Minireview

Avian genomics lends insights into endocrine function in birds

C.V. Mello *, P.V. Lovell

Dept. Behavioral Neuroscience, Oregon Health & Science University, L470, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, United States

ABSTRACT

The genomics era has brought along the completed sequencing of a large number of bird genomes that cover a broad range of the avian phylogenetic tree (>30 orders), leading to major novel insights into avian biology and evolution. Among recent findings, the discovery that birds lack a large number of protein coding genes that are organized in highly conserved syntenic clusters in other vertebrates is very intriguing, given the physiological importance of many of these genes. A considerable number of them play prominent endocrine roles, suggesting that birds evolved compensatory genetic or physiological mechanisms that allowed them to survive and thrive in spite of these losses. While further studies are needed to establish the exact extent of avian gene losses, these findings point to birds as potentially highly relevant model organisms for exploring the genetic basis and possible therapeutic approaches for a wide range of endocrine functions and disorders.

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1. A tale of gains and losses

The availability of bird genomes, initially for chicken and zebra finches, and later for a much larger number of species covering a broad range of the avian phylogenetic tree, has led to remarkable advances in our understanding of avian biology (Hillier et al., 2004; Jarvis et al., 2014; Warren et al., 2010; Zhang et al., 2014a). Currently >70 avian genomes representing >30 avian orders are available at NCBI, and the number keeps rising. In fact, birds are the vertebrate group with the largest number of completed genome assemblies to date. Besides providing unprecedented insights into avian genome evolution and forming the basis for a major re-definition of avian phylogeny, detailed analyses of these resources have led to numerous novel insights into the genetic basis of avian specific traits.

Comparative analysis has uncovered several examples of apparent gene duplications and/or family expansions, as well as avian-specific gene losses (Hillier et al., 2004; Huang et al., 2013; Khan et al., 2015; Kong et al., 2010; Steiger et al., 2009a,b; Warren et al., 2010; Wirthlin et al., 2014; Zhang et al., 2014b). Of particular interest, we have identified a large number of genes organized in syntenic clusters that are largely conserved in other vertebrates, including reptiles and mammals, but that are missing in avian genomes (Lovell et al., 2014). The relatively large size of these avian missing gene clusters makes it unlikely that their absence in birds is simply or completely due to incomplete genome sequencing or assembly. Rather, their preferred occurrence in specific chromosomal locations in other vertebrates (Lovell et al., 2014), as well as the fact that the genes that flank these clusters in non-avian genomes are often seen in close synteny in birds (Lovell et al., 2015b; Warren et al., 2017); Mello and Lovell, unpublished observations), support the notion that they were actually lost, in part likely due to chromosomal rearrangements. Because these avian

* Corresponding author.
E-mail addresses: melloc@ohsu.edu (C.V. Mello), lovellp@ohsu.edu (P.V. Lovell).

missing genes are largely present in crocodiles (Lovell et al., 2014), it is likely that their loss occurred in an organism ancestral to extant birds, possibly during the course of the evolution of the dinosaurian lineage that originated birds.

We note that determining the exact extent of gene family expansions and contractions in a given species or group can be quite challenging (Denton et al., 2014). In the case of birds, an important limiting factor is that most currently available avian genomes still contain a considerable number of gaps, representing regions that are difficult to sequence and/or assemble. Avian genomes also present a number of sequenced but unplaced segments, and/or tandemly placed repeat segments flanked by gaps that split or duplicate gene prediction in ambiguous manners. Because of these issues, it can sometimes be difficult to differentiate true duplications from assembly artifacts, and true losses from incomplete sequencing or assembly (see details in Lovell et al., 2014; Wirthlin et al., 2014).

