Perspective: Mendel did not study common, naturally occurring phenotypes

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Abstract

Modern genetics research increasingly reveals that what is commonly termed Mendelian genetics occurs rarely in nature, especially with regard to the effects that genetic variation exerts on human characteristics. It has been argued that an inappropriate emphasis on Mendel's work could distort the public understanding of genetics and indeed in the UK Mendel has been completely dropped from the official school syllabus. There is a widespread misunderstanding that Mendel studied common phenotypes such as height and colour in individual pea plants. In fact, he studied a handful of specially selected phenotypes which he observed to be always dichotomous in 22 specially bred varieties of pea and studied crosses between individuals from these different varieties. This approach enabled him to study a small number of phenotypes which did in fact exhibit truly Mendelian transmission. Modern molecular genetic studies have now demonstrated that these phenotypes result from loss of function variants which result in markedly reduced activity of specific proteins and which hence have recessive effects. Understanding that Mendel studied the effects of loss of function mutations in crosses between artificially bred varieties, rather than naturally occurring variation in a population, could allow his work to continue to be taught as part of a modern genetics curriculum.

Keywords

Mendel; dominant; recessive; pea.

Background

In a recent high profile review of the applicability of Mendelian concepts to human genetics, Zschocke and colleagues repeat the commonly made, but false, claim that Mendel studied "common traits in the garden pea" (1). Likewise, what should be an authoritative educational article presents the view that Mendel studied the common pea plant, *Pisum sativum*, that he observed a number of traits such as plant height (tall or short) and pea colour (green or yellow), and that he discovered that when he made crosses between plants then, for each trait, one form exhibited dominance and the other recessiveness (2).

As knowledge of human genetics has exploded in recent years it has become more and more apparent that what is generally referred to as Mendelian genetics has very little role in human genetic variation, especially insofar as it impacts common, easily observable features which distinguish individuals. Concerns have been raised that an overemphasis on Mendel's insights in school education risks producing a distorted view in which genes are perceived as overly deterministic of individuals' characteristics (3,4). Such concerns appear to have been taken so seriously that in the latest version of the UK National Curriculum for schools there is no mention at all of Mendel or his work, meaning that there is no necessity for children to have even heard of him (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/335174/SECONDARY_national_curriculum_-_Science_220714.pdf). Here, I make the case that there is surprising ignorance regarding what Mendel actually did, even among some experts in

genetics, and that a better understanding of his experiments allows for a much more comfortable accommodation of his work into our modern views of genetics.

The distorted accounts of Mendel's work mentioned above fail to give adequate weight to the following three key facts:

The primary units of study were not individual pea plants sampled from a single population but rather plants which were grown from seeds provided by commercial suppliers and which could be described as different varieties of pea, or even different species. The crosses were between individuals from diverse varieties, not between individuals within a population.

The seven traits Mendel studied, out of all the characteristics which differed between varieties, were deliberately chosen by him to be those which were clearly dichotomous and which could be definitively assigned to one or other of two distinct forms in all of the 22 varieties he studied.

For four of the seven traits he studied, a molecular genetic basis has now been elucidated and for every one of these the recessive phenotype is the result of a mutation which results in complete or near complete loss of function of a single gene product.

As explained below, these features meant that he was able to study traits which did indeed have a Mendelian pattern of transmission, even though such variation is in fact the exception rather than the rule in nature. For his own account of his work I will use the translation of his 1866 paper into English produced by Abbott and Fairbanks and where appropriate I will simply quote verbatim from it rather than debate the true meaning of particular words of phrases as they were originally written (5).

Crosses between artificially bred varieties

The first thing to note is that Mendel mentions initial experiments with *Leguminosae* and concludes that the genus *Pisum* was suitable because, *"Several completely independent forms of this genus possess uniform characters that are easily and certainly distinguishable, and they give rise to perfectly fertile hybrid progeny when reciprocally crossed."* He writes that *"34, more or less different pea varieties were obtained from several seed suppliers"*. As mentioned above, these varieties differed so much that he notes that there is debate among experts as to whether some should be considered as subspecies of *Pisum sativum* or whether some were better described *"as independent species, P. quadratum, P. saccharatum, and P. umbellatum."*

The fact that he experimented on commercially produced varieties has two crucial implications which are overlooked by a casual account that he performed crosses between pea plants. The first point is that the varieties could be very different from each other, far more so than would typically occur between members of a single population. Each variety had been subject to intensive breeding over many generations with the specific object of producing different stable forms which would breed true and predictably produce the characteristics which were described in their catalogues (6). Therefore, what Mendel studied was hybridization among artificially created populations, not within natural ones.

The second point is that the commercial breeding process within an artificial environment allowed for suppliers to select characteristics which might be seen as reducing fitness, were the plant to be left to grow in the wild. For example, it is clear that peas have evolved a complex mechanism to produce the pigment anthocyanin, suggesting that doing so improves fitness. However, if breeders

perceived that having white flowers was sometimes a desirable characteristic then they could select in favour of it (7). The progeny of a plant with white flowers could be used to produce a variety with this as a stable characteristic even if in the wild the lack of pigmentation might be a disadvantage.

A simplified view of the process of establishing diverse varieties using artificial selection would be to state that at the level of molecular genetics two mechanisms can be active. One is that selection occurs on the basis of standing variation underlying a polygenic trait such that the end result is to produce a variety which has a very high frequency of alleles at multiple loci all acting in the same direction. The second mechanism is that occasionally an individual might be homozygous for a recessively acting mutation with a major effect size and then selective breeding from the progeny of that individual could be used to produce a variety for which all members were homozygous for the recessive allele. It seems likely that the production of the varieties which Mendel obtained from his suppliers had led to a handful of characteristics which resulted from the latter scenario.

