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Exploring the Conceptual Challenges of Integrating Epigenetics in Secondary-Level Science Teaching

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Abstract

Rapidly occurring advancements in molecular genetics, such as recent developments in epigenetics, are challenging traditional genetics as it is taught at schools. For example, the adoption of epigenetics—which provides molecular mechanisms for the environment to directly alter phenotypic variation—would mean that pivotal tenets in genetics instruction, such as the central dogma, will require revision. Despite the important implications of epigenetic mechanisms in human health and biological evolution, it is seldom considered at secondary school. The aim of this research was to evaluate the possibility of introducing epigenetics to secondary school students, to foresee the conceptual barriers that might arise and, accordingly, to give some clues which might guide instruction. A short introductory lecture on epigenetics, followed by an open-ended question based in a real case showed that more than half of the students (424 students in 12 schools) were able to understand that environmental factors influence differential gene expression, and over 25% of the students at grade 12 mentioned also some epigenetic molecular mechanisms. However, the students held some conceptual barriers likely hindering comprehension of epigenetics: lack of basic genetic knowledge, genetic determinism, and misunderstanding of the process of adaptation to the environment. The results of this research suggest that it is feasible to introduce epigenetics in secondary school curriculum: at lower levels, special attention should be paid to avoid inducing misconceptions that can work as conceptual barriers to complex genetic concepts exceeding linear determinism; the explicit teaching of technical details might better be addressed at later, post-obligatory levels.

Keywords Environmental genetics · Epigenetics · Genetic determinism · Knowledge progression · Regulation of gene expression · Secondary school

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Introduction

Personal decision-making, participation in civic and cultural affairs, and even economic productivity require the population to be scientifically literate. The increasing exposure to mass media requires informed citizens able to deal critically with this overwhelming burden of information at their disposal. A vast amount of this information is related to genetics (Donovan and Venville 2014): genetic basis of disease, genetic therapies, the applications of genetic sequencing to forensics or medical diagnostics, cloning and genetically modified organisms, among others. This information is not always correct (Bowling et al. 2008). Likewise, an increasing percentage of jobs in research and biomedicine requires profiles with good command of genetics. Genetics is vital for understanding what being human means, and it has multiple connections to social and cultural issues, and so it is of capital importance for making decisions about ethically and socially controversial issues. In this context, the school should provide basic but adequate foundations of genetics, to ensure the acquisition of "genetic literacy" as a part of scientific literacy (Boerwinkel et al. 2017).

Genetics is well represented in the curriculum of Spanish secondary school (grades 10–12). The topics that are usually covered at these courses include nucleic acids, genes and chromosomes, replication and expression of genetic information, Mendelian genetics and the theory of chromosomal inheritance, and the basis of biotechnology. This array of topics is in broad agreement with desirable practical knowledge identified as important by science teachers (Finley et al. 1982).

Traditionally, in schools, gene expression is formulated following the classic view of the central dogma of molecular biology, which, in short, states that genes specify the sequence of mRNA molecules, which in turn specify the sequence of proteins. This deterministic vision of genetics has been mainstream in the school for the last half century: genes alone determine some or many individual traits of organisms, including human beings (Aivelo and Uitto 2015). This is an oversimplification of a much more complex reality, as it deliberately excludes polygenic and multifactorial traits (e.g., eye color or height) (Gericke et al. 2017), and this may fuel the problems students often have to understand the relationships between genotype and phenotype (Tsui and Treagust 2007; Venville and Donovan 2005). Examples commonly used in class are simple and minimize the interaction among genes or between genes and their environment (Dougherty 2009), promoting, albeit inadvertently, a *hereditarianist* ideology (Castéra et al. 2008). In the traditional discourse, genetic diversity caused by random mutations is identified as the primary source of evolution. In fact, according to the most prevalent Darwinian and neo-Darwinian theories, adaptation and evolution are seen as the product of selection acting upon the genetic diversity created by mutation. In genetics, instruction continues to emphasize Mendelian ratios and monogenic traits and disorders, often to the exclusion of inherent complexity (Dougherty 2009).

However, this view is more and more irreconcilable with the current scientific knowledge in the field of genetics. The first indication is that phenotypic change rates and genotypic mutation rates are dramatically different (Burger 2005). In fact, there is a consensus that genes alone do not determine entirely phenotype; instead, developmental processes include complex interactions among genes, regulatory factors, and the environment (Puig and Aleixandre 2015). A large number of biological phenomena have been observed that cannot be easily explained by differences in genetic sequence: the existence of identical twins which suffer from different diseases, the generally small percentage of a disease population found to have a correlated genetic mutation, the increase in frequency of many diseases in only a couple decades, or the fact that hundreds of environmental contaminants which are not able to alter DNA sequence have been shown to cause disease or alter phenotype later in life (Skinner 2015).

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In response to the discrepancies between the genetic concepts taught at school and those needed by citizens in their daily life, in the last decade, there has been a growing pressure to update or re-examine the contents and methodology used for teaching genetics (Aivelo and Uitto 2015; Batzli et al. 2014). For example, there have been some proposals to begin genetics instruction with common quantitative traits, which might include—but not be limited to—health and disease traits; these schemes rely on building the conceptual base for interpreting the genetic and environmental influence on those traits before immersing students in the genetics of rare monogenic traits (Dougherty 2009; Jamieson and Radick 2017). Other visions advocate that it would be more logical and developmentally appropriate to introduce concrete physical entities such as DNA (Donovan and Venville 2005) and proteins (Duncan et al. 2009) before discussing the more abstract notions of genes and alleles.