It is also well established that high GC content can make specific genomic regions difficult to sequence, assemble, and/or PCR-amplify, likely due to stable secondary structures, particularly when inverted repeats are also present (e.g., see Chen et al., 2013). Some reports have recently called attention to the possibility that particularly high GC content may have severely limited the ability to sequence and/or correctly assemble a significant number of genes in avian genomes (Hron et al., 2015; Lovell et al., 2015b). In some cases, there is evidence for the presence of specific genes previously thought to be missing based on searches of expression databases (e.g. RNAseq short read archives). Examples are the long sought-after avian leptin (Friedman-Einat et al., 2014; Huang et al., 2014; Millar, 2014; Seroussi et al., 2016), and tumor necrosis factor (TNF; Bornelov et al., 2017; Hong et al., 2006). Transcriptome-based findings need to be taken with caution, though, when they are the sole evidence for the presence of a given gene, due to the lack of synteny evidence to conclusively establish orthology. Indeed, we have identified several instances where closely related genes or paralogs have been incorrectly identified as a gene of interest (e.g. DAT, SERT2; Lovell et al., 2014, 2015a, Table S5). Importantly, recent advances in genome sequencing have led to significant improvements in the chicken and zebra finch genome assemblies (Warren et al., 2017; Mello, unpublished; Jarvis, unpublished). Such advances are largely due to the emergence of Pacbio-based technology, which is more efficient in resolving regions that are particularly GC-rich or that contain multiple highly repetitive motifs (Rhoads and Au, 2015). As a result, a small set of genes previously thought to be missing in birds, as well as a much larger set previously found in other birds but missing in the chicken genome only, have now been sequenced, and in many cases placed onto specific chromosomes of the current chicken assembly (galgal5; Warren et al., 2017). Nonetheless, the majority of the avian missing syntenic genes first described by Lovell et al., 2014, remain absent in avian genomes, supporting the core finding of syntenic gene losses in birds (further details on the full set of genes that have now been found in chicken, or that are still missing in chicken or in all birds, can be seen in Tables S3–S6 in Warren et al., 2017). Notably, it is well established that avian genomes are on average 1/3 of the size of the genomes of reptiles or mammals, which is largely attributed to shortening of intergenic and intronic regions (Hillier et al., 2004; Hughes and Piontkivska, 2005; Zhang et al., 2014b). Intriguingly, this reduction in genome size is thought to have already occurred in the dinosaur lineage that led to extant birds, possibly associated with the metabolic demands of flight but likely preceding the emergence of this trait (Organ et al., 2007). The finding of missing gene clusters (Lovell et al., 2014) provides evidence that the evolution of bird genomes was also marked by the loss of a considerable number of protein coding genes that are otherwise conserved in most vertebrates.

These avian gene losses are intriguing because a large number of the missing genes play important, even essential roles in organisms like mammals, where most available data on the function of these genes derives from (as detailed in Lovell et al., 2014). Thus, birds must have somehow developed compensations that allowed them to survive the loss of these genes. Theoretically, compensatory mechanisms could range from genetic to physiological ones. For example, novel paralogs or duplications/expansions of related family members, as well as modifications of more distantly related genes and proteins, could have provided molecular compensation for the gene losses (Lovell et al., 2014; Table S5). Alternatively, birds may have evolved physiological modifications that allowed them to adapt to specific losses of genes and related pathways. In some cases, the recently discovered gene losses may provide an explanation for avian-specific or characteristic traits whose genetic basis was previously unclear (Lovell et al., 2014, Tables S7 and S15). Importantly, investigation of such possible adaptations and compensations could lead to novel insights into the genetic basis of the specific molecular pathways or physiological traits, and in some cases help establish birds as a particularly suitable or informative model to study phenotypes related to human genetic diseases and syndromes.

2. Gene losses with implications for endocrine function

Bioinformatics analysis of the missing gene clusters described in the preceding section provides important insights into the possible functional consequences of avian gene losses. Many of these genes were found to be involved in a wide range of physiological roles in other vertebrates, and a considerable number are actually associated with endocrine functions (Lovell et al., 2014). The evidence comes largely from the existence of mouse phenotypes caused by loss-of-function mutations that affect the endocrine system (Table 1). In many cases the knockout of a single gene is sufficient to cause the phenotype in mice, whereas for others the phenotype requires multiple gene knockouts. For yet other missing genes, the evidence for an endocrine role derives from published studies of endocrine pathways and mechanisms. This includes cases where gene loss was previously suspected based on non-detection in gene expression analysis, or a lack of biological activity in specific molecular or biochemical assays. In such cases, the genomic finding corroborates previous tentative inferences about potential gene losses.

We discuss below some intriguing cases where missing genes seem to group into functional pathways or physiological roles, or where we believe further studies of birds may be particularly informative or insightful with regards to specific endocrine pathways or functions. For a larger number of genes, the possible pathways and mechanisms whereby their loss leads to an endocrine phenotype are presently unknown; those genes are not discussed further (but see Table 1 for list).

While the functional loss of several of these genes results in a phenotype that indicates a role in the regulation of weight, eating, and nutritional state, a subset of them are more specifically involved in various aspects of lipid metabolism and homeostasis. For instance, NR1H2 has been linked to lipid homeostasis and inflammation (Joseph et al., 2003). It encodes a protein that heterodimerizes with retinoid X receptors (RXRs), and thus it likely acts by modulating transcription of downstream genes. Precisely how the loss of this gene would impact lipid metabolism is currently unknown. In contrast, apolipoprotein M (APOM) is an important constituent of high density lipoproteins (HDLs), whose primary functions include the liver uptake of circulating cholesterol and providing cholesterol to steroidogenic organs like adrenals and gonads (Huang et al., 2015). Indeed, there is significant

Table 1
Missing genes in birds that affect endocrine related organ systems/functions when knocked out singly or in combinations with other genes in mice (Modified from Lovell et al., 2014; classifications based on MGI; www.informatix.jax.org).

Organ/system	MGI phenotype (single knockout)[i]	MGI phenotype (multiple knockouts)[ii]	Pubmed/entrez gene[iii]
Insulin, pancreas, lipids	ABCD1, APOM, BCAT2, CPT1C, ESRRA, FGF21, GSK3A, NR1H2, RETN, RIPK3, RLN3, SERPINI2, SERTAD1	SLC6A8	BGN, LRP10, NFATC4, PPP1R3E
Weight and eating	APEX2, APLP1, ARAF, AVPR2, BCAT2, BGN, CPT1C, ERF, ESRRA, FGF21, GSK3A, MARCH9, PRKACA, PRSS8, RLN3, SERPINI2, SLC6A8, SLC7A7, TIMP1	CDKN2D, EPN1, MAMSTR, RAB3D	NTF4
Gametes, gonads, reproduction	CCDC159, CCNB1IP1, CDKN2D, ELK1, GAPDHS, PRKACA, SLC7A7, TBX6, TIMP1	BGN, EGLN2, EPN1, NR1H2, PARP2, POU5F1	ASF1B, DNAAF3, GAPDHS, IZUMO2, RLN3, TSKS, TSSK4

i) single knockout sufficient to cause endocrine phenotype; ii) endocrine phenotype requires knockout of this gene combined with other genes; iii) links to endocrine function based on published literature on gene function and Entrez Gene summaries.

evidence that APOM variants are associated with risk for atherosclerosis and coronary heart disease. Furthermore, there is growing evidence that APOM may be involved in some aspects of insulin action and susceptibility to type II diabetes, indicating broader roles in metabolic and endocrine regulation. LRP10 on the other hand, encodes one of several proteins related to the low density lipoprotein receptors (LDLR), the so-called LDLR-related proteins, or LRPs (Willnow, 1999). LDLR plays a major role in the internalization of cholesterol in most tissues by binding and taking up circulating low density lipoprotein (LDLs), the major type of cholesterol carrying serum particles in mammals (Go and Mani, 2012; Jeon and Blacklow, 2005). LRPs, on the other hand, are a heterogeneous gene family and can be considered auxiliary to LDLR, possibly playing a 'scavenger' role when circulating cholesterol levels are saturating the main lipoprotein receptors, but they could also play other as yet undefined internalization roles (Willnow, 1999). LRP10 is thought to be particularly important in the uptake of apolipoprotein E (APOE) containing lipoprotein particles (Sugiyama et al., 2000). Intriguingly, APOE is also thought to be absent in birds, based on biochemical assays (Barakat and St Clair, 1985). Consistent with this observation, an APOE locus has not been identified in any of the bird genomes currently available. Interestingly, even though APOE is on human chr19, its apparent loss was not included among the reported avian missing gene clusters related to human chr19 (Lovell et al., 2014). APOE's syntenic region has proven particularly difficult to reconstruct in avian genomes, thus it is presently unclear whether the APOE loss was related to the other missing conserved gene blocks reported by Lovell et al., 2014. Furthermore, an APOE gene prediction is not present in lizard, which initially suggested an ancestral sauropsid loss, but an APOE ortholog has now been found in alligators, supporting an avian-specific loss. It is also noteworthy that LDLR itself, while not missing in birds, does appear to have diverged greatly across major avian and vertebrate groups, presumably resulting in LDLRs with very different structural configurations and functional properties (Mello and Lovell, unpublished observation). Overall, the fact that major players in the internalization of cholesterol are missing or modified in birds suggests that this important aspect of lipid metabolism must differ significantly between birds and mammals, and/or mechanisms exist that compensate for such losses in birds.

Several other genes have knockout phenotypes more directly associated with whole-body energy homeostasis, regulation of weight, adipose tissue function and obesity, and/or tissue responsivity to insulin. This group includes CPT1C, which has an effect on the regulation of feeding behavior (Casals et al., 2016), RETN (resistin), which is known to be secreted by adipocytes and has links to obesity and type II diabetes (Filkova et al., 2013; Sassek et al., 2013), and RLN3, a member of the relaxin family of insulin-like hormones, which is expressed mostly in the brain

and is involved in stress, memory, and appetite regulation (Higgins et al., 2010; McGowan et al., 2009). Intriguingly, the absence of these genes in birds could potentially be related to the known low sensitivity to insulin and the generally high circulating glucose levels that are characteristic of many bird species (Braun and Sweazea, 2008), possibly representing a general avian trait. In this regard, it is interesting that FGF21, which stimulates the uptake of glucose in adipose tissue, is also missing in birds (Lovell et al., 2014; although preliminary searches of transcriptome data have questioned that loss, see Bornelov et al., 2017). It is also noteworthy that the insulin-regulated glucose transporter (SLC2A4, a.k.a. GLUT4) is generally thought to be missing in birds (Kono et al., 2005; Seki et al., 2003; Sweazea and Braun, 2006; Welch et al., 2013), but preliminary analysis suggests that it may be present in at least some birds, although possibly with low conservation with mammals (Mello and Lovell, unpublished). As for RLN3, a paralog is present in birds (RLN3L), which has a similar structure as RNL3 in terms of major domains, and thus may have provided compensation for the loss of the RNL3 ortholog in birds (Lovell et al., 2014). RNL3L is likely the product of an ancestral duplication of RNL3, as it is also present in reptiles, and in non-eutherian mammals. However, it is not present in humans, which could reflect a loss in the eutherian lineage. These observations suggest that a genetic compensation for a possible RNL3 loss would be immediately present for most vertebrates, but not for non-eutherian mammals. Lastly, SERPINI2, while not directly associated with a weight or insulin-related phenotype, is known to be down-regulated in pancreatic carcinogenesis, suggesting at least an indirect link with pancreatic function (Chang et al., 2000; Higgins et al., 2017; Ozaki et al., 1998).

Other missing genes relate to a diverse range of endocrine-related and growth functions. In the case of PRKACA, constitutive activation by somatic mutations or genomic duplications are associated with hyperplasias and adenomas of the adrenal cortex and with corticotropin-independent Cushing's syndrome (Carney et al., 2015; Sargent, 2014). An intriguing possibility is that birds might be particularly resistant to the development of this type of adrenal cortex dysfunction and Cushing's syndrome. PRSS8 is involved in water and electrolyte balance, through proteolytic activation of the epithelial sodium channel, and may also play a role in epithelial barrier formation (Leyvraz et al., 2005). A more in-depth mechanistic understanding of the involvement of these two genes within the context of adrenal function and electrolyte balance could perhaps be obtained by gain of function approaches involving gene overexpression in an avian transgenic context, or through tissue injections of viral vectors with overexpression constructs. The biglycan (BGN) gene has a known involvement in skeletal-muscle growth, development and regeneration, as well as in specific aspects of collagen fibril assembly (Casar et al., 2004; Corsi et al., 2002). It would be very interesting to determine whether these

functions are more susceptible to disruptions in birds due to the loss of BGN, for example during the conditions of accelerated growth as seen in the poultry industry, or whether birds evolved adaptive mechanisms that allowed them to fully compensate for this gene loss. The estrogen related receptor alpha (ESRRA) encodes a nuclear protein with kinship to the estrogen receptor. It acts as a site-specific transcription regulator that interacts with the general transcription factor TFIIB, through direct protein-protein interactions. As a result, it modulates the expression of several estrogen-responsive genes, such as lactoferrin (Zhang and Teng, 2000), osteopontin (Vanacker et al., 1998b; Zirngibl et al., 2008), the medium-chain acyl coenzyme A dehydrogenase (MCAD; Maehara et al., 2003; Sladek et al., 1997) and the thyroid hormone receptor (Vanacker et al., 1998a). Together with estrogen receptors, ESRRA can be considered a co-regulator of estrogen target genes. Because this co-regulator of estrogen targets is missing in birds, important aspects of gene responsivity to estrogen are also likely to differ significantly between birds and mammals, but possible functional consequences of the ESRRA absence are unknown at present. An intriguing possibility is that the ESRRA loss might somehow be related to the puzzling and unique findings in the context of brain sex differences and neural differentiation in birds. For instance, female zebra finches induced to grow testes lack masculinized song neural circuits (Wade and Arnold, 1996; Wade et al., 1996), while males that possess ovaries, but lack testes develop normal circuits and even sing, demonstrating a role of sex chromosome genes in this brain sex difference. However, if female zebra finches are treated at hatch with estradiol, they develop a partially masculinized song system and are even able to sing (Wade and Arnold, 2004), pointing to complex and still unexplained interactions between sex hormones and chromosomes in determining this dimorphism. It is also worth mentioning here Kisspeptin, thought to mediate the onset of puberty in mammals by regulating the expression of hypothalamic GnRH (gonadotrophin-releasing hormone). Kisspeptin-related peptides and corresponding genes have been convincingly shown to be absent in birds, due to gene loss or pseudogenization (Pasquier et al., 2014). Of note, Kiss3 is located in a region of human chromosome 19 that contains many of the avian syntenic missing gene clusters described in Lovell et al. (2014) but similarly to the APOE case discussed above, it was not included in the original set of avian missing genes because it was also missing in lizards. To date, Kiss3 has not been found in any sauropsid, and may in fact represent an ancestral loss in this entire group. This suggests that GnRH regulation in the entire sauropsid lineage, not just in birds, differs significantly from mammals.

It is also noteworthy that several other avian missing genes have been implicated in serious human disorders or syndromes (Table 2). In some specific cases the gene loss is the established genetic cause of a well-known endocrine disorder (e.g. AVPR2 loss leading to diabetes insipidus Anesi et al., 2012; Spanakis et al., 2008), or has a suspected involvement in a major endocrine function (e.g. RETN function linked to susceptibility to type II diabetes mellitus and insulin resistance (Chung et al., 2014; Hivert et al., 2009; Zaidi and Shirwany, 2015). In most other cases, the gene loss is associated with complex syndromes that involve, among many other functions, major impairments in general growth and development, including abnormalities in the formation and/or growth of brain, bone, joint, and muscle. In yet other cases the dysfunction is associated with impairments in metabolic pathways (e.g. aminoacid biosynthesis and transport). It is highly intriguing that these syndrome manifestations are not apparent in birds, in spite of the absence of these genes. This fact indicates that further studies of how the related pathways and tissues are modified in birds are likely to provide important and novel insights into naturally evolved compensatory mechanisms, and even suggest some possi-

Table 2
Missing genes in birds that are associated with a human genetic syndrome or disorder (Modified from Lovell et al., 2014; Summaries are excerpts from OMIM, www.omim.org).

Gene	Human Genetic Syndrome/Disorder
ABCD1	Adrenoleukodystrophy, an X-chromosome recessively inherited demyelinating disorder of the nervous system
AVPR2	Nephrogenic Diabetes Insipidus (NDI)
BCAT2	Elevated serum branched chain amino acids, decreased spontaneous movement, thin hair; also seen in humans with maple syrup urine disease
CCDC114	Autosomal recessive ciliopathy characterized by infantile onset of chronic sinopulmonary infections resulting from immotile cilia and defective clearance.
CEBPE	Specific Granule Deficiency, a rare congenital disorder that results in neutrophil functional deficits and association with recurrent infections
CORO1A	Immunodeficiency characterized by early-onset recurrent infections, including oral thrush and postvaccination varicella
DNAAF3	Primary ciliary dyskinesia type 2 (CILD2), an autosomal recessive disorder that results in recurrent respiratory infections, otitis media, sinusitis, and chronic cough
DOCK6	Adams-Oliver syndrome 2, an autosomal recessive congenital anomaly syndrome characterized by aplasia cutis congenital and terminal transverse limb defects.
ERF	Craniosynostosis, an abnormality of skull growth involving premature fusion of the cranial sutures
FERMT3	Autosomal recessive leukocyte adhesion deficiency syndrome-III (LAD-III), a disorder characterized by delayed wound healing and bleeding problems
FGD1	Aarskog-Scott syndrome (faciogenital dysplasia and X-linked mental retardation, syndromatic 16); includes short stature, brachydactyly, joint hyperextensibility, hypertelorism, among other symptoms
GDI1	X-linked nonspecific mental retardation
ITPKC	Increased susceptibility to Kawasaki disease, an acute vasculitis of infants and children characterized by prolonged fever, polymorphous skin rash, erythema of the oral mucosa, lips, and tongue, palms, and soles
MYH14	Autosomal dominant hearing impairment.
NTF4	Abnormal appearance of the optic disc (optic nerve head) accompanied by a slowly progressive loss of visual sensitivity
PACS1	Mental retardation, autosomal dominant 17, which is characterized by mental retardation, distinct craniofacial features, and genital abnormalities
RETN	Increased susceptibility to non-insulin-dependent diabetes mellitus (type II), and insulin resistance
RPGRIP1	Leber Congenital Amaurosis 6, a homozygous or compound heterozygous mutation that leads to early onset childhood retinal dystrophies, including vision loss, nystagmus, and severe retinal dysfunction
SLC6A8	X-linked creatine deficiency syndrome that is characterized by mental retardation, severe speech delay, behavioral abnormalities, and seizures
SLC7A7	Lysinuric protein intolerance (LPI) related to the deficient transport of basic amino acids
STXBP2	Familial hemophagocytic lymphohistiocytosis, a rare autosomal recessive disorder characterized by infiltration of organs by activated lyphocytes and macrophages
SYN1	Epilepsy, X-Linked, with Variable Learning Disabilities and Behavior Disorders
SYP	X-linked mental retardation 96 (XLMR)
TRPM4	Progressive Familial Heart Block, Type Ib, a progressive disorder that leads to bundle branch blockage

ble therapeutic strategies to for these major syndromes and diseases. Of note, there is growing awareness that some gene 'knockout' mutations in humans can appear to be silent, with no obvious phenotypes (e.g. Narasimhan et al., 2016). Possible explanations include variable penetrance of mutations, compensatory mechanisms that attenuate the impact of a given knockout (consistent with the fact that some mice knockouts only show a phenotype when combined with other knockouts), but also incomplete or imperfect databases documenting the human knockouts. For the avian missing genes being discussed here, the 'knockout' con-

sists of examples of gene losses, not just knockout mutations, so issues like allele penetrance seem less relevant. Furthermore, the extensive annotation/curation efforts in Lovell et al. (2014) have effectively excluded the possibility that apparent gene losses simply reflect curatorial errors from automated annotation algorithms.

3. Future directions

While the findings discussed here are highly intriguing, much remains to be done to firmly establish the scope and implications of the avian losses of these important genes. Definite conclusions on the extent of the losses will require the completion of high quality assemblies that incorporate difficult to sequence/assemble regions. This includes avian microchromosomes, which have been particularly refractory to completion, likely due to a combination of particularly high GC content and the very high occurrence of repetitive elements and motifs (Gordon et al., 2007; Warren et al., 2017). It will also be important to ascertain the orthology of the genes for which transcriptome-based short read reconstructions is the sole evidence of their existence. Whenever possible, mapping of short reads to the genome assembly will be instrumental for differentiating cases of possible paralogy, and incorporation of unplaced assembled segments into larger scaffolds will facilitate syntenic assessment of orthology. Equally important will be a careful evaluation of conservation of sequence and domain organization of the genes that are eventually found, especially those placed in microchromosomes and other difficult to sequence or assemble regions. Perhaps most exciting of all, it seems likely that novel important insights into gene function could be gained by manipulations such as re-introducing these missing genes into experimental avian model organisms through transgenesis or tissue-specific overexpression with viral vectors-based methodologies (Abe et al., 2015; Agate et al., 2009; Bosselman et al., 1989; Liu et al., 2015; Poynter et al., 2009; Scott et al., 2010; Tanaka et al., 2016; Velho and Lois, 2014). Such approaches could test whether/how the respective pathways and tissues are sensitive to gene reinsertion, or alternatively whether birds have become refractory to the molecular actions of these genes as a result of the evolutionary processes that led to the emergence of modern avian species.

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