Selection of dichotomous traits for study

This brings us to the second aspect of Mendel's methodology which is too frequently overlooked, which is that he deliberately selected as objects of study exactly those characteristics which would, it turned out, conform with the expectations of what we now call Mendelian genetics. It is very clear that he was well aware of that this did not represent inheritance in general because he writes this about the results of earlier experiments on ornamental plants in relation to the form of hybrids: *"With individual characters that are particularly noticeable, like those related to the form and size of the leaves and to the pubescence of the individual parts, the intermediate form is in fact almost always apparent; in other cases, however, one of the two original parental characters possesses such an overwhelming dominance that it is difficult or quite impossible to find the other in the hybrid."* The "intermediate form" he describes is exactly what we would expect from a polygenic trait in which one variety might carry many alleles increasing leaf size, the other many alleles reducing leaf size and the hybrid would then have a more equal distribution of alleles and hence an intermediate leaf size. Interestingly, he notes that only *"one or two"* characters might exhibit the lack of an intermediate form characteristic of a Mendelian trait.

Following a 2 year trial in which he confirmed that the varieties bred true Mendel selected 22 of them for cross-fertilisation. In terms of the steps he followed in order to select particular characters to study he wrote the following: *"Some of these characters, however, do not permit certain and sharp separation because the difference rests on a "more or less" that is difficult to determine. Such characters could not be used for the individual experiments, which had to be limited to characters that appear clearly and decidedly in the plants."* He then goes on to list the seven characters which on this basis went on to be included in the experiments. When he goes on to report the results of hybridisation he writes: *"Each of the seven hybrid characters either resembles one of the two original parental characters so perfectly that the other one escapes observation or is so like it that a confident distinction cannot be made."*

From this account it would appear that by choosing characters that were always dichotomous he was able to identify seven which did indeed demonstrate clear Mendelian transmission. It is not absolutely clear that his choice of characters was not also influenced by earlier experimental crosses which allowed him to note hybrids having *"intermediate forms",* but it seems at least possible that selecting characters which were dichotomous across all 22 varieties might indeed have been sufficient. If one selected a character which reliably differed between just two varieties, then of course it might simply have polygenic inheritance. However, one can imagine that were a phenotype to be under polygenic determination, then in some varieties breeders might have selected extreme forms of this phenotype but in other varieties other characters might have been the focus of

selection and hence intermediate values for the phenotype in question could appear. Thus, it might be that phenotypes which took dichotomous forms and appeared *"clearly and decidedly"* across all 22 varieties might indeed be those determined by Mendelian genetics.

To reinforce this point, it is worth pointing out that the characters Mendel studied were quite complex and closely defined and were not simply traits such as "height" or "colour". They are clearly listed in the original paper, but for example the "height" character relates to the difference in the length of the stem and Mendel notes that this was very different in different varieties, though almost invariant within them, and that for experiments with this character *"the long stem of 6–7 feet was united with the short one of 0.75–1.5 feet."* Thus, he was studying height as a clearly dichotomous trait controlled by what some have referred to as the "dwarfing gene" rather than the normal variation of height within a population (8).

Molecular basis for the traits studied

The third important fact relevant to understanding Mendel's work relates to the underlying molecular genetic mechanisms underlying the traits he studied. (Of course, he himself would have been completely unaware of these.) To date, a number of examples of variants acting in a Mendelian fashion to produce the phenotypes he observed have been identified:

- Whether a pea is smooth or wrinkled is determined by an isoform of SBEI, which converts amylose into amylopectin, and a 0.8 kb insertion which disrupts the *SBEI* gene to yield no functioning product acts recessively to produce the wrinkled phenotype (9). This is because peas lacking amylopectin have a higher sucrose content which osmotically draws water into the pea and when this is subsequently lost the pea becomes wrinkled.
- A nonsynonymous variant which changes an alanine to a threonine residue in a gibberellin 3 beta-hydroxylase, involved in the synthesis of a gibberellin, which acts as a growth hormone, causes reduced enzymatic activity and acts recessively to produce a marked reduction in stem length (8,10).
- Normally as peas mature chlorophyll is degraded and the seeds change colour from green to yellow but variants resulting in loss of magnesium decheletase activity can act recessively to prevent this process occurring, resulting in seeds which remain green (11–13).
- A splice site variant in a gene for the transcription factor bHLH acts recessively to prevent the formation of the pigment anthocyanin, resulting in white flowers and seed coats (7).

In each of the above scenarios there is what may be regarded as a normal phenotype, in which there is at least one copy of a gene which yields a functioning protein product, and an abnormal phenotype, in which both copies of the gene harbour variants which could be described as mutations with the result that protein functionality is markedly reduced or absent. This of course exactly mirrors the mechanisms underlying classical Mendelian recessive disorders in human genetics such as cystic fibrosis, phenylketonuria and oculocutaneous albinism, in which a single normal copy of the gene is sufficient to prevent the condition becoming manifest in carriers.

Conclusion

An accurate account of Mendel's work would make it clear that he was not studying naturally occurring phenotypic variation within a population, analogous to human hair or eye colour, but was studying essentially abnormal phenotypes which resulted from the loss of normal function in both copies of a gene. Such phenotypes have parallels in a number of human diseases. Presented in this way, his findings would fit well with the perspectives which we now have of human genetics and an account of his work could retain a place in the modern genetics curriculum. On this basis, I argue that Mendel should indeed be routinely included secondary school teaching.

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