C. R. Biologies xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Comptes Rendus Biologies

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Trajectories of genetics, 150 years after Mendel / Trajectoires de la génétique, 150 ans après Mendel

Beyond the simplicity of Mendelian inheritance

Derrière la simplicité de l'hérédité mendélienne

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ARTICLE INFO

Article history:
Received 11 March 2016
Accepted after revision 12 April 2016
Available online xxx

Keywords:
Genotypes
Phenotypes
Expressivity
Penetrance
Inheritance
Monogenic mutations
Yeast

ABSTRACT

Elucidating the underlying rules that govern the phenotypic diversity observed in natural populations is an old but still unaccomplished goal in biology. In 1865, Gregor Mendel paved the way for the dissection of the underlying genetic basis of traits by setting out to understand the principles of heredity. To date, we still lack a global overview of the spectrum and continuum existing between Mendelian and complex traits within any natural population. In this respect, we recently performed a species-wide survey of Mendelian traits across a large population of isolates using the yeast *Saccharomyces cerevisiae*. By analyzing the distribution and the inheritance patterns of the trait, we have clearly shown that monogenic mutations can display a significant, variable, and continuous expressivity across different genetic backgrounds. Our study also demonstrated that combining the elegancy of both classical genetics and high-throughput genomics is more than valuable to dissect the genotype–phenotype relationship in natural populations.

Mots clés :
Génotypes
Phénotypes
Expressivité
Pénétrance
Hérédité
Mutations monogéniques
Levure

RÉSUMÉ

L'élucidation des règles gouvernant la diversité phénotypique observée entre individus d'une même espèce est un objectif ancien en biologie, mais toujours loin d'être atteint. En 1865, Gregor Mendel a posé les bases théoriques de l'hérédité, permettant l'exploration actuelle des origines génétiques des phénotypes. Cependant, nous n'avons toujours pas de vision globale du spectre et du continuum existant entre les traits mendéliens et complexes au sein des populations naturelles. Dans ce cadre, nous avons récemment initié une étude à large échelle des traits mendéliens en utilisant la levure *Saccharomyces cerevisiae* comme organisme modèle. En analysant la distribution et l'hérédité des traits, nous avons clairement pu montrer que les mutations monogéniques peuvent avoir une expressivité variable et continue dans différents fonds génétiques. Notre étude montre également que la combinaison de la génétique classique et de la génomique à haut débit est plus que précieuse pour disséquer la relation génotype–phénotype.

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http://dx.doi.org/10.1016/j.crvi.2016.04.006

Please cite this article in press as: J. Schacherer, Beyond the simplicity of Mendelian inheritance, C. R. Biologies (2016), http://dx.doi.org/10.1016/j.crvi.2016.04.006

1. Trait variation and natural populations

Natural populations are characterized by an astonishing phenotypic diversity. Observing, exploring and dissecting the biodiversity have clearly improved our knowledge in biology. The variations observed among individuals of the same species represent an evident powerful raw material to dissect and have a better insight into the relation existing between genetic variants and phenotypes. Moreover, the advances of high-throughput genotyping and phenotyping technologies have greatly enhanced the power of determining the genetic basis of traits in model as well as in non-model organisms [1]. Genome sequencing of a large number of individuals no longer represents a bottleneck. Consequently, a comprehensive dissection of the genetic mechanisms underlying natural phenotypic diversity seems to be within easy reach. In the era of "big data", we could think that all is joined together to systematically map the genetic origins of traits within any species by using classical mapping approaches such as linkage analysis and genome-wide association studies. Briefly, in linkage mapping, the causative loci are mapped using the progeny of crosses between genetically divergent individuals, in which the genetic variants that contribute to phenotypic variation segregates in the recombinant offspring. By contrast, genome-wide association studies use a large sample of unrelated individuals from the same species and look directly for correlations between phenotypes and genotypes. These mapping strategies are massively used and mostly fruitful in many organisms, including the human being.

Alongside these major advances, however, it must be noted that there are some limitations. And this is clearly shown by all genotype–phenotype correlation studies in humans and other model eukaryotes such as *Arabidopsis thaliana* and *Caenorhabditis elegans*, where identified causal loci by GWAS (Genome-Wide Association Studies) explained relatively little of the heritability of most complex traits. Multiple justifications for this unexplained part, which is called "missing heritability", have been suggested, including a large number of variants with small effects, rare variants, poorly detected structural variants, and low power to estimate gene–gene and gene–environment interactions [2,3]. As a result, we have today a slightly better view of the genetic architecture of traits (*i.e.* number, type, effect size and frequency of variants involved traits), but it is very far to be exhaustive.

2. Following the footsteps of Gregor Mendel and Hermann Joseph Muller

A better understanding of the genetic architecture of traits requires a deeper knowledge of the effect of genetic variants at the population level. This is stating the obvious but the question is how we can reach that. Deeper mapping studies by linkage or association, as mentioned previously, will definitely bring some insight into this problem, but will be insufficient. Additional and new strategies are essential and necessary. In such a context, sometimes it is useful to stop and look in the rear-view mirror. By doing so, we can obviously see way behind a Moravian scientist friar dealing with *Pisum sativum*, the common pea plant [4]. Indeed, natural populations were first used to observe the patterns of inheritance of traits *i.e.* looking at the segregation of traits in offspring and performing classical genetics. In fact, we tend to forget about this powerful and elegant way to investigate traits in the crowd of the fast and ever-growing high-throughput sequencing and phenotyping possibilities. Obviously, such a strategy *per se* is difficult, if not impossible, to apply to human traits such as diseases when the genetic origin is complex and not monogenic. It is obviously not possible to simply choose parents and obtain the best crosses that will be informative. However, studies of inheritance patterns led to remarkable discoveries over the past century in model organisms such as plants, yeast, worms, and mammals.

Everything started around 1865 when Gregor Mendel elegantly introduced the concept of dissecting how traits are transferred for generation after generation [4]. He clearly set out to understand the principles of heredity. Mendel's originality was present in many aspects of his studies. First, the choice of the model system–the pea plants–allowed controlling their fertilization and consequently the possibility to arrange various parental combinations, among which informative ones. Moreover, *Pisum sativum* being self-fertilized, the traits remain invariant and the parental lines of peas could be easily pure-breeders or homozygous. Second, Mendel selected and deeply dissected very simple traits, such as pea colour and shape. When Mendel cross-fertilized wrinkled pea plants with smooth ones, he did not get progeny with semi-wrinkly seeds, for example. Finally, he conducted his experiments in a quantitative manner and accurately counted the number of the different phenotypic types in direct progeny. He was the first to think and believe that the mechanism of inheritance is reflected by the ratio or proportion of each trait of the offspring. Obviously, it became quickly evident that most of the traits are more complex and show a deviation from what is now called a Mendelian inheritance. In 1920, Edgar Altenburg and Hermann J. Muller (the latest being best remembered for his discovery of genetic effects of X-ray) characterized the first complex trait using *Drosophila* as a model organism [5]. In a masterful genetic analysis, they identified the individual units, which affected the deformation of the wing shape of flies, called "truncate". Sets of suitable, informative and elegant crosses were performed to follow the inheritance pattern and ultimately identify the three loci involved in the trait. They pointed out that the traits depend on genetic variations of all sorts–major locus as well as their modifiers–and found how the units interacted. They also have shown that variability was sometimes environmental. Importantly, they validated and provided concrete evidence about the nature of hereditary elements, leading to the integration of Darwinism and Mendelism, *i.e.* the modern evolutionary synthesis.

3. Monogenic mutations, penetrance and expressivity

Beyond the simplicity of Mendelian inheritance, there is the hidden complexity of how genetic variants exert a

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