Some of these new approaches emphasize the influence of environment in phenotype including notions about epigenetics. Epigenetics has become one of the most promising fields in biomedical research. The number of research articles published in the last years has increased exponentially, at a compound annual growth rate (CAGR) of 12.2% for the period 2012–2015 (Razvi and Oosta 2016). Epigenetics explains the arousal of different phenotypes from identical genotypes, and it is mediated by chemical alterations (DNA methylation and histone acetylation or phosphorylation among others) that do not affect the nucleic acid sequence and other regulatory factors such as noncoding RNAs. Epigenetic "tags" are attached to the genome in response to external factors, where "external" refers both to the cell ambiance (as in embryonic cell differentiation) or extrinsic elements, such as diet (Heijmans et al. 2008), exposure to toxins (Lindroth et al. 2015), or temperature (Skinner 2015). Epigenetic regulation controls some biological processes such as cell differentiation during embryonic development, the mechanism of imprinting, and physiological adjustment to the environment.

All these epigenetic mechanisms are widely accepted and backed by relevant literature (Allis and Jenuwein 2016). However, there are some aspects that remain controversial, at least in humans, as it is the case for transgenerational heredity. In the first steps of early development, most of the epigenetic tags are erased; however, a fraction of them resist the reprogramming, being transferred to the offspring (Majnik and Lane 2014; Youngson and Whitelaw 2008). The possibility of transgenerational transmission means that epigenetic modification may also affect the phenotype of the following generations, even after the triggering environmental factors have changed. Although this hypothesis has been tested (in plants, fruit flies, mice, and *Caenorhabditis elegans* models (Prokopuk et al. 2015)), and suggested in humans (Costa et al. 2018), evidence of transgenerational epigenetics remains inconclusive (Bohacek and Mansuy 2017; Horsthemke 2018).

Flawed epigenetic regulation is responsible for important diseases, such as obesity, autoimmune diseases, cancer (Pickersgill et al. 2013), or mental disorders (Lee and Avramopoulos 2014). A clear example of this is the evidence of the influence of diet and exercise on the individual risk of developing type 2 diabetes mellitus (T2DM). Many pieces of research have demonstrated that pairs of monozygotic twins (i.e., genetically identical individuals), where only one of them suffer from obesity or T2DM, bear epigenomic differences in genes involved in metabolic regulation. Even more, it has been reported that short-term high-fat diet and exercise in healthy individuals leads to changes in the epigenome of the skeletal muscle, and that these changes could be transmitted to the offspring (Barrès and Zierath 2016). Furthermore, there are already drugs and diagnostic tests based on epigenetic manipulations in clinical trials (Cramer et al. 2015; Rodríguez-Paredes and Esteller 2011).

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At this stage of the development of scientific knowledge, and its relevance at the individual level (Riscuta et al. 2018), we defend that basic genetic literacy should include the notion of differential gene expression, affected by the environment and other genes at one or many of the steps involved in producing a trait (Boerwinkel et al. 2017; Dougherty et al. 2011). Moreover, given the decisive role of epigenetics for embryonic development, and its growing relevance for the interpretation of quotidian issues (exposure to toxins, diet, and others), we dare to say that epigenetics should be considered too. Acquiring this basic genetic literacy would be helpful for making appropriate decisions at the individual level, but affecting potentially the next generation(s). As a consequence of the inclusion of these new insights, the canonical central dogma of molecular biology may require dramatic revision (Fig. 1).

Although it could be argued whether basic literacy should encompass epigenetics and other advanced concepts of genetics, such as the regulatory roles of small RNAs or chromatin remodeling (Dougherty 2009), many students will never go to university, and among those who go, only a fraction will choose scientific careers, so it seems appropriate to introduce these essential concepts while in secondary school, or at least lay the foundations for it.

In the USA, the New Generation Standards include these concepts in the Core ideas LS3A (Inheritance of traits) and LS3B (Variation of traits) (the NGSS Lead States 2013). PISA Assessments, which have turned into unofficial education standards, only mention genetic

