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Research Paper: chHDAC11 mRNA Expression During Prenatal and Postnatal Chicken (Gallus gallus) Brain Development

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Running Title HDAC11 Role in Prenatal and Postnatal Chicken Brain Development

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ABSTRACT

Background: Histone deacetylation plays an essential role in transcriptional regulation of cell cycle progression and other evolutionary processes. Several results confirm the importance of the latest found HDAC11 gene to deacetylate histone core in neurons and their supportive cells in developing the vertebrate Central Nervous System (CNS).

Objectives: This study investigates the HDAC11 potential role in early chicken CNS development by studying its mRNA expression profile which may have unique means in studying human subjects.

Materials & Methods: Chicken HDAC11 RNAs were reverse transcribed to cDNAs, and the amount of chHDAC11 transcripts was measured by ΔCT mean calculation using the real-time quantitative PCR method. One-way ANOVA and Duncan's analysis (SigmaStat software version 4.0) were used to test the statistical significance of the results. The levels of significance were set at $P \leq 0.05$. Quantitative data are presented as Mean±SD.

Results: The amount of HDAC11 mRNAs gradually increases, at least 2-3 times, from as early as day 14 (E14/HH40) of prenatal cortex formation to day P0 (E20=HH45) and continue to increase to day 40 in both cortical and hippocampal regions of the postnatal chicken brain during development ($*P \leq 0.05$). HDAC11 mRNA is not only expressed in the postnatal cortex and hippocampi regions but also—for the first time—in the developing brain during the prenatal period.

Conclusion: Our results show a possibly important role for the latest found HDAC11 conserved gene in the development of vertebrates' embryonic brain, which in turn may have a significant impact on understanding human brain development.

Keywords: Gene expression regulation, Developmental, Cerebral cortex, Brain

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Highlights

- *HDAC11* is an epigenetic gene expression regulator and the latest found member of class IV. HDACs are expressed during the early chicken brain model of development.

- *HDAC11* is not only expressed in the early postnatal developing brain but also during the prenatal period.

Introduction

Transcriptional regulation is controlled by coupling the DNA-binding proteins to promoters, enhancers, and suppressor regions of transcriptional machinery in the cell nucleus. These proteins are the activators or repressors of gene expression; however, besides these regulatory proteins, chromatin modification plays an essential role in regulating gene expression. In this context, the transubstantiation of nucleosome structure is associated with gene activation by converting the compact structure of chromatin to an open configuration [1, 2]. So, chromatin modification is a key element of gene transcription regulation in eukaryotic cells. A set of post-translational modifications, including acetylation, phosphorylation, ubiquitination, and so on, in addition to deacetylation, occur in the domains of histone tails [3].

Reversible histone acetylation is a dynamic process controlled by interfering with two superfamilies of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). Based on sequence similarities, HDACs are divided into four classes of I, II, III, and IV [4]. *HDAC11*, a zinc-dependent HDAC, is the only member of class IV with close similarity to class I and, to some extent, to class II of HDACs [5]. In the Central Nervous System (CNS), histone deacetylation is linked to neural gene expression or activation [6] and neural cell development [7-10]. Of HDACs, *HDAC11* is localized in the nucleus and interacts with—mainly cytoplasmic—HDAC6 in vivo. The association between *HDAC11* and HDAC6 has recently been shown to modulate the T-cell gene expression profile as a transcriptional activator [11, 12]. A high expression level of *HDAC11* has been shown in a few organs, including the brains of mice [13] and humans [14], suggesting a potentially important regulatory role for this molecule in CNS development. *HDAC11* has been addressed to interfere in a schizophrenia-associated gene expression in knockout mice model [15] and mitotic cell cycle progression and survival of human neuroblastoma cell line in vitro [16].

Distinct expression of *HDAC11* has been reported in monoaminergic and neuropeptidergic neurons of the murine brain, whereas its immunoreactivity has been observed in both cytoplasmic and nucleosomal structures. *HDAC11* immunoreactivity has also been shown in dendritic structures in the hypothalamus [17]. In the developing CNS of rats, acetylation of histones H3 and H4 gradually decreases with increasing the animal's age in vivo [10, 18] and, in cultured adult rat hippocampal neural precursor cells in vitro [8]. Whereas *HDAC11*'s deacetylation role in rat's CNS has been attributed to the development of oligodendrocytes, cortical, and hippocampal granule neurons [19].

Liu et al. and Torres et al. link the function of *HDAC11* to the first two weeks of the postnatal developing brain of rats and mice [13, 20]. To our knowledge, however, the information concerning *HDAC11* role in prenatal developing CNS is absent. We have recently shown that prenatal *HDAC11* expression changes, but only in the developing brains of mice [21]. In this paper, we offer such changes in chicken prenatal and postnatal brain development, which we consider an exciting finding. This finding is partly because *HDAC11* has been considered a novel drug target in cancer treatment by using potential HDAC inhibitor components (HDACi) in recent years [22]. In this regard and a recent attempt, chicken embryo models have been used to study human cancer and cardiovascular diseases [23]. Xenotransplantation of human stem cells into the chicken embryo [24, 25] and creating a hybrid human-chick embryo have been as recent top scientific news reported [26, 27].

The importance of *HDAC11* as a novel regulator of gene expression in either development of cancer or CNS has not been fully understood yet. Thus, we designed this study to investigate the expression profile of histone deacetylase 11 mRNAs during cortical and hippocampal prenatal and postnatal chicken brain development. This study, in turn, may have special usage in either human CNS development or cancer studies soon.

Materials and Methods

Sampling and animals

Three groups of fertilized eggs (*Gallus gallus domesticus*) were collected from a local supplier and incubated at 38.7°C. The brain tissues of the embryos at the age of 14 (E14), 17 (E17), and 20 (E20) days (HH 40, 43, 45, respectively, according to Hamburger/Hamilton classification) were prepared (Hamburger & Hamilton 1951). Four groups of chickens, including days 1 (P1), 5 (P5), 20 (P20), and 40 (P40) old (p=postnatal), were obtained from different aviculture, and their brain tissues were prepared. Fresh removed tissues were immediately used in experiments or otherwise, were snap freezing in liquid nitrogen, immediately after removal until use. A minimum of six samples were counted in each group and, all experiments were performed at least 3 times. The gender of embryos and early postnatal pups were not apparent, and thus the potential gender biological effect(s) on the result of this study was not considered. The maintenance and care of experimental animals complied with National Institutes of Health (NIH) guidelines for the humane use of laboratory animals so that all the animal procedures, including anesthesia and care of experimental animals, were carried out following the Animals Scientific Procedure (Act, 1986).

RNA extraction, cDNA synthesis, and real-time quantitative PCR:

Total RNA was extracted from fresh or stored in liquid nitrogen cortices and hippocampi of chicken brains using TRIzol@ reagent, according to the manufacturer's instructions (Invitrogen, USA). The quality and quantity of extracted RNAs were specified by either gel electrophoresis experiment (data not shown) or spectrophotometer measurement at A260 nanometer wavelength and A260/A280 ratio calculation (Kruss, Germany). All mRNAs samples were treated with DNaseI (Thermo Fisher Scientific) to eliminate possible genomic DNA contamination in RNA samples. Then, 2 µg of total RNAs from each sample was used for reverse transcription reaction using cDNA synthesis kit and oligo d(T) primers according to the manufacturer's instruction (#K1622, Fermentas, Lithuania [Thermo Fisher Scientific]).

Real-time quantitative PCR was performed in CFX96 (Bio-Rad, USA), based on SYBR Green/fluorescein detection systems. To detect chicken *HDAC11* transcripts in a real-time qPCR study, we have designed our specific primers using primer3 software version 4.1.0 (University of Massachusetts Medical School) to amplify a unique region of 234 base pairs from Gallus gallus *HDAC11* gene (NM_001277141.1: NCBI database). The forward primer sequence used was 5′-TGTGCAAGCACGGGAGGCTA-3′, and the reverse primer was 5′-TCCCACGTTGATTGCCCAGC-3′ (nucleotides from 365 to 384 and, 580 to 599 on NM_001277141.1 NCBI database, respectively) and the amplification of the desired fragment was successfully achieved. The optimum average Tm for this primer set was 61°C. For q-PCR, each sample was run in triplicate, and each experiment was performed by at least two times.

The mean threshold cycle (Ct) value for each assay was used for the next calculations, and the comparative Ct value method was used to analyze the results. The ch*HDAC11* Ct values were normalized by subtracting Ct means of target gene (ch*HDAC11*) in each sample to Ct values of those chicken GAPDH and 18S rRNA housekeeping gene expression to obtain ΔCt mean. The ΔCt mean values were then taken to calculate the present to reference changes of ch*HDAC11* expression in time points studied. We have used two housekeeping genes in this study to avoid obtaining any possible false-positive results. It is alleged that the 18S rRNA gene, in no way, would have any fluctuation in expression during different parts/stages of the developing brain.

To determine *HDAC11* involvement in prenatal and postnatal development in the chicken brain, we have analyzed the expression of this gene by using cortical parts of the brain from 14-, 17-, and 20-day-old embryos (prenatal), as well as 1-, 5-, 20-, and 40-day-old chicks (postnatal). The same procedure was performed for the hippocampi parts of the brain at days 17 and 20 embryos (before birth) and 1-, 5-, 20-, and 40-day-old chicks (after birth). The 14-day-old (E14 = HH 40) embryo's hippocampus was not apparent enough to be isolated.

Statistical analysis

One-way ANOVA was used to test statistical significance among the groups and was followed by comparing each group's mean using Duncan's test in SigmaStat software for Windows v. 4.0.0.37. The levels of significance were set at $P \leq 0.05$. Quantitative data are presented as Mean±SD.

Results

The expression of *HDAC11* mRNA was quantified using the relative quantification method of real-time PCR compared to that of P0 "whole brain" as a template

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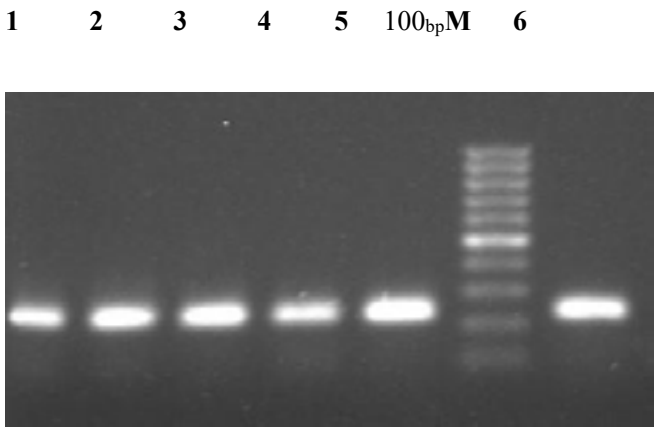

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Figure 1. 234_{bp} cDNA amplified fragments of *chHDAC11* from days E20 (HH45), E17 (HH43), and E14 (HH40) of *Gallus gallus* embryonic cortex of prenatal developing brain (lanes 1 to 3, respectively)

Lane 4 represents A "whole brain" sample of P0 (E20=HH45) as a positive control. M, a 100bp DNA marker fragments and lane 5 represent a "whole brain" sample of P0, not being treated with DNaseI (represents as a positive control since all initial mRNAs samples from 1 to 4, excluding lane 5, were treated with DNaseI to eliminate any genomic DNA trace.

(P0=E20=HH45=20-day-old chicken embryo). The data obtained from real-time PCR was normalized to at least two housekeeping genes, i.e., chicken GAPDH and 18S ribosomal RNAs. The specificity of primers designed for real-time PCR was checked by agarose gel electrophoresis analysis for a correctly amplified region of 234 base pairs on the chicken *HDAC11* gene (Figure 1).

As quantified by quantitative PCR, the abundance of chicken *HDAC11* mRNAs increases from the early prenatal day of 14 (E14=HH40) for cortex and 17 (E17=HH43) for hippocampus until the day of 40 after birth for both cortex and hippocampi of postnatal development. The relative value of ch*HDAC11* mRNAs expression in the cortex region increases from the first prenatal weeks with a significant increase in 1-day-old chickens. It then peaks at day 5 compared to its rapid decrease at day 20. The expression levels will constantly rise from day 20 until chicks turn 40, making this point statistically significant with a P-value of less than 0.05 (Figure 2-A & B).

Similarly, the relative abundance of *HDAC11* mRNAs in the hippocampus gradually increases from early prenatal weeks until day 20 of postnatal development. It then suddenly increases until it reaches its highest level in 40-day-old chicken, which makes ch*HDAC11* expression statistically significant at this point in hippocampi ($P<0.05$) (Figure 3).

All data are relative expression quantities of ch*HDAC11* mRNAs expression compared to "whole-brain" samples as described above. We did not study the events, which may occur in days after P40. We also did not measure the potential expression of *HDAC11* protein at the time points studied, and therefore, we have only reported *HDAC11* mRNAs expression in this study. We are aware that many events may interfere with the translation of ch*HDAC11* gene transcripts to functionally mature and biologically active protein.

Discussion

We found that *HDAC11* mRNA has elevated expression levels during early chick prenatal and postnatal cortex development with a reduction in the expression on day 20 after birth (postnatal). According to our obtained data, the expression of *HDAC11* in chick hippocampi, however, steadily increases from early developmental periods (prenatal) till day 40 after birth (postnatal stages).

During embryonic development, the rates of neurogenesis and neuron migration are high between embryonic days of 14 (E14) to 18 (E18), but the differentiation and maturation of neuroglia occur only during the postnatal period [28]. By influencing cells' epigenetic status, histone deacetylases (HDACs) can change gene expression patterns without altering genome structure; hence, they play a significant role in controlling neural cell cycle progression, survival, and differentiation [29]. Numerous histone deacetylases—mostly those of classes I and II—have widespread expression patterns during brain development, indicating their specific role in neural development [30]. For example, the expression of histone deacetylases 1 and 2 has shown to be essential for neuron differentiation and specification in the mouse brain.

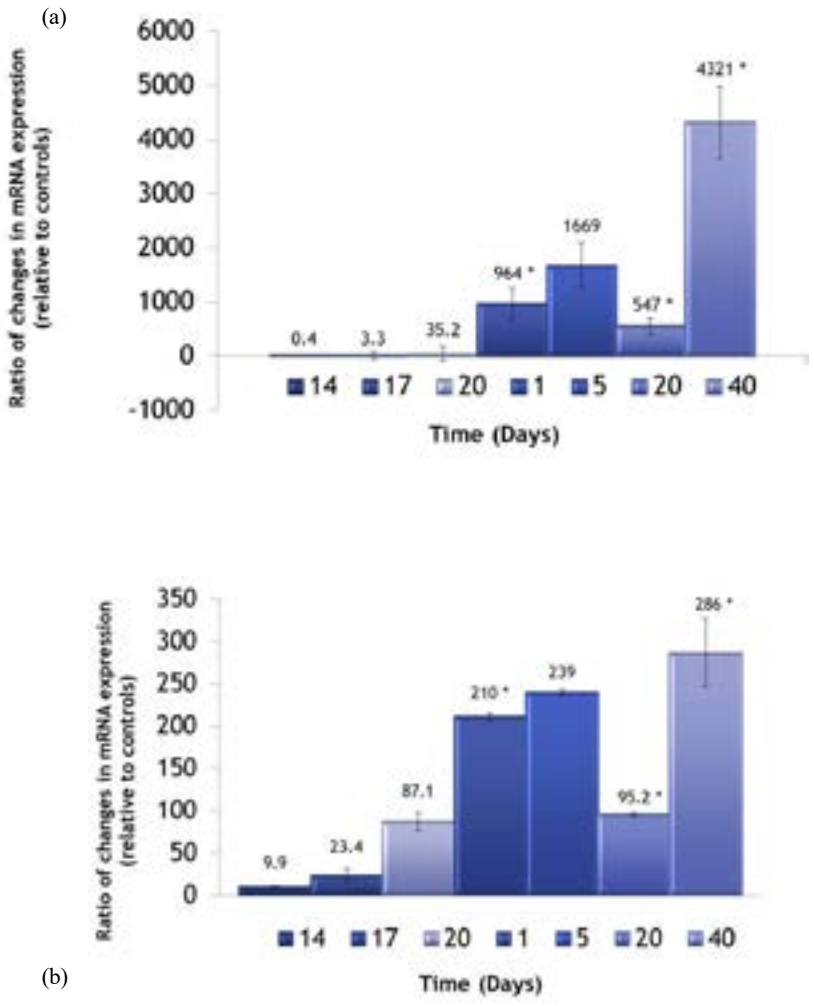

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Figure 2. Relative (% of reference) expression of *chHDAC11* mRNAs in Cerebral Cortex (CTX) during prenatal and postnatal chicken brain development. the mrna expression measured relative to that of P0 (E20=HH45) whole brain and normalized against to at least two *chgapdh* (a) and chicken 18s rrnas (*18s*) (b) housekeeping genes

Each column shows the mean relative value of mRNA levels from all triplicate samples for real-time quantitative PCR. Bars represent Mean±SD from at least 6-8 samples. Asterisks indicate statistical significance according to Duncan's test (*P≤0.05).

Olson et al. have shown that mice lacking HDAC1 or HDAC2 show no obvious phenotype changes in their neuronal progenitors while lacking both HDAC1 and HDAC2 in their developing nervous system show obvious phenotypes changes, including severe hippocampal abnormalities, loss of cerebellar foliation, irregularity of cortical neurons in their CNS and lethality by postnatal day of 7 [31]. In Olson et al. study, the specific time points, i.e., E14.5 - E15.5, when phenotypic abnormalities appear, are essential because, at these time points, high levels of neuronal differentiation and migration occur. Neural cell differentiation is highly sensitive to alterations in HDAC1 and HDAC2 expression, so the complete inhibition of these genes activities has resulted in neural differentiation arrest and cell death [31]. Phylogenetically, *HDAC11* is a zinc-dependent HDACs and very similar to members of class I HDACs.

Chicken embryonic CNS develops similarly to that of mammals [28]. Therefore, we do not rule out the relevance of our result for ch*HDAC11* expression in chicken prenatal embryonic cortex and hippocampi development with that discussed in Olson et al. result above. A separate study using TSA (Trichostatin A)—a class I HDACs expression inhibitor—has shown a significant decrease in vitro or a complete stop in neurogenesis in vivo in mouse ganglionic eminence. According to this study, HDACs control neurogenesis by inhibiting the BMP2/4 (bone morphological protein) signaling pathway in the brain's cortex and ganglionic eminence [32]. *HDAC11* has

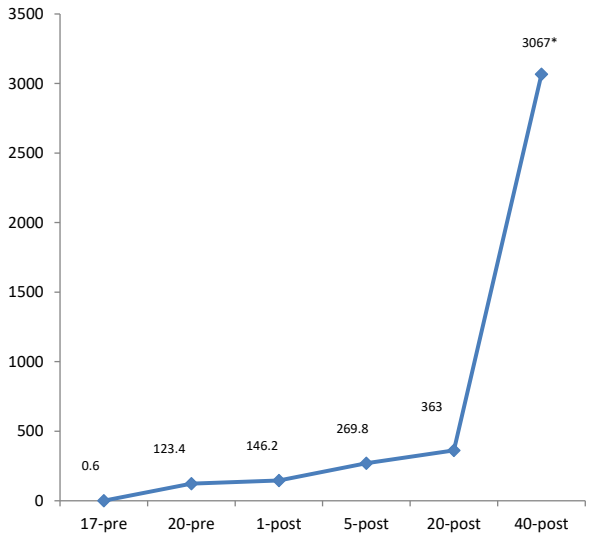

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Figure 3. Mean relative (% of reference) expression of *chHDAC11* mRNAs in Hippocampus (HIP) during prenatal and postnatal chicken brain development (pre, prenatal; post, postnatal)

The mRNA expression was measured relative to that of P0 (E20=HH45) "whole brain" and was normalized against at least two *ch*GAPDH and ch18s rRNAs (*18s*) housekeeping genes. Values are presented as mean±SD from at least 6-8 samples. Asterisks indicate statistical significance (*P≤0.05).

elevated expression levels in five regions of the rat brain, including cortex, hippocampus, brain stem, cerebellum, and diencephalon during the first postnatal week, with the highest level of expression in 40-day-old rats [19].

Similarly, in our study, *HDAC11* has elevated expression levels in the chick's postnatal cortex and hippocampi, with the highest levels of expression in 40-day-old mice (Figures 2 and 3). Liu et al. have found that along with their maturation, both growing and mature oligodendrocytes and neurons react with *HDAC11*-specific antibodies in many parts of the developing brain, including the cerebral cortex and hippocampus [13]. Surprisingly, acetylation of histones H3 and H4 gradually decreases with cell maturation in cortical neurons of rats [18] and oligodendrocyte-rich regions of corpus callosum during rat postnatal development [10].

The *HDAC11* ability to remove an acetyl group from H3 and H4 core histone proteins has already been proven [14]. Furthermore, it has been shown that suppressing *HDAC11* expression using RNA interference technology in cultured oligodendroglia cell lines can also increase the amount of histone H3 acetylation [13]. Based on the above-detailed descriptions, we, therefore, suggest that in our study too, *HDAC11* is possibly involved in neurogenesis during embryonic development at days of 14, 17, and 20 prenatal (HH 40, 43, 45, respectively), when the most neurogenesis occurs. The increasing *HDAC11* expression follows throughout the whole postnatal brain development period despite a significant decrease on day 20, after birth (Figure 2). Since myelination by oligodendrocytes becomes completed in the third postnatal week, i.e., the day 20 [33], it can be argued that *HDAC11* expression decreases at this time point, which might be linked to stopping of oligodendrocytes outwork for myelin formation in postnatal chicken developing cortex. Myelination is started during the postnatal period; however, oligodendrocyte progenitors appear only during embryonic development [34] and are presented as immature cells in the brain stem on the first postnatal day [33]. Based on the above-described literature and obtained results in our study, we suggest that *HDAC11* may have a possible role in oligodendrocytes (glial cell) differentiation in chick's prenatal and very early postnatal cortex development.

As mentioned above, in our study, ch*HDAC11* expression has constantly been increasing in the hippocampus from day 17 (E17=HH43) prenatal to day 40 of postnatal development (Figure 3). This finding is consistent, in part, with Liu H et al. report of increasing *HDAC11* expression in rat hippocampus during postnatal development [13]. According to this study, most mature oligodendrocytes and mature neurons were firmly bound to *HDAC11* antibody, while astrocytes did not show such immune responses [35]. In these experiments, hippocampal granule neurons, cortical neurons, and giant brain stem neurons have produced a strong immune response

to *HDAC11* antibody while cerebellar granule cells and cerebellar Purkinje cells produce a weak response.

We have previously shown that cultured rat hippocampal progenitor cells show an increase in the expression of class II HDACs [36]. As described by Hamburger and Hamilton [37], the differentiation of supporting cells in the central chicken nervous system occurs during postnatal brain development. We, therefore, argue that the observed gradually increasing HDAC11 expression in the postnatal developing chicken hippocampus in this study shows its importance to support the differentiation and maturation of oligodendrocytes and other supportive cells in chicken postnatal hippocampal development.

The *HDAC11* is the novel and the only member of class IV HDACs, which despite its potential epigenetic role in the regulation of gene expression in development, has the unknown function(s). Most studies in past decades have been concentrated on class I and II members and SIRTs family genes (class III) and, mostly on cancer-related proliferation phenomenon or inhibition of HDACs functions using HDACs inhibitor molecules (HDACi). This trend has limited us to comprehensively compare our findings with "crowded" published results in the literature. Nevertheless, the chicken model of development has acquired special value in recent years for study. The chicken embryo has been used as a useful experimental model to study human diseases, including cancer [23, 38, 39]. In this regard, xenotransplantation of human stem cells into chick embryos [24] has finally resulted in the creation of "hybrid human-chicken" embryos [26, 27] which would help neuroscientists to understand human embryonic development better.

Conclusion

On the whole, our data suggest that *HDAC11*—similar to HDAC1 and HDAC2—has a possible role in evolutionary processes of neural cells development and, possibly in some glial cells, such as oligodendrocyte cells' maturation and or migration in both cortex and hippocampi of the chicken brain during prenatal and postnatal periods of development. Our current results may help developmental experts or neuroscientists to understand better the molecular machinery underlying human neural cells growing in the brain during both embryonic and postnatal development. For further studies, we suggest investigating the interaction between *HDAC11* and other HADCs with histone acetyltransferase (HATs) molecules to find how epigenetic events tightly regulate the expression of essential key regulating genes during the early development of the chicken model of the brain.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were done in compliance with the ethical guidelines of the 2013 Declaration of Helsinki. All methods used to handle laboratory animals in this study were within National Institutes of Health (NIH) and University of Guilan guidelines, following the Animals Scientific Procedure (Act, 1986).

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This study was extracted from the MSc. thesis of the first author at the Department of Biology, Faculty of Sciences, University of Guilan.

Authors contributions

Conceptualization, methodology, supervision, writing - review, and editing: Farzam Ajamian; Investigation, methodology, and writing - original draft: Seyedeh Rezvaneh Moadabpoor and Afsaneh Shokri; Methodology: Farhad Mashaiekhi and Mohammad Mehdi Sohani.

Conflict of interest

The authors declared no conflict of interest.

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