et al.*, 1905; Morgan, 1911). However, other phenomena, such as maternal genetic effects, where genes expressed in the mother affect the expression of traits in the offspring, can arise from what are essentially Mendelian factors, but lead to an indirect connection between the genotype and phenotype (Cheverud and Wolf, 2009; Wolf and Wade, 2016). Recognition of the potential for such indirect connections between genotype and phenotype has sparked a range of investigations that have demonstrated that this can be an important component of inheritance (Hadfield, 2012). There is also an array of scenarios where DNA is inherited, but is not autosomal (or even nuclear), which will typically lead to an exception to Mendel's laws, but still conforms to the underlying process in which allelic differences determine phenotypic differences. This includes sex chromosomes (see (Charlesworth, 2022; Ruiz-Herrera and Waters, 2022), this volume), cytoplasmic inheritance (including organelles, plasmids etc.; see (Camus *et al.*, 2022), this volume), and other extra-chromosomal factors.

Meiosis is the fundamental process underlying Mendelian genetics, as the chromosomal transactions occurring during meiosis enable the Mendelian laws of segregation and of independent assortment. While meiosis leads to the formation of gametes in sexual species, it does not require separate sexes. Consequently, because Mendel based his work on garden peas (*Pisum sativum*), which are hermaphroditic, his laws of heredity failed to recognize the potential role of sex-limited or sex-linked inheritance. However, in many multicellular eukaryotes, sex is determined by the presence of sex chromosomes (Bachtrog *et al.*, 2014), creating the opportunity for sex-linked inheritance, which, while it violates Mendelian laws, provides a simple extension of the principles of Mendelian inheritance. Generally, one sex is homogametic (e.g. XX chromosomes in female mammals or ZZ chromosomes in male birds), whereas the opposite sex is heterogametic (e.g. XY chromosomes in male mammals and WZ chromosomes in female birds). During meiosis, homologous autosomes pair and recombine, which subsequently enables their correct segregation. The homomorphic sex chromosomes (XX, ZZ) behave just like autosomes as they are homologous to each other (and hence can essentially follow the principles of Mendelian inheritance). However, the prerequisite of homologous pairing and recombination for accurate segregation creates a major problem with heteromorphic sex chromosomes (XY, WZ) since they are not homologous to each other. Although the X and Y chromosomes in mammals often harbour pseudoautosomal regions at their respective tips that allow for pairing and recombination, and aid in their segregation, they overlap very little in their genic content, which allows for sex-linked inheritance. The evolutionary divergence of heteromorphic sex chromosomes can generate selection pressures (e.g., via degeneration of the sex-limited chromosome and the likelihood of sex chromosome loss) that interact with properties of meiosis (e.g., rate of recombination and the processes that enable meiotic sex chromosome pairing) to shape broad taxonomic patterns of sex chromosome evolution (Ruiz-Herrera and Waters, 2022).). Mendel studied a plant species without separate sexes (which is the overwhelming norm in diploid plants). Although the sex chromosomes of plant species (Charlesworth, 2019; Leite Montalvão *et al.*, 2021) are less well studied than their mammalian counterparts, visibly different sex chromosomes occur in a range of species. The existence of sex chromosomes even in more ancient plant lineages such as bryophytes (mosses and liverworts) was demonstrated more than 100 years ago (Allen, 1917), and they represent a particularly intriguing and enigmatic system, because bryophyte sex chromosomes determine the sex of the haploid gametophyte. As a consequence, the diploid sporophyte will always contain heteromorphic sex chromosomes. This situation is thus very different from diploid plants

and animals, and offers a unique vantage point on sex chromosome evolution (Charlesworth, 2022) that demonstrates an important exception to Mendel's laws. There are also phenomena in which variation is still strictly determined by inheritance of allelic differences, but some process leads to a violation of the law of segregation. The simplest example is the case where transmission is biased because meiosis is 'unfair'. This violation is referred to as meiotic drive and can be caused by chromosome segregation distortions during meiotic cell division or later-on by events during gametogenesis; the former is often called 'true meiotic drive' (see (Searle and Pardo-Manuel de Villena, 2022), this volume). Meiotic drivers are selfish genetic elements that game the system during plant and animal oogenesis. Because oocytes are generated by asymmetric meiotic divisions, the fitness of an allele depends critically on whether it ends up in the egg or a polar body. Meiotic drivers are more likely to be transmitted to the egg, thus ensuring their inheritance into the next generation. It is easy to imagine how meiotic drivers can mould the genetic make-up of populations (Searle and Pardo-Manuel de Villena, 2022). Meiotic drive is likely to be a common phenomenon that can have important impacts on population genetics and evolution and is of key interest for its application to population control (see (Veller, 2022), this volume). Importantly, meiotic drive can also be suppressed, and Veller (2022) presents a mathematical model to examine selection on suppressors that are linked or unlinked to the original drive locus to understand the circumstances that favour these two types of suppressors. Transmission distortion can also arise from processes such as gene conversion and postmeiotic segregation that alter allelic inheritance in meiosis. Gene conversion and postmeiotic segregation events result from the repair of programmed meiotic DNA double-strand breaks via homologous recombination and represent non-reciprocal genetic exchanges (Hunter, 2015). These processes alter the distribution frequencies of alleles in gametes, thus defying Mendelian laws (see (Lorenz and Mpaulo, 2022), this volume).

In addition to these various phenomena that essentially modify the effect or inheritance of DNA-based variation, it is possible that epigenetic phenomena can modify the genotype-phenotype relationship and lead to different patterns of inheritance, even with the same DNA sequences. Genomic imprinting is the consequence of epigenetic marks differentially established in the male and female germlines resulting in such genes being expressed according to parental origin (Bartolomei and Ferguson-Smith, 2011). The process of genomic imprinting therefore disrupts the Mendelian equivalence of the parental genomes on offspring phenotype. It is noteworthy that in mammalian systems, germline-derived epigenetic modifications with the exception of imprints, are erased in early development. Furthermore, during germline development, epigenetic marks, including imprints, are erased and new marks reconstructed such that epigenetic states acquired in one generation are not generally transmitted to the next. Across a broad array of organisms, epigenetic marks alter the accessibility of DNA sequences, which can result in promotion or repression of gene expression depending on the properties of the tagged sequence. For example, DNA methylation can lead to modification of chromatin structure, leading to transcriptional inactivation of a sequence. DNA methylation can depend on a range of factors and can be altered by environmental conditions, leading to variability in patterns of inheritance. The epigenetic control of gene expression, such as in the case of genomic imprinting, can shape patterns of inheritance (O'Brien and Wolf, 2019), and can play important roles in determining incidence of key diseases such as cancer (see (Dobosz *et al.*, 2022), this volume) and cardiovascular disease (Dong *et al.*, 2002). Intriguingly, transgenerational inheritance violating Mendelian laws can also be achieved through RNA and protein molecules rather than genomic imprinting (Harvey *et al.*, 2018; Kaletsky *et al.*, 2020; Toker *et al.*, 2022). Recently, such factors have been implicated in contexts in which the influence of the environment experienced by one generation has been observed in the next (Miska and Ferguson-Smith, 2016; Conine and Rando, 2022). This may be considered reminiscent of the transmission of gemmules proposed by Darwin in his provisional theory of inheritance known as Pangenesis. Mendel's response to Pangenesis is reviewed by van Dijk and Ellis (2022). In summary, the above-mentioned epigenetic phenomena illustrate that inheritance can be entirely non-genetic. Although once cast aside as an extension of Lamarckian inheritance (Mayr, 1982), research in the last two decades has argued for the potential importance of non-genetic inheritance in evolutionary and ecological processes (Day and Bonduriansky, 2011; Bonduriansky *et al.*, 2012), which has been buoyed by the identification of a number of potential causal mechanisms (Toth, 2015; Baugh and Day, 2020; Adrian-Kalchhauser *et al.*, 2020).

The field of genetics is definitely richer for the recognition of the diversity of phenomena that lead to violations of Mendel's laws. While it still makes sense to

introduce students to the logics of transmission genetics by outlining the conceptual basis to Mendel's laws, an understanding of heredity goes well beyond these elementary principles. An appreciation for the exceptions to Mendelian 'laws' do not so much complicate matters as they clarify the real nature of how traits are inherited, and thus support the conceptual underpinnings that drove Mendel's thoughts. As we celebrate Mendel's 200th birthday, it is clear that the field that his insights helped found will continue to advance as further exceptions to his laws are identified and dissected.

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