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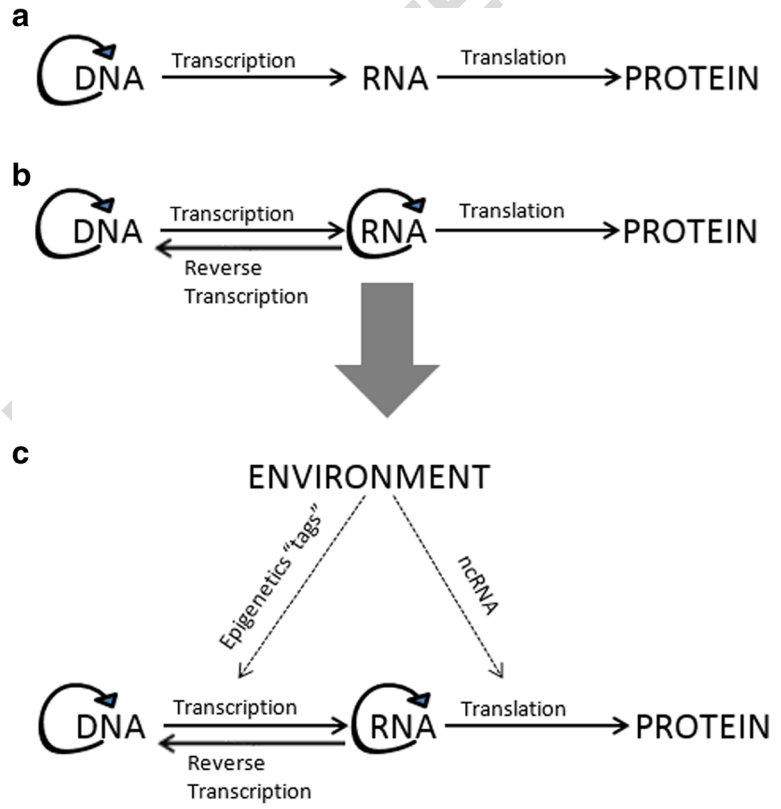

Fig. 1 Evolution of the central dogma of molecular biology. **a** Most common vision in current textbooks of grade 10; **b** most common vision in current textbooks of grade 12; **c** proposed revision of the central dogma, including epigenetics. ncRNA, noncoding RNA

variation, without considering interaction with the environment (OCDE 2016). The Spanish curriculum for secondary school (Spain, Ministry of Education Culture, and Sports 2015) includes the first mentions to genetics in grade 10 (*4° ESO*); at this level, only transcription is considered, with no mention of the regulation of the genes. In grades 11–12 (*Bachiller*) there are already some ideas about regulation, although prokaryotic gene expression regulation is overrepresented compared to the eukaryotic regulation systems, maybe due to the complexity of the eukaryotic model. More attention is paid to the molecular mechanisms of regulation than to the practical effect of this regulation. The Spanish curriculum does not mention epigenetics, and the textbooks mentioning either epigenetics (e.g., Panadero et al. 2014) or the molecular mechanisms that it entails are exceptional. A review of Spanish recent textbooks of grade 12 (date of edition 2009–2014) showed that only 1 out of 9 books included the term epigenetics, methylation is mentioned in another two, and miRNA are mentioned in four of them as examples of RNA molecules, with no reference to their regulatory role.

Some limited attempts have been made to bring epigenetics to schools. These attempts have been more frequent in USA (Bass et al. 2016; Colón-Berlingeri 2010; Drits-Esser et al. 2014a, 2014b; Stark 2010) than in Europe (Aivelo and Uitto 2015; Jamieson and Radick 2017; Kampourakis 2017). In contrast, with the absence of epigenetics in curricula, textbooks, and instruction, there has been an escalation of online resources to teach epigenetics at secondary and even primary levels (http://learn.genetics. utah.edu/content/epigenetics/; http://www.letsgethealthy.org/students/games/epigenetics-game/; https://neuron.illinois.edu/units/what-makes-honey-bees-work-together).

Therefore, assuming the interest of introducing epigenetics (at least, the basis of it) at compulsory and post-compulsory secondary school levels, this research aims to (1) detect conceptual barriers held by scholars that might hamper understanding of this topic, (2) to ascertain which related concepts students introduce in *impromptu* explanations, and (3) to derive some guidelines which, accounting for these limitations, allow for a more efficient teaching.

More precisely, our research questions were:

1. What conceptual challenges (blanks in knowledge, misconceptions, alternative explanatory frameworks, naive conception, etc.) do the students hold, which may be difficult to reconcile with epigenetic explanatory schemes?
2. Which concepts related to epigenetics do the students incorporate to explain scenarios of acclimation to external factors? Is there any progression in the order of acquisition of these concepts?

Methods

Selection of the Sample

In Spain, the secondary school comprises ages between 14 and 18 and includes four compulsory courses (*ESO*—grades 7–10) and two more optional (*Bachiller*—grades 11–12), which give access to higher education (vocational training or university). This cross-sectional research has been conducted at grades 10 to 12 (hereafter G10–G12).

We made an open call to the 69 schools in Navarra which host internships of the Master of Secondary School Teachers. Finally, 12 schools participated in the research. We obtained data from 424 students (306 at G10 and 118 at G11–12). All the answers were anonymous but coded.

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In all schools, the research was conducted after regular genetic instruction; i.e., the relevant pieces of the course syllabus had been already covered, precisely as if this research was not being conducted. No specific references to epigenetics were made, and none of the authors participated in this previous teaching.

Basic Knowledge of Gene Constancy and Regulation: Multiple-Choice Test

We first analyzed students' knowledge about DNA content, gene expression, and the influence of environmental factors on phenotype variability through a multiple-choice test. The test included five questions about the constancy and expression of genetic information. Questions were inspired by previously published questionnaires which addressed student's misconceptions and conceptual barriers in genetics (Banet and Ayuso 2000; Gericke et al. 2017), and experts in genetics and didactic validation further verified it. The comparison with a pilot group of 84 students of G10–G12, which closely matches the sample of this study, allowed us to investigate the suitability of the questionnaire, concerning length, comprehensibility of the items, order, etc., and to introduce the required modifications.

Students were allowed 15 min in the classroom to complete the test. They were expected to know that, albeit all the cells in an organism come from a single zygote, gene expression is tissue-dependent. Equally, genetically identical organisms (monozygotic twins, cloned animals) may express different phenotypes, without necessarily having their genome altered (Fig. 2).

Together with the answers, the questions included a set of options revealing a deterministic view (Fig. 2): cells and individuals that look different must have different DNA sequences because the genome determines univocally the phenotype. According to that, the only possible source of variability are mutations which alter the genome.

The rest of the distractors included common misconceptions in genetics (Fig. 2).

Explanations Involving Epigenetics: Open-Ended Question

After a short introductory lecture on epigenetics, the students were requested to explain a real case that could be attributed, in the authors' view, to epigenetic mechanisms. Both are described further in the following.

The entry event consisted of a short educational talk on epigenetics, based on the video *Epigenetics* (http://www.oercommons.org/courses/epigenetics/view) (NovaScienceNow 2016). The video (in English with subtitles) was played and stopped at certain points in time to explain certain concepts (in Spanish or Basque, the mother tongue of the students). Explanations were adjusted to the level (G10–G12) and included information about the significance of epigenetics—the importance of epigenetics in different biological processes, like cell differentiation, the involvement of epigenetics in some diseases, and its utility for the design of medications—and the molecular mechanisms it involves.

The video explains that monozygotic twins are genetically identical; however, through life, they develop differently, to the point of looking dissimilar. Additionally, they can suffer from different diseases, including genetic diseases. These patterns may be caused by epigenetic modifications, which affect gene expression. At a molecular level, these epigenetic modifications can be caused by DNA methylation and histone acetylation. The video includes an animation in which the presence or absence of the modifications causes the genome to be switched on/off, which, in turn, impedes or allows transcription. The epigenetic pattern of each individual can be modified by the interaction of

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Do all the cells of an organism share an identical DNA sequence?

1. a) Yes, but only in organisms with sexual reproduction.
   b) No, it depends on the type of tissue they belong to.
   c) Yes; all the cells come for a single one: the zygote.
   d) No, the gametes have just half of the sequence.

2. Do all the cells of an organism express the same genes?
   a) Yes, because all of them have the same genetic information.
   b) No, it depends on the type of tissue they belong to.
   c) Yes, they all belong to the same organism.
   d) It's true for the somatic cells; the gametes express half of the sequence.

3. Do monozygotic twins have exactly the same genetic information?
   a) No, the genetic information of each individual is unique and unrepeatable.
   b) No; they are twins, but they are just as alike as brothers or sisters.
   c) Yes, they were born at the same time from the same mother.
   d) Yes, they come from the mitotic division of the same cell: the zygote.

4. Do monozygotic twins suffer always the same diseases?
   a) Yes, because they share the same genome.
   b) No, in the case of infectious diseases. Yes for genetic diseases.
   c) Not necessarily: some diseases will depend upon their life habits.
   d) Yes; even in the case of infectious diseases, they have the same predisposition.

5. Queen and worker bees are females. The queens are bigger and spend all their life reproducing. The workers are smaller and sterile. Queens and workers are genetically identical, but they are brought up with a different diet: the larvae that eat royal jelly develop as queens; the rest, as workers. How can this phenomenon be explained?
   a) *There is no explanation. If they are genetically identical, as monozygotic twins, they should also appear equal.*
   b) There must be something in the royal jelly that alters the genotype of the bees.
   c) There must be something in the royal jelly that alters the phenotype of the bees.
   d) *There must be something in the royal jelly that causes mutations in the bees.*

Combination of answers for alternative explanatory schemes

	Q2	Q3	Q4	Q5	Q6
correct	c	b	d	c	c
deterministic	b	a	a	a/b	a/b/d

Q3 **Fig. 2** Initial test with an indication of correct (in bold) and deterministic (in italics) answers

the organism with external factors, such as nutrients or toxins, and may be heritable to a certain extent. Altogether, the video plus the explanation had a length of approximately 30–35 min, and we allowed for some students questions for about 20 min more.

Right after, and in order to evaluate the comprehension level they had reached, the students were requested to explain a real case involving adaptive physiological responses to environmental conditions. They were shown a text and requested to provide a plausible explanation, for which they had a maximum of 20 min. The excerpt summarized a real research conducted in Northern Sweden (Kaati et al. 2002). It reported the incidence of cardiovascular pathologies and diabetes in a generation, and related it with the food availability at their grandparents' time (Fig. 3); according to the authors of the study, it could be explained resourcing to epigenetic mechanisms. The students were expected to show any of the following explanations: the grandparents' diet might have induced genetic changes which cause changes in the gene expression; these changes do not necessarily involve mutations and may have been inherited by the next generations affecting the grandchildren's health.

Statistical Analysis

All the statistical analyses were done in RStudio (Version 1.0.136 – © 2009–2016 RStudio, Inc.), which operates with R-3.2.2 (R Core Team 2015). The answers to the questions of the multiple-choice test were tested for homogeneity (X^2) between courses (G10–G12). Since the distribution of answers was heterogeneous, they were further analyzed separately.

To analyze the open question, we unpacked the concept of epigenetics into small, independent concepts that could be readily measurable; as the revision of the answers progressed, some additional concepts were identified and added to the list. Then, answers were coded using this scheme: a "1" indicated the idea was present, while a "0" indicated it was absent. This helps to codify the responses of the students without being conditioned by predefined models (Stevens et al. 2009). Genetic-related misconceptions or global exploratory frameworks were also registered and coded.

The results from the first school ($n = 38$) were independently coded by both researchers to check agreement between observers, and an accord on how to apply the coding scheme was made. The two raters evaluated approximately half the responses separately using the defined coding rules. All the doubtful cases were examined and coded again jointly until an agreement between observers was reached (García-Carmona 2018). Overall, inter-rater agreement was high, which suggested a consistent coding.

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The Överkalix district, in Northern Sweden, has a harsh climate, characterized by long and cold winters. During the XIXth and the beginning of the XXth century, there were few roads in the region, and road transport was very limited by snow and ice. Thus, from time to time the people in the region suffered from hunger. In the 80's some researchers assessed the effect of the diet on these people and their descendants: more specifically, they studied the cohorts born in 1890, 1905 and 1920. They examined their life expectancy and the risk of suffering from cardiovascular diseases and diabetes. The results were unexpected: those individuals whose parents and grandparents had experienced food-shortage during their childhood had longer life-expectancies than the children and grandchildren of individuals having been fed without restrictions. Could you explain this fact from the point of view of genetics?

Fig. 3 Text of the open-ended question

Our goal was not to focus on specific learning gains but to ascertain the variety of ideas held by the students (Todd and Kenyon 2016). The data coded for the relevant concepts were assembled and sorted into a Guttman scale, which then allowed us to characterize the knowledge of individual students (Stevens et al. 2009). A Guttman scale is formed by items which are arranged in a reproducible hierarchy of difficulty or sophistication. This scale indicates a progression of ideas: the students that are located at a certain level dominate this level and the previous ones, but not necessarily the following ones. For each level, individual students were given a "1" if they had met or exceeded the progression level and "0" if not yet. For example, a student identifying with the first level would be scored "10[illegible]", while another student identifying with the fourth level would be scored "11[illegible]". Ordered progressions are useful for establishing empirical progressions, i.e., models of student learning that describe ways of reasoning within a domain, in order of increasing sophistication. In a learning progression, the upper anchor is an entirely accurate understanding of a big idea, whereas the intermediate levels and lower anchor may vary for accepted knowledge, or even be scientifically inaccurate, but represent a productive stepping stone that places the students in a better place to reach more sophisticated ideas (Todd and Kenyon 2016). The significance of each step was tested using the McNemar 2×2 test, a test of marginal homogeneity; this allowed us to ascertain whether it was an ordered progression. A significant step means that the two steps being connected represent distinct knowledge levels (B is more difficult than A). For more details on the methodology, see Stevens et al. (2009).

Each student was assigned to the highest level reached, with a nuance: level 2 was considered indispensable to understand the notion of epigenetics. So, only the students who had mentioned the ideas in this level were susceptible to be classified at a higher level (3, 4, or 5). That limitation was introduced to avoid considering random answers, or those having picked up loose elements from the talk, without sound understanding.

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Results

Multiple-Choice Test

The highest percentage of students chose the correct answer in most cases. The only exception was Q2 at G10. The match rate was very variable among questions and courses (31.6–77.4%) (Table 1).

32.3% and 48.1% of the students, in G10 and G11–12, respectively, correctly identified that all the cells of an individual come from a single one, the zygote, and thus have identical DNA sequence (Q1, *c*). They also know that gene expression depends on the tissue cells belong to (Q2, *b* 31.6–51.9%). The highest success rate (60.5–77.4%) was for the statement that monozygotic twins share identical genetic information (Q3, *d*), though they can develop different diseases depending on their lifestyle (52.6–61.3%; Q4, *c*). 40.2–66.0% interpreted that lifestyle (diet) can alter the phenotype (Q5, *c*), without introducing changes in the genotype.

The percentage of students giving the right answer was higher in G11–12 than in G10, except in question 4 (Table 1; column *p*), where they were equal.

However, the answers revealing a deterministic conception (Fig. 2) got also many hits (Table 1). In Q1, 23.7% (G10)–13.2% (G11–12) of the students said that it depends on the tissue to which they belong (*b*); in Q2, 20.3–17.9% affirmed that all the cells express the same genes because they have identical genetic information (*a*). In Q3, as much as 22.3–14.2%

t1.1 **Table 1** Percentage of students who chose each option, per question and course, and probability (p value) of the comparison (X^2) between courses

t1.2 Question	G10 $n = 306$				G11–G12 $n = 118$				G11–12 vs. G10	
t1.3	*a*	*b*	*c*	*d*	*a*	*b*	*c*	*d*	X^2	*p*
t1.4 1	13.4	**23.7**	*32.3*	29.6	11.3	**13.2**	*48.1*	25.5	10.55	0.0321
t1.5 2	**20.3**	*31.6*	10.3	37.1	**17.9**	*51.9*	4.7	22.6	17.39	0.001
t1.6 3	**22.3**	7.6	8.9	*60.5*	**14.2**	4.7	0.9	*77.4*	14.70	0.005
t1.7 4	**4.5**	**37.1**	*52.6*	3.8	**3.8**	**30.2**	*61.3*	1.9	3.09	0.379
t1.8 5	**8.2**	**27.1**	*40.2*	**23.4**	**3.8**	**12.3**	*66.0*	**11.3**	26.72	0. 000

The correct answers are in italic. Deterministic views are in bold

defended that each individual (even monozygotic twins) has unique and unrepeatable genetic information (*a*) and 41.6–34.0% assumed that identical genomes determine they will suffer from the same genetic diseases (Q4, $a + b$). 59.8–34.0% of the students mention mutations, or changes in the genome, as the only possible source of developmental changes in the individuals (Q5; $a + b + d$).

