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Investigating the genetic basis of vertebrate dispersal combining RNA-seq, RAD-seq and quantitative genetics

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Abstract

Although animal dispersal is known to play key roles in ecological and evolutionary processes such as colonization, population extinction and local adaptation, little is known about its genetic basis, particularly in vertebrates. Untapping the genetic basis of dispersal should deepen our understanding of how dispersal behaviour evolves, the molecular mechanisms that regulate it and link it to other phenotypic aspects in order to form the so-called dispersal syndromes. Here, we comprehensively combined quantitative genetics, genome-wide sequencing and transcriptome sequencing to investigate the genetic basis of natal dispersal in a known ecological and evolutionary model of vertebrate dispersal: the common lizard, *Zootoca vivipara*. Our study supports the heritability of dispersal in semi-natural populations, with less variation attributable to maternal and natal environment effects. In addition, we found an association between natal dispersal and both variation in the carbonic anhydrase (*CA10*) gene, and in the expression of several genes (*TGFB2*, *SLC6A4*, *NOS1*) involved in central nervous system functioning. These findings suggest that neurotransmitters (serotonin and nitric oxide) are involved in the regulation of dispersal and shaping

dispersal syndromes. Several genes from the circadian clock (*CRY2*, *KCTD21*) were also differentially expressed between disperser and resident lizards, supporting that the circadian rhythm, known to be involved in long-distance migration in other taxa, might affect dispersal as well. Since neuronal and circadian pathways are relatively well conserved across vertebrates, our results are likely to be generalisable, and we therefore encourage future studies to further investigate the role of these pathways in shaping dispersal in vertebrates.

KEYWORDS
behaviour, circadian clock, dispersal, gene expression, genomics, neurotransmitters

1 | INTRODUCTION

Dispersal is a cornerstone of ecological and evolutionary processes (Clobert, Baguette, et al., 2012; Clobert, Massot, & Le Galliard, 2012) but the genetic factors that underlie dispersal remain largely unknown (Saastamoinen et al., 2018). Dispersal fuels meta-population dynamics and channels gene flow among populations (Ronce, 2007). Processes such as extinction, colonization, and local adaptation cannot be fully understood without questioning how dispersal itself evolves (e.g., Block & Levine, 2021). Despite dispersal having been traditionally considered a stochastic process (Lowe & McPeek, 2014), mounting evidence supports that traits such as dispersal propensity or distance vary substantially among individuals of a population (Bowler & Benton, 2009; Haag et al., 2005; Steyn et al., 2016). The attention has shifted towards the need to understand how an individual's internal factors such as its genetics or physiology influence dispersal behavioural phases (departure, transience and settlement), and towards the relative importance of genetic versus environmental factors in driving dispersal and its evolution (Clobert et al., 2009; Saastamoinen et al., 2018). Yet, our current understanding of the genetic and molecular pathways underpinning dispersal remains limited, particularly in vertebrates.

Unravelling the genetic basis of dispersal – identifying both the contribution of genetic variation as well as the genes and genetic variants associated with dispersal – is challenging for at least three reasons. First, although some species present clearly distinct and identifiable dispersal morphs (e.g., Caillaud et al., 2002), dispersal is a cryptic phenotype in most species (Wheat, 2012). This makes it difficult to discern which individuals in a population will disperse and to compare their genetic make-up with that of nondispersing individuals (i.e., residents). Second, dispersal propensity, distance and timing are largely dependent on multiple environmental factors (population density, predation, inbreeding, among others; Fronhofer et al., 2018; Matthysen, 2005; Perrin & Mazalov, 1999). We can thus expect a relatively small contribution of genetic factors to variation in dispersal, limiting the detection of its heritability and causal genetic variants. Moreover, different environmental factors may not necessarily trigger dispersal through the same genetic pathways, which entails that individuals phenotyped as dispersers may be a heterogeneous pool in terms of causal genetics drivers. Third, dispersal is a complex trait given that it often associates with a suite of physiological, behavioural, morphological, and life-history traits (the so-called dispersal syndromes: Clobert et al., 2009), and these associations are likely to change with the environmental context (Cote et al., 2017). Such phenotypic complexity underlying dispersal is likely to multiply the number of underlying molecular pathways, complexifying the genetic basis of dispersal and consequently, its study.

Most of our understanding of the genetic basis of dispersal comes from invertebrate species, even though only a few species have been studied and a few candidate genes have been discovered so far. In well-studied model systems such as *Drosophila melanogaster* and *Caenorhabditis elegans*, genes found to underpin dispersal relate to different foraging strategies that ultimately entail differences in dispersal propensity (the foraging gene, *for*, in *D. melanogaster*, and the G protein-coupled receptor gene, *NPR-1*, in *C. elegans*: Edelsparre et al., 2014; Gloria-Soria & Azevedo, 2008). Work on the Glanville fritillary butterfly (*Melitaea cinxia*, a model system for studying dispersal) strongly suggests that dispersal capacity in this species associates to variation at a gene related to metabolism and flight performance, the phosphoglucose isomerase gene, *Pgi* (Niitepõld & Saastamoinen, 2017). In the pea aphid *Acyrthosiphon pisum*, male wingless (resident) and winged (disperser) morphs were mapped to a narrow region in the X chromosome, the *api* locus (Caillaud et al., 2002). In winged males, the *api* locus contains a duplication of the gene *follistatin*, which functions in cell development and ecdysis (Li et al., 2020).

The genetic basis of dispersal in vertebrates has been studied in less detail, and even estimates of heritability of traits directly linked to dispersal such as dispersal propensity or distance remain rare (Saastamoinen et al., 2018). A tandem repeat in the serotonin transporter, *SLCA4*, was found in association with dispersal age in rhesus macaques (*Macaca mulatta*) (Trefilov et al., 2000). Using a candidate gene approach, Chakarov et al. (2013) provided evidence for an association of variation at the genes of the circadian clock and natal dispersal in the common buzzard (*Buteo buteo*). The involvement of the circadian clock in dispersal was not echoed in a recent transcriptomic study in yellow-bellied marmots (Armenta et al., 2019), where mainly genes involved in metabolism and immune system were highlighted. The type of tissue used in this later transcriptomic study

– blood – may be of limited representativeness of the transcriptomic changes that causes dispersal. Arguably more appropriate tissues were used in studies on cane toads (*Rhinella marina*) investigating gene expression differences linked to dispersal in the brain and skeletal muscle (Rollins et al., 2015; Yagound et al., 2021). Several genes linked to metabolism and locomotor activity were highlighted by such studies. Unfortunately, individual dispersal was not directly assessed in these studies. Instead, individuals from populations at different points in a colonization gradient were used as a proxy of populations differences in dispersal capacity, making it difficult to assess to what extent the highlighted genetic pathways are actually linked to dispersal or to general population and environmental differences.