Confusion among alleles, genes, and chromosomes was also evident. 29.6–25.5% of the students indicated that the gametes had half of the sequence (Q1, *d*), as if each chromosome of the pair of homologues contained half of the genes, and 37.1–22.6% said that the gametes expressed half the sequence, further mixing this confusion with the deterministic conception (Q2, *d*).

Open-Ended Question

We analyzed the students' answers and coded them for the appearance of the eight unitary concepts related to epigenetics designed a priori (Table 2), plus the misconceptions or global explanation patterns we detected during the coding process (Tables 3 and 4).

The concepts were fitted to a Guttman scale, which was based on 394 valid answers (278 G10, 116 G11–12), and had a CR of 95.5% (Abdi 2010). The scale resulted in the following progression (Table 3), where reaching each successive level means having acquired the previous ones.

That is to say, the students first understand that epigenetics deals with differential gene expression due to ambient factors, and are then able to incorporate details about the molecular mechanisms involved or the features of the process.

t2.1 **Table 2** Unitary concepts about epigenetics present in the students' answers

t2.2 Unitary concepts
t2.3 Gene expression—differential gene expression (may include phrases such as *activation/inactivation*, *switching on/off* the genes, etc.)
t2.4 Ambient factors—The environment or lifestyle modified the expression (not accepted if the student mentions lifestyle (diet, fitness, temperature...) without explicit reference to genetics).
t2.5 DNA constancy—Phenotypic change is possible without a change in the genomic sequence.
t2.6 Change in the epigenome—explicitly mentions the word "epigenome" or a change in the epigenome
t2.7 Chromatin altered—The structure of the chromatin is modified.
t2.8 Inheritance of epigenetic changes—The change or the regulation can be inherited.
t2.9 Molecular mechanism—Acetylation or methylation is named.
t2.10 Tags—indicates the presence of "marks," "tags," "labels"... in the epigenome

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t3.1 **Table 3** Progression of conceptual knowledge about epigenetics

t3.2 Level	Concept[1]	
t3.3 5	A. Chromatin altered	B. DNA constancy
t3.4 4	Inheritance of epigenetic changes	
t3.5 3	Molecular mechanism (methylation, acetylatio Tags	
t3.6 2	A. Gene expression	B. Changes in the epigenome
t3.7 1	Ambient factors	

[1] For more detailed descriptions, see Table 2

Half (50.0%) of the students at G10 gave incomplete answers to the proposed scenario (level 0), as compared with 27.6% of students at G11–12 ($X^2 = 6.5549$, df = 1, $p = 0.01$). Likewise, students at G11–12 mentioned more often the molecular mechanisms involved or that it is an inheritable change that does not modify the DNA sequence (levels 3–5; Fig. 4) ($X^2 = 37.515$, df = 1, p value < 0.001).

A total of 68 students used, alone or in combination, several misconceptions about basic genetic facts (Table 4). They were evenly distributed between courses ($p > 0.05$ for all comparisons). They were also homogeneously represented across knowledge levels.

Alternative Frameworks

We identified two main ways of globally explaining the adaptation process: first, "mutation", where students attribute differences in the response to environmental conditions to mutations and, second, "inheritance of acquired characters," referring to the idea that characters developed during the lifetime are transmitted to the descendants.

A total of 52 of the 392 valid answers (13.3%) resorted to mutations to explain the changes experienced by the descendants in response to the environmental conditions to which their ancestors were exposed. Besides, 11.7% of the students (46) gave explanations compatible with the inheritance of acquired characters; i.e., going through harsh conditions (hunger) made the individuals more resistant, and this change can endure. No differences were found between G10 and G12 for any of the concepts (X^2 test $p = 0.75$, $p = 0.30$, respectively). Both explanations were most prevalent among students at the lowest levels (0–1) (Table 5).

Discussion

This study aimed to ascertain the barriers and opportunities for introducing epigenetics in the curriculum of secondary school in Spain. With this purpose, we assessed students' basic

t4.1 **Table 4** Misconceptions about genetic facts

t4.2 Misconceptions or errors
t4.3 Adaptation of individuals—Survival rates increase because the individuals, or their genes, are better adapted.
t4.4 Obtaining and developing genes—The ambient factors introduce or induce the creation of new genes.
t4.5 Genes for good/bad things—expressions like "the gene of survival" and "the gene of disease"
t4.6 Modification means disease—Unaltered genomes result in healthy individuals, and modifications introduce diseases.

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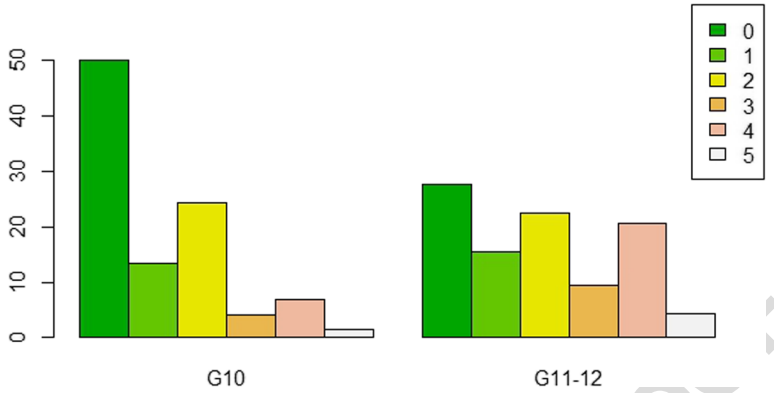

Fig. 4 Percentage of students (%) at each knowledge level in the progression (as described in Table 3)

knowledge about constancy and regulation of the DNA expression and evaluated the concepts the students incorporated when explaining a real research question. These two instruments were useful for estimating the conceptual challenges they presented, and that could prevent from incorporating epigenetic regulation mechanisms. Lastly, we elaborate some recommendations for teaching epigenetics in secondary school, taking into consideration the difficulties and strengths of this approach.

As aforementioned, the Spanish curriculum for G10–12 does not consider epigenetics and covers only barely the regulation of the gene expression. However, we noticed that students at different levels were able to understand some key ideas and to integrate them to explain a complex (real) situation, where epigenetic regulation is involved (50% at G10 and 70% at G11–12). Around 40% of students at G10 and G11–12 incorporated differential cell expression, the influence of the ambient in the genotype, and changes in epigenome (knowledge levels 1–2; Table 3). The gap widens as complexity increases: 30% of students at G11–12 and only 10% at G10 mentioned the molecular mechanisms involved in epigenetics, the heritability of epigenetic changes, and the modification of chromatin structure (levels 3–5).

Despite these promising results, we detected at least three barriers: blanks in the application of basic genetic knowledge, genetic determinism, and misleading understanding of adaptation to the environment.

First, students' answers including expressions such as *genes adapt* or *to lose or to gain a gene* denote implicitly they lack basic genetic knowledge about gene expression and the way it

t5.1 **Table 5** Number (*n*) of students and percentage (%) mentioning mutation or inheritance of acquired characters, per knowledge level (Table 3)

t5.2	Levels	Mutation		Inheritance of acquired characters	
t5.3		(*n*)	(%)	(*n*)	(%)
t5.4	5	0	0	1	11.1
t5.5	4	2	4.6	1	4.7
t5.6	3	1	4.5	3	13.6
t5.7	2	8	8.5	5	5.3
t5.8	1	19	34.5	13	23.6
t5.9	0	22	12.8	23	13.4
t5.10	Total	52	13.3	46	11.7

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is regulated. These gaps in knowledge also become evident in the answers to the multiple-choice test (particularly Q1 and Q2). This basic genetic knowledge is essential because, as reported before (Todd et al. 2017), students cannot understand individual or generational changes if they do not understand first how genes are expressed.

One of the most challenging ideas for students to learn is that genes alone do not determine characters, but are involved in trait development. To understand this statement, students face two obstacles: first, to understand the role of proteins in determining the phenotype and, second, to connect concepts from different levels of organization: genes and DNA molecules belong to the submicroscopic level; cells and organelles, to the micro level; and phenotype characters, to the macro level (Lewis et al. 2000; Tibell and Rundgren 2010). The connection between the protein and the phenotype is not explained at schools (Thörne and Gericke 2014), and thus, the students are unable to close the gap between levels and apply molecular knowledge to phenotype. As such, some authors (e.g., Duncan & Hmelo-Silver, 2009) suggest that more attention should be paid to the role of proteins in determining the phenotype.

The second gross difficulty to understand epigenetics could be an acceptance—at least partly instruction-induced—of genetic determinism. Although the open-ended question was asked right after the introductory video and explanation, and the students were encouraged to apply the new concepts in their argumentation, as much as 13.3% of students attributed the changes observed in the descendants exclusively to mutations in the ancestors. Many pieces of educational research have shown that the relative influences of environment and genotype on the determination of traits are poorly covered in secondary school, and that mutation continues to be portrayed as the main source of variability.

The third limitation found to hinder comprehension of epigenetics is the meaning attributed by students to adaptation and evolution. Students used terms like *adaptation of individual* or *adaptation of gene*s; topping on that, some students expressed that *mutation resulted in "bad things"* or conceived it as a fast process affecting individuals and no populations, thus showing a misunderstanding of these phenomena. Additionally, the customary use of the word adaptation may entail an added obstacle to understand the genetic meaning of the term: in everyday language, adaptation implies an intentional willfulness of changing, collectively or individually, that could be achieved even in a short period. However, in genetic terms, populations (and no individuals) adapt, as a result of genetic variability (mutations and epigenetic changes) that increase or decrease fitness given some environmental conditions. As such, adaptation is only realized over long periods, encompassing many generations.

It is remarkable that an additional group of 46 students (11.7%) explained the proposed scenario in terms of inheritable lifetime adaptation, although without mentioning any molecular implication. Although the Lamarckian theory is usually presented as obsolete, and having been surpassed by Darwinism, nowadays, there is evidence that at least some acquired characters are inherited (Minkina and Hunter 2018). Indeed, some authors propose a unified theory of evolution which encompasses both lines of thought (Skinner 2015). This inheritance can be explained by epigenetic mechanisms (although transgenerational heritability of the epigenetic tags remains controversial (Bohacek and Mansuy 2017). Answers to the open-ended activity showed that a number of the students align, if only intuitively, with the Lamarckian postulate that acquired characters are heritable. This may be due to Lamarck's ideas being closer to common sense than the abstract Darwinian theories, that is, more acceptable for young students (Gené 1990). Although there is no doubt that some of Lamarck's postulates have been surpassed by modern knowledge in the field of genetics, epigenetics provides an efficient way of integrating both worlds towards a unified theory of evolution (Skinner 2015).

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As a consequence of the observed shortfalls in the knowledge about genetics, many investigators have considered necessary to introduce substantial changes in both the programs and strategies used to teach biological inheritance in order to facilitate conceptual change and promote more meaningful learning (Banet and Ayuso 2000; Duncan et al. 2016; Todd et al. 2017). In this case, it appears convenient to update the curriculum to introduce some notions about epigenetics. This does not necessarily imply increasing the course load, already very high, with an abundance of contents that may lead the students to rote learning. Most of the time, at least for middle school, it would be enough with using more appropriate images, as shown in Fig. 1, or introducing nuances into our expressions (as suggested in the following paragraphs). Innovation in teaching can involve changes in methodologies, often mediated by technologies, which foster a redefinition of the learning scenarios. But it should also encompass a continuous revision of concepts, to acknowledge relevant advancements in the respective fields of expertise, and, more important, to select contents that are relevant in raising competent citizens able to thrive in the world of today.

Yet, if we wished to reform the curriculum, it would be advisable to respect certain recommendations emanated from our empirical results. Notably, the progression of learning that we outline can shed some light on the order in which concepts should be introduced. Our cross-sectional data provide insight into the ability of students to incorporate the ideas presented into their explanatory frameworks, and which conceptual obstacles may they have. Research has shown that progressing too far in one construct, or strand, before the understanding of other concepts at that level has been developed will likely hinder student learning. Details at a level that is too advanced will likely not have any meaning to students because they are not connected to other ideas in a useful manner (Roseman et al. 2008). Only information necessary to explain level-appropriate phenomena should be introduced to students (Kesidou and Roseman 2002).

Taking our results into account, we would suggest that:

- The possibility of regulation of the expression by external factors should be explicitly addressed from the lowest levels (G10). The recognition of the importance of differences in the gene expression and the impact of ambient factors constitutes the first conceptual stage, a prerequisite for reaching more elaborated levels of understanding.
- Higher courses (G11–G12) could be a better moment to introduce features of the process and, especially, the molecular mechanisms involved. Students at this age have already studied chemistry and are more acquainted with the terminology, which may facilitate sense-making. In lower levels, one of the main concepts related to epigenetics (i.e., the regulation of gene expression could be due to chemical modifications that, without modifying DNA sequence, alter the structure of chromatin making it more or less accessible) can be addressed by simpler models of chemical bonds.
- It is especially important, when addressing adaptation and biological evolution, not to present mutations as the sole source of variability, because this contributes to reinforcing the determinist alternative. Teachers should instead state overtly that phenotypic or developmental changes may occur as a result of the interaction with ambient factors.
- Considering the intuitive conceptions of students about evolution, Lamarckian postulates should better be used as a jumping-off point for introducing epigenetics, also considering that genetics and epigenetics are not alternative but complementary views.

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This intervention aimed explicitly at characterizing the students' understanding. Any intervention intended to produce permanent changes in learning should include a broader range of activities (i.e., hands-on activities and discussions) over an extended period.

Before considering these proposals (Banet and Ayuso 2000), meaningful learning about the relationships between chromosomes and genes and inheritance information, and between mitotic division and inheritance, should be prior (Banet and Ayuso 2000).

Although this research was not designed to systematically probe teachers' conceptions, from our interaction with them during the interventions, it is clear that the primary source of deterministic views is the tuition. As a result, efforts should be made to build bridges between science and the school, keeping the teachers updated and aware of the adequate instructional strategies.

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Q1. Please check if the keywords were correctly captured and presented.
Q2. Please check if the genus name of *C. elegans* was correctly spelled out.
Q3. Figure 2 contains poor quality of text inside the artwork. Please do not re-use the file that we have rejected or attempt to increase its resolution and re-save. It is originally poor, therefore, increasing the resolution will not solve the quality problem. We suggest that you provide us the original format. We prefer replacement figures containing vector/editable objects rather than embedded images. Preferred file formats are eps, ai, tiff and pdf.
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Q5. Ref. "Duncan & Hmelo-Silver, 2009" is cited in the body but its bibliographic information is missing. Kindly provide its bibliographic information in the list.
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