Here, we describe a holistic study in which we investigated the genetic basis of natal dispersal in the European common lizard (*Zootoca vivipara*). This species is a well-established model system to study vertebrate dispersal in the wild as well as in semi-natural experimental settings (reviewed in Clobert, Baguette, et al., 2012; Clobert, Massot, & Le Galliard, 2012; Cote & Clobert, 2012). Here, we combine the use of (i) animal models (Wilson et al., 2010) to decompose variation in natal dispersal into genetic and nongenetic factors, (ii) restriction-site associated markers (RAD sequencing, RADseq; (Baird et al., 2008) to search for genomic regions associated with natal dispersal, and (iii) transcriptome sequencing (RNA sequencing, RNAseq; Mortazavi et al., 2008) to investigate gene expression differences associated with natal dispersal. We assessed natal dispersal of lizards originating from natural populations within the Metatron; an experimental system of enclosed semi-natural populations connected by corridors and conceived for the study of dispersal and population dynamics in an ecologically realistic context (Legrand et al., 2012).

2 | MATERIALS AND METHODS

2.1 | Species and population of study

The common lizard is a small ground dwelling lizard that inhabits cold and humid habitats across Eurasia. In live bearing populations, females lay on average five uncalcified eggs from which juveniles emerge within one to 2 h. Juveniles are independent at birth and dispersal occurs mainly during the first months of life (Massot et al., 2002). The multiple factors triggering dispersal in this species include abiotic factors (humidity and temperature; (e.g., Bestion et al., 2015, 20015b; Massot et al., 2002), social factors (e.g., density and kin competition; Galliard et al., 2003), community factors (e.g., predation; Bestion et al., 2014), and internal factors (e.g., social behaviour; Cote & Clobert, 2007, stress level; Meylan, 2002).

Here, we used a database built from successive semi-natural experiments to study dispersal and that took place between 2011 and 2017. Semi-natural populations were established in the Metatron: a system of semi-natural enclosures connected together through 19 m long corridors divided lengthwise allowing lizards to disperse and the bidirectional monitoring of their movements (Legrand et al., 2012). The system successfully mimic natural dispersal (Cote & Clobert, 2012). In wild populations, juveniles (body length of 1.5–2.5 cm), moving 30 m or more away from their natal sites (i.e., the distance between the centre of two enclosures connected by a 19 m corridor) can be defined as dispersers as only small fraction of them (2%) return back to the natal site (Clobert et al., 1994). Similar setups have been repeatedly used to study dispersal in the common lizard and successfully mimic natural dispersal decision in reaction to main external and internal drivers (Boudjemadi et al., 1999; Cote & Clobert, 2007; Le Galliard et al., 2005).

The populations were originally founded in 2010 with lizards from natural populations in the Cevennes (France, 44°27' N, 3°44′ E). Between 2011 and 2017, different experiments were conducted to study dispersal and how it is influenced by climatic conditions or maternal effects (see Bestion et al., 2014; Bestion, Clobert, & Cote, 2015; Pellerin et al., 2022). For each experiment, we formed 10 to 16 populations by releasing adults, yearlings and neonates into enclosed patches within a humid-prairie habitat in early July (Legrand et al., 2012). Population density as well as age- and sex-structure matched those of natural populations (Bestion, Cucherousset, et al., 2015; Massot et al., 1992). Neonates were born in the laboratory, marked individually by toe clipping, and release in the enclosures right after (no association between dispersal status and the number of clipped toes was found, $t_{886} = 0.90$, $p = .37$). Each year, we monitored natal dispersal between early July and the end of September by keeping the corridors open. Between 2011 and 2013, we placed pitfall traps at the end of each 19 m (one-way) corridor to capture and identify dispersers on a daily basis. From mid-September to mid-October, we conducted three capture-recapture sessions to assess summer survival (allowing us to capture ~93% of the survivors) and to identify juveniles that could be classed as resident among those released in early July (i.e., to avoid wrongly classifying nonsurviving juveniles as residents). Between 2014 and 2017, pitfall traps were removed allowing lizards to freely disperse between pairs of enclosures through the two-way corridors. During similar capture-recapture sessions conducted between mid-September to mid-October, we identified juveniles as residents when captured in the enclosure that they were released into in early July and as dispersers when captured in a different one. For each new experiment (each year between 2011–2015), lizard populations were re-established by mixing individuals from different populations avoiding inbreeding.

2.2 | Quantitative genetics

Pooling the data from all experiments conducted in the Metatron between 2011 and 2017, we built a pedigree containing 3656 lizards. The pedigree included 404 founders (309 females and 101 males of unknown maternal and paternal origin captured directly in natural populations of the Cevennes). Maternal identity was known in most cases because juveniles were born directly in the laboratory.

Paternities were assigned by genotyping each juvenile, its mother and all reproductive males in the populations for a panel of eight microsatellite markers (Richard et al., 2012). Paternity was resolved by subtracting the mother's alleles from a juvenile's genotype and by matching the remaining alleles with those of the potential father candidates. Mother identity was not known in seven cases only (0.2%) for neonates directly born in the experimental populations. Father identity was missing in 803 cases (24.9%) because juveniles born from gravid females captured in natural populations were regularly introduced in the Metatron. Individuals with unknown mothers or fathers were assigned a dummy mother or father (Charmantier & Réale, 2005). When individuals were known to come from the same clutch, the same dummy parents were given to each of them.

We used a threshold animal model (i.e., binomial model with a probit link function) to estimate the heritability of natal dispersal from the pedigree. The threshold model assumes the existence of a latent continuous quantitative trait (liability) underlying a binary trait (here, natal dispersal). Change from one discrete state to the next (e.g., from being resident to disperse) is expected to result from the accumulation of genetic and/or environmental variation until the quantitative trait overpasses a threshold (Reid & Acker, 2022). For the threshold animal model, we used data on 888 juvenile lizards whose dispersal status (N = 123 dispersers, N = 765 residents) was monitored during their first month of life as explained above (i.e., they were alive in mid-September). For the individuals of known dispersal status, mother identity was known in 99.3% of the cases and father identity in 92.3%. Mean maternal and paternal sibship size was 3.7 and 4.3 juveniles, respectively, and the maximum pedigree depth was five generations.

We used the R package nadiv (Wolak, 2012) in R (version 4.0.3, R Core Team, 2019) to derive the additive genetic relationship matrix from the pedigree and used it to estimate the additive genetic variance (V_a) of natal dispersal by fitting an animal model with the R package MCMCglmm (Hadfield, 2010). We further decomposed variance of natal dispersal by estimating maternal (V_m) and natal environment (V_e) effects by fitting as random factors mother ID and the enclosure in which a juvenile was released. As fixed factors, we included sex and year. We used a χ^2 distribution with one degree of freedom as priors for the random factors as suggested by De Villemereuil et al. (2013) and fixed the residual variance (V_r) to 1. We let the MCMC run for 10.1 M iterations with a burnin of 0.1 M and a thinning interval of 1000 iterations. The final effective sampling was ≥9675 for all terms (Table S1). We tested whether the inclusion of an additive genetic term in the animal model resulted in a substantially better fit by comparing the DIC values of a model with and without including a V_a term. We used the same approach to test for improvements in model fit in relation to V_m and V_e. We ran models twice to verify that the level of variation between runs with the same model specification was negligible (ΔDIC <0.1).

We calculated narrow sense heritability (h^2) in the liability scale as the ratio between V_a and the sum of V_a, V_m, V_e, V_r, and the variance explained by the fixed factors (V_f). We calculated heritability in the observed data scale using the function QGparams as implemented in the *R* package QGglmm by accounting also for the variance explained by the fixed effects (De Villemereuil et al., 2016). We calculated the proportion of variance explained by V_m, and V_e using the same approach.

2.3 | Genome-wide association study

2.3.1 | Tissue collection, DNA extraction, library preparation, and sequencing

We extracted DNA from tail samples of 235 juveniles born in 2011 and 2013 (N = 55 dispersers, N = 180 residents) using the DNeasy Blood & Tissue kit (Qiagen). The preparation of genotype-by-sequencing, GBS, libraries was outsourced to Novogene (Tai Sun Wai, Hong Kong). Between 0.3 and 0.6 μg of DNA were digested with the enzymes MseI and NlaIII, fragments were ligated to barcoded adapters, amplified by PCR, and size selected using the AMPure XP kit (Beckman Coulter) according to the manufacturer's instructions. Libraries were pooled and sequenced (150 bp paired-end) on 15 lanes in Illumina HiSeq machines. On average, we obtained 3.9 M paired-end reads per individual (±0.9 M reads SD).

2.3.2 | Single nucleotide polymorphism (SNP) and genotype calling

We used Trimmomatic (version 0.36, Bolger et al., 2014) to remove Illumina-adapter sequences from the raw reads and to perform an adaptive quality trimming of low quality bases (MAXINFO option with strictness of 0.2 and target read length of 100 bp). We aligned the trimmed reads to the reference genome of *Zootoca vivipara* (GCA_011800845.1, Yurchenko et al., 2020) using bwa-mem2 (version 2.0, Vasimuddin et al., 2019) with default parameters and we marked optical duplicates using picard (MarkDuplicates option, version 2.20.7, Broad Institute, 2019). Mapping rate after removing optical duplicates was high (mean [± SD]: 97.5% ± 0.5, considering only properly mapped pairs: 91.1% ± 1.0). Mean fragment size was 247.8 bp ± 4.2, mean depth 10.8 ± 2.2, and the mean percentage of bases of the reference genome covered was 6.2% ± 0.8.

We used the workflow of Genome Analysis Toolkit (gatk, version 4.1.9, McKenna et al., 2010) to call for variants and genotypes. We used gatk HaplotypeCaller function to call for variants from the individual raw alignments and then the function GenotypeGVCFs to perform the joint genotyping of all samples. We hard filtered the resulting variant file to retain only biallelic SNPs with a quality by depth greater than 2.0, root mean square mapping quality above 50, Fisher strand smaller than 60, and read position rank sum test above −8. We further filtered the SNPs set to retain those SNPs that could be genotyped in more than 80% of the samples and for which mean depth was above 10 and below four times the mean coverage of 16.43. The remaining 610,780 SNPs were used to recalibrate the base quality scores of the reads

to correct for any bias in quality assessment during sequencing. After this, we repeated all the described process to call for variants. We applied the same hard filter to the new set of variants and retained those SNPs that were genotyped in more than 80% of the samples, with a mean depth above 10 and four times below the mean coverage (22.03x), and for which the less common allele was present in at least two samples. The final number of biallelic SNPs retained was 411,921 with an average coverage of 23.06 (range: 10–88.01).

2.3.3 | Association test

We used gemma (version 0.98.4, Zhou & Stephens, 2012) to test for associations between individual SNPs and dispersal status. To account for the potential effect of different covariables, we extracted the residuals from a generalized linear mixed model where we modelled dispersal status (binomial) as a function of sex (fixed effect) and mother ID, and natal environment (enclosure ID) (random effects). Models were run in R with the function glmer (lme4 package, Bates et al., 2015). We used gemma to estimate genome-wide relatedness from the SNP data that was previously filtered to remove SNPs with a minor allele frequency below 0.01 (249,452 SNPs were retained). Information on relatedness and the residuals of dispersal status were then used in gemma to run the association Wald's tests. To account for multiple testing, we used the R package qvalues (Storey et al., 2021) to estimate the q-values for the p-values yielded by gemma. We fixed the false discovery rate at $q \leq 0.1$.

2.4 | Differential gene expression (RNA-seq)

2.4.1 | Tissue collection, RNA extraction, library preparation, and sequencing

In 2013, we selected six dispersers and six residents among the juveniles recaptured in September. For the selected individuals to be representative of all dispersers and residents in the populations, we first chose six dispersers belonging to six different populations of initial release and to six different populations of post-dispersal release. Populations were subjected to two climatic conditions as part of another experiment. Climatic treatments before dispersal and after dispersal were both equally distributed (three individuals from the present-day and three from the warm treatment, see Bestion, Clobert, & Cote, 2015; Bestion, Cucherousset, et al., 2015 for details about climatic treatments). It resulted into two dispersers which moved from a present-day to a warm enclosure, two dispersers which moved from a warm to a present-day enclosure, one disperser moving from a warm to a warm enclosure and one disperser moving from a present-day to a present-day enclosure. The sex-ratio was similar to the population sex-ratio, meaning four female and two male dispersers. These six dispersers were issued from six different families and were not significantly different from nonselected dispersers at several traits (date of birth, body size, body mass, natal thermal preference and activity, sociability and exploration levels; all $p \geq .4$, all $R^2 \leq 0.02$). This procedure allows us to have the dispersers' phenotypic characteristics representative to the entire pool of dispersers. Second, we choose residents among the pool of residents to match the sex-ratio, the climatic treatments and the pre- and post-dispersal populations of dispersers. Only one resident could not match the populations of dispersers, but residents were still from six different populations. Residents were also from six different families, also different from those of the dispersers, and were chosen to match nonselected residents on their date of birth, body size, body mass, natal thermal preference and activity, sociability and exploration levels (all $p \geq .23$, $R^2 \leq 0.01$).

After their capture, the selected residents and dispersers were kept for 1 week in a laboratory common garden before euthanizing them to prevent immediate effects of enclosure conditions on gene expression. The tissues of dispersers were therefore sampled 30.2 ± 6.9 SE days after dispersal (range: 16–60 days). We chose this procedure rather than collecting samples right after dispersal to focus on lasting, more constitutive differences among dispersers and residents in gene expression and to be able to choose among the entire pool of individuals without interrupting the main experiment. This is probably a conservative choice because the delay between dispersal and tissue collection to result in the homogenisation of gene expression profiles of disperser and resident lizards. For euthanasia, we chose the most humane method that would limit to the minimum animal suffering without compromising gene expression. We maintained lizards at 4°C for 4 h to put them in a lethargic state before decapitated them. The head was immediately put into a sterilized tube and flash frozen in liquid nitrogen. We then collected the right hind leg and flash frozen it in liquid nitrogen. Samples were stored at −80°C until RNA extraction. Euthanasia and tissue collection lasted less than 20 s. In order to minimize sampling time and secure RNA quality, the entire head and hind leg samples were collected. Each part contains tissues of direct interest in dispersal (brain and skeletal muscle, respectively) and includes others that expected to participate in dispersal as well (head: sensory visual, auditive and chemoreception organs, hind leg: peripheral nervous system, bone and bone narrow tissues).

RNA was extracted using a RNeasy Plus Universal Mini Kit (Qiagen) and immediately stored at −80°C. Samples were sent to the GeT Platform of Genotoul (Castanet-Tolosan) for library preparation and sequencing. RNA quantity and quality were assessed with an Agilent 2010 Bioanalyser (Agilent Technologies). All samples were of good quality (RIN ≥7.6, Table S2). For each sample, cDNA stranded libraries were prepared from isolated messenger RNA using TruSeq RNA Sample Prep Kits version 2 (Illumina). Libraries were quantified via real-time quantitative PCR using an ABI7900HT (ThermoFisher Scientific) (Table S1). Thirty fmol of each of the 24 libraries were pooled and sequenced (100 bp paired-end) together in 4 Hiseq2000 Illumina lanes, resulting in a total of 813 M paired-end reads (mean [± SD]: 29.5 M paired reads ±8.8 for head samples, and 38.2 M paired reads ±6.4 for hind leg samples, Table S3).

2.4.2 | Gene expression quantification

We used Trimmomatic (version 0.36, Bolger et al., 2014) to remove Illumina-adapter sequences from the raw reads and to perform an adaptive quality trimming of low quality bases (MAXINFO option with strictness of 0.8 and target read length of 75 bp). We discarded all the unpaired reads and reads that resulted shorter than 75 bp after trimming, keeping a total of 730 M paired-end reads (mean [± SD]: 26.4 M reads ±8.1 for head samples, and 34.4 M reads ±5.6 for hind leg samples, Table S3). We aligned the reads to the reference genome of *Zootoca vivipara* (GCA_011800845.1, Yurchenko et al., 2020) using *HISAT2* (version 2.2.1, Kim et al., 2015 see also Pertea et al., 2016). The proportion of reads that aligned to the genome (excluding reads with multiple alignments) was high for both head and hind leg samples (mean [± SD]: 90.7% ± 0.9 for head samples, and 93.% ± 0.7 for hind leg samples, Table S3).

We quantified gene expression using two alternative methods. On the one hand, we quantified transcript expression from the bam alignments yielded by HISAT2 using stringtie (Pertea et al., 2016). On the other hand, we used an alignment-free tool: kallisto (version 0.44.0, Bray et al., 2016) to quantify transcript expression via pseudo-alignment of the trimmed reads. The correspondence between both counting methods was high for highly expressed genes but decreased substantially for lowly expressed genes (Figure S1). We accounted for such methodological disparity in gene expression quantification by running the subsequent differential expression (DE) analyses with the count data yielded by both stringtie and kallisto.

For both counting methods, we restricted quantification to the gene and pseudo-gene features already annotated in the *Zootoca vivipara*'s reference genome (Table S4). This comprised 22,184 genes and 647 pseudogenes. On average, 86.88% of the reads aligned to the reference transcriptome (89.11% ± 0.31 for the head samples and 84.63% ± 0.59 for the hind leg samples) and were used to quantify gene expression. We ran BUSCO (version 4.0.6, Simão et al., 2015) to assess the quality of the transcriptome by looking for the presence and completeness of known orthologues of Metazoa (N = 954 orthologues) and Vertebrata (N = 3354). Up to 99.3 and 98.7% of metazoan and vertebrate orthologues were recovered from the reference transcriptome, with only few of them fragmented (0.0 and 0.45% for metazoan and vertebrate orthologues, respectively).

2.4.3 | Differential gene expression analyses

We used the R package DESeq2 (version 1.28.1, Love et al., 2014) to normalize gene expression counts and to estimate and test for DE between disperser and resident lizards. Before the analyses, we filtered out genes with zero expression in the head or the hind leg tissues of more 10 individuals and genes with mean raw count across all individuals and tissues below 7. A total of 16,972 genes and 17,382 genes passed this filter for the stringtie and kallisto data sets, respectively. We estimated size factors and dispersion using the default DESeq2 parameters and we used negative binomial GLM as implemented in DESeq2 to test for DE. The models included dispersal status (disperser vs. resident), body part (head vs. hind leg), their interaction, and the effect of lizard ID nested within dispersal status. This last term was added to account for the hierarchical structure of our design: two repeated measurements (body parts) per individual. Post hoc contrasts were used to test for DE between dispersers and residents within each body part. We also tested for DE using the R package edgeR, which uses an alternative method of gene count normalization and estimation of dispersion than DESeq2 (Robinson et al., 2010). We obtained rather similar results with edgeR: 85%–94% of the DE genes detected by edgeR were also detected by DESeq2 (Figure S2).

After the DE analysis, we applied a jackknife approach to control for the bias that the expression profile of a single individual might have had on detecting a DE gene. We reran the DE analyses excluding each individual at a time. For each body part and counting method, we considered a gene as differentially expressed between dispersers and residents if (i) the p-value (adjusted for multiple testing using the method of Benjamini & Hochberg, 1995) was ≤ .05 (two-tailed) and if (ii) the p-value after having excluded any of the individuals was always ≤ .05 (two-tailed). Approximately, one fourth of the genes that were initially found to be differentially expressed were discarded using the jackknife approach described (Table S5). Finally, we controlled for the differences between stringtie and kallisto in counting gene expression by reporting as differentially expressed genes only those genes that were found to be differentially expressed using both counting methods (Figure S3).

2.4.4 | Gene ontology analyses

For each body part, we conducted a gene ontology (GO) analysis of the set of differentially expressed genes to test for GO enrichment in relation to the set of all genes tested for DE. GO terms for each gene were retrieved by blasting the longest isoform of each gene against the protein data base swissprot (downloaded 6 November, 2020; Boutet et al., 2007). We used blastx with an e-value ≤0.01 and a maximum of 10 target sequences, keeping the matching sequence with the highest bit score for each query (blast version 2.10.1, Altschul et al., 1990). For each gene with a swissprot annotation (91.4% of the genes), we search for its corresponding GO annotations of biological processes using the QuickGo site of the European Bioinformatics Institute, EMBL-EBI (www.ebi.ac.uk/QuickGO, last access 17 November, 2020). A total of 20,200 genes were successfully associated with at least one GO term (90.5% of the transcriptome). GO analyses were conducted with the R package topGO (version 2.40.0, Alexa & Rahnenführer, 2019). We tested for enrichment of GO terms by scoring the GO terms with a mixture of the algorithms elim and weight and using Fisher's exact tests (Alexa et al., 2006). This approach reduces the false-positive rate by accounting for the intercorrelated structure of GO terms (Alexa et al., 2006). GO terms with scores ≤0.01 were considered as significantly enriched.

3 | RESULTS

3.1 | Quantitative genetics of natal dispersal

The animal model including an additive genetic (V_a) term resulted in a substantially better fit (ΔDIC = 18.9) than a model considering no V_a for dispersal (N = 888). The estimates of narrow sense heritability were low-to-moderate and lower credible intervals (CI) were close to zero (h^2 on the liability scale = 0.35 [1.9 ·10^{-07}–0.58 95% CI], h^2 on the observed scale = 0.17 [1.0 ·10^{-07}–0.29 95% CI]). Modelling maternal effects on dispersal did not improve the model's fit (ΔDIC = 0.60) and had a trivial contribution to variation in dispersal (<0.01 [1.8 ·10^{-09}–0.09 95% CI] contrary to the effects of the natal population (ΔDIC = 37.53, variance contribution: 0.14 [0.06–0.27 95% CI] on the liability scale, 0.08 [0.03–0.14 95% CI] on the observed scale).

3.2 | Genome-wide association study of dispersal behaviour

One SNP at the linkage group 2 of the common lizard reference genome was significantly associated to natal dispersal (Figure 1a). The SNP was found in an intronic region of the carbonic anhydrase gene (*CA10*) (position 289,041 within the 309,442 bp of the gene) (Figure 1b). The protein coded by *CA10* is catalytically inactive and recent findings point to an evolutionary conserved function as a ligand of neurexin in the presynapses of the central nervous system (Sterky et al., 2017; Tao et al., 2019).

3.3 | Gene expression differences associated to dispersal

We found 66 genes significantly upregulated and 85 genes significantly downregulated in the head tissues of the disperser lizards (Figure 2a,c, Table S6). In the hind leg tissues, we found 198 genes significantly upregulated in dispersers and 222 downregulated (Figure 2b,d, Table S6). Around one third of the total variance in the differentially expressed (DE) genes was associated with dispersal status (Figure 2e,f). DE genes were evenly distributed along the genome (Figure 1c) and the number of DE genes per linkage group of the genome was strongly correlated with the number of genes annotated in each group (r = .84, p < .001).

Among the genes with the largest expression differences (Figure 2a,b, Table S5), we found genes with suspected functions in development. This included transforming growth factor β-2 (*TGFB2*); Figure 3a): a pleiotropic cytokine that recent findings link to the development of serotonergic neurons and the synthesis and metabolism of serotonin (Chleilat et al., 2019), and potassium channel tetramerization domain (*KCTD21*); Figure. 3b), which is expected to promote the degradation of HDAC1: an important protein regulating development via the Hedgehog pathway (De Smaele et al., 2011) and also involved in the regulation of the circadian clock (Takahashi, 2017). We also found genes linked to metabolism of sugars including *SLC2A1* (facilitatative glucose transporter member 1, Figure 3c), which codes for the most important transporter of glucose and thereby of energy to the brain (Koch & Weber, 2019), and genes linked to the metabolism of lipids and steroids (e.g., *CYP2G1*, which may be related to the metabolism of steroid hormones: Hua et al., 1997, Figure 3d). We found genes related to the muscular system: for example, parvalbumin like EF-hand containing (*PVALEF*) (Figure 3e), a gene part of the parvalbumin family that functions in muscle contraction, and genes related to the immune system: such as *TRIM27*, involved in the regulation of CD4-T cells (Figure 3f, Cai et al., 2011), and *MXRA5*, involved in the anti-inflammatory response (Figure 2g, Poveda et al., 2017).

The gene ontology (GO) analysis showed that DE genes in relation to dispersal were enriched for a diverse suite of biological processes (Table 1). In the head, enriched categories included some related to the musculature (GO's: response to muscle activity, actin filament severing, and sarcomere organization), immune response (phagosome acidification, I-kappaB phosphorylation), and metabolism (negative regulation of gluconeogenesis). In this latter category, we found a core circadian

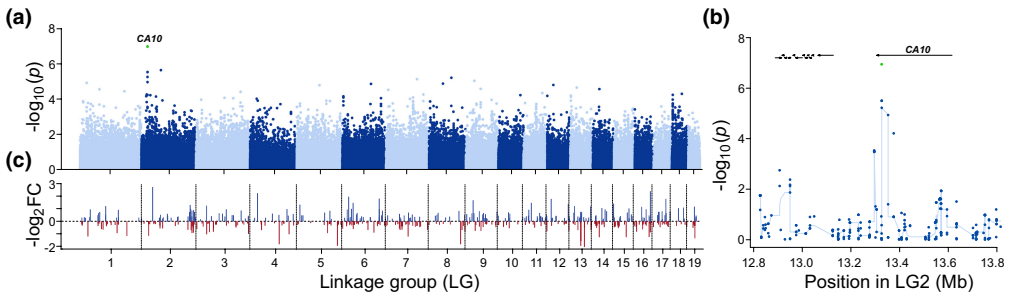

FIGURE 1 Genetic basis of natal dispersal behaviour in common lizards. Manhattan plot (a) showing the negative logarithms of the Wald test p-values on the association between the residuals of dispersal status (see Materials and methods for more details) and polymorphic variation at 249,452 single nucleotide polymorphisms (SNPs) of the 19 linkage groups of the reference genome of the common lizard. The SNP within the gene *CA10* with a q-value below 0.1 is shown in green. Detail of the region around the significant SNP within the gene *CA10* is shown in (b). Positions along the genome of the genes differentially expressed in dispersers and residents including their -log2 fold change (FC) (c).

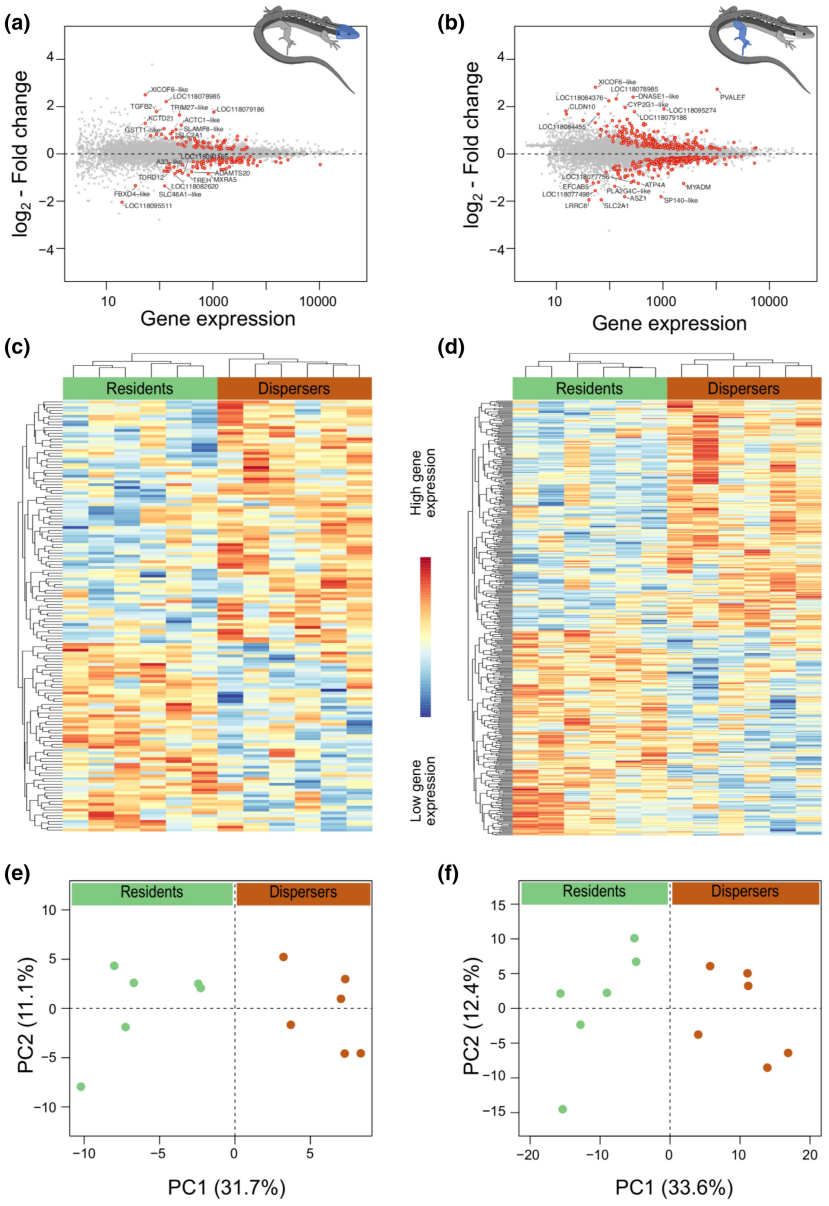

FIGURE 2 Differential gene expression in the head and hind leg tissues of disperser and resident common lizards. Change in gene expression in the head (a) and hind leg (b) tissues of disperser versus resident lizards in relation to mean expression levels. Red dots indicate significant differentially expressed (DE) genes, labelled for the 20 most DE genes (Table S6, see also the explanation of significance thresholds to detect DE in the methods section). Heatmaps showing the expression levels across resident and disperser lizards (columns) for each DE gene (rows) in the head (c) and hind leg (d) tissues. Expression levels are standardized across individuals for each gene and top (side) dendrograms represent the clustering of lizard samples (DE genes) based on Euclidean distances. Results from principal component (PC) analyses on the lizards' expression levels for the DE genes found in the head (e) and hind leg (f) tissues. Shown are the scores of resident lizards (light green dots) and disperser lizards (dark brown dots) for the first two PCs.

clock gene, *CRY2* (Hazlerigg & Wagner, 2006; Vallone et al., 2007), an inhibitor of gluconeogenesis (Zhang et al., 2010) and promoter of lipogenesis (Machicao et al., 2016) that was upregulated in dispersers (Figure 3h) as well as *FAM3A*, an inhibitor of gluconeogenesis and of lipogenesis being downregulated in dispersers (Wang et al., 2014). Other enriched categories were related to pigmentation (GO: endosome to melanosome transport) and the synthesis of polyamines (spermidine metabolic process, polyamine biosynthetic process), the latter category including the gene *SRM* that produces spermidine (an aging related polyamine in animals (Madeo et al., 2018)).

In the leg muscles, the enriched categories found relate to serotonin uptake, including main genes of the central nervous system (*NOS1*, *SLC6A4*, *SLC22A3*) (Figure 3i,j), all upregulated in the dispersers, and to glucose (cellular response to hexose stimulus) and lipid regulation (protein import into peroxisome matrix), calcium signalling (regulation of ryanodine-sensitive calcium-release channel activity), and immunology (positive regulation of peptide secretion).

4 | DISCUSSION

In this study, we aimed to shed light on the genetic basis of vertebrate dispersal, focusing on a well-studied model of natal dispersal, the European common lizard. We found support for a low-to-moderate heritability of dispersal, with maternal and natal environment effects having a smaller contribution than additive genetic variation. Our genomic scan revealed that variation at the gene carbonic anhydrase, CA10, associates with dispersal in this species while our transcriptomic data indicated that gene expression differences in the head and hind leg tissues of dispersers versus residents involve multiple biological functions related to metabolism as well as the muscular and immune systems. We argue that some of the highlighted pathways (those related to the circadian clock and different neurotransmitters) constitute a promising avenue of research for understanding how dispersal is proximally controlled (and ultimately evolve) in vertebrates.

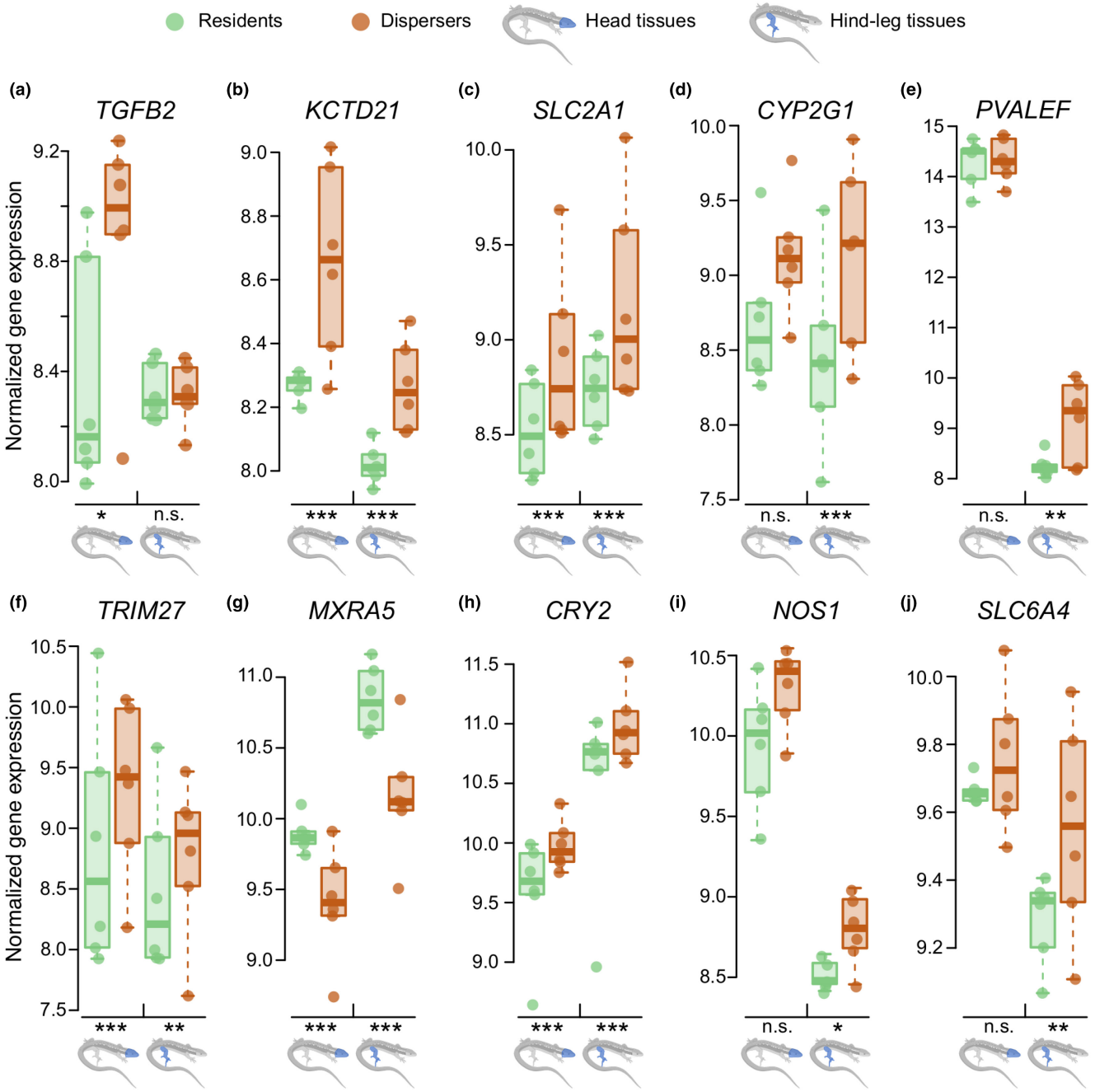

FIGURE 3 Genes differentially expressed in the head and hind leg tissues of disperser and resident common lizards. Gene expression in the head and hind leg tissues of resident (light green dots and box-and-whisker plots) and disperser lizards (dark brown dots and box-and-whisker plots) for a subset of the genes (see Results). Asterisks indicate the significance (adjusted for multiple testing) of the differential expression tests within each body part (n.s.: $p > 0.05$, *: $p \leq .05$, **: $p \leq .01$, ***: $p \leq .001$).

Heritability estimates of dispersal in vertebrates are rare and mainly focused on indirect proxies (such as performance traits: sprint speed, swimming capacity) and on certain taxa such as birds (Saastamoinen et al., 2018). To the best of our knowledge, we provide here with the first estimate of the heritability of dispersal propensity in a nonavian reptile. Our heritability estimates (h^2 = 0.35 in the liability scale) are within the range of those observed in birds (0.2–0.49; Saastamoinen et al., 2018) with the exception of those encountered in *Sialia mexicana* (h^2 = 0.95 in the liability scale and h^2 = 0.60 in the observed scale; Duckworth & Kruuk, 2009). They are also in line with heritability estimates generally observed for behavioural traits (Dochtermann et al., 2019). A low heritability was expected given that environmental factors substantially influence dispersal decisions (Clobert, Baguette, et al., 2012; Clobert, Massot, & Le Galliard, 2012). Yet, we found that, in our experimental populations, variation due to maternal effects was negligible with the natal environment contributing to dispersal variation but to a lesser extent than additive genetic variation. Part of the residual variation

TABLE 1 Gene ontology (GO) analysis of the set of genes differentially expressed in the head and hind leg tissues of disperser common lizards.

GO category ID	GO category	Score	Genes in GO category	Upregulated genes in GO category	Downregulated genes in GO category	Genes
GO terms enriched in the head tissues of disperser lizards						
GO:0032483	Regulation of Rab protein signal transduction	0.0011	6	0	2	*DENND4A* (−), *DENND1A* (−)
GO:0043137	DNA replication, removal of RNA primer	0.0011	6	1	1	*FEN1*-like (+), *RNASEH2A* (−)
GO:1903251	Multiciliated epithelial cell differentiation	0.0011	6	2	0	*TTC8* (+), *CEP63* (+)
GO:0033299	Secretion of lysosomal enzymes	0.0021	8	2	0	*BLOC1S6* (+), *GNPTAB* (+)
GO:0035646	Endosome to melanosome transport	0.0027	9	2	0	*RAB38* (+), *BLOC1S6* (+)
GO:0008216	Spermidine metabolic process	0.0033	10	1	1	*SPEE* (+), *SRM* (−)
GO:0010954	Positive regulation of protein processing	0.0033	10	1	1	*TRFM*-like (−), *RHBDD1* (+)
GO:0045214	Sarcomere organization	0.0038	36	0	3	*TNNT2* (−), *CSRP3* (−), *SYNPO2L* (−)
GO:0000733	DNA strand renaturation	0.0040	11	1	1	*SMARCA1* (+), *RECQL* (−)
GO:0090383	Phagosome acidification	0.0048	12	2	0	*SLAF8*-like (+), *RAB38* (+)
GO:0006596	Polyamine biosynthetic process	0.0056	13	1	1	*SPEE* (+), *SRM* (−)
GO:0007252	I-kappaB phosphorylation	0.0075	15	1	1	*CD14* (+), *CHUK* (−)
GO:0045721	Negative regulation of gluconeogenesis	0.0075	15	1	1	*CRY2* (+), *FAM3A* (−)
GO:0051014	Actin filament severing	0.0075	15	0	2	*CSRP3* (−), *FLII* (−)
GO:2000001	Regulation of DNA damage checkpoint	0.0075	15	1	1	*FBX4* (−), *CUL4A* (+)
GO:0014850	Response to muscle activity	0.0085	16	1	1	*MTFP1* (−), *PRKAG3* (+)
GO terms enriched in the hind legs of disperser lizards						
GO:0051610	Serotonin uptake	0.00054	7	3	0	*NOS1* (+), *SLC22A3* (+), *SLC6A4* (+)
GO:0071331	Cellular response to hexose stimulus	0.00193	94	4	1	*GTR5* (*LOC118086832*) (+), *GTR5* (*LOC118086920*) (+), *FKBP1B* (+), *OXCT1* (+), *ERN1* (−)
GO:0016558	Protein import into peroxisome matrix	0.00310	12	1	2	*PEX6* (−), *PEX10* (−), *PEX1* (+)

(Continues)

TABLE 1 (Continued)

GO category ID	GO category	Score	Genes in GO category	Upregulated genes in GO category	Downregulated genes in GO category	Genes
GO:0060314	Regulation of ryanodine-sensitive calcium-release channel activity	0.00395	13	3	0	*FKBP1B* (+), *NOS1* (+), *JPH4* (+)
GO:0006620	Posttranslational protein targeting to endoplasmic reticulum membrane	0.00606	15	1	2	*MACF1* (*LOC118089705*) (−), *SEC61A2* (+), *SEC63* (−)
GO:0002793	Positive regulation of peptide secretion	0.00620	125	2	4	*TFR2* (+), *S10A9* (*LOC118076466*) (−), *S10A9* (*LOC118076257*) (−), *VAMP8* (−), *OXCT1* (+), *TMEDA* (−)

Note: The GO terms significantly enriched (score ≤0.01) are shown for each gene set. DE expressed genes within each gene category are listed, ordered by decreasing absolute fold-change values, with the direction of the fold-change indicated between parenthesis (+,upregulated in dispersers; −, downregulated in dispersers).

may still be due to environmental factors for which the natal populations have none or little differences among them. Indeed, important environmental factors differ among our semi-natural populations (e.g., lizard density, climatic conditions), which nevertheless shared similar (yet variable) conditions to a large extent (e.g., similar levels of relatedness, social and habitat structure or food abundance). While residual variation may include further variation of environmental origin, we can also expect it to include further (nonadditive) genetic variation originating from genotype-per-environment effects as well as epistatic effects (Falconer & MacKay, 1996), both of which are likely to be important in determining dispersal (Cote et al., 2017). Thus, while our study suggests a low heritability of dispersal and perhaps low evolvability (Queller, 2017), further studies are still needed to better leverage the contribution that genetic factors may have on dispersal.

Our transcriptomic data suggests that different molecular pathways are related to dispersal. We found differences in the expression of genes related to metabolism as well as to the muscular and immune systems. These findings are in line with previous transcription studies in vertebrate and insects (Armenta et al., 2019; Brisson et al., 2007; Kvist et al., 2015; Rollins et al., 2015; Vellichirammal et al., 2014). They also reinforce the idea that dispersal entails costs (e.g., energetic costs, elevated exposure to parasites and pathogens; Bonte et al., 2012) and that dispersers differ from residents in various aspects of their phenotype (e.g., locomotor morphology, activity levels, social behaviour) forming the so-called dispersal syndromes (Clobert et al., 2009). Our data does not allow to resolve whether the observed gene expression changes have a causal or preparatory role in dispersal or are the consequences of dispersal itself. Moreover, we did not conduct the expression analysis on specific tissues, which would have offered perhaps a clearer picture of potential causative genetic pathways underlying dispersal. Nevertheless, we believe that some of the highlighted pathways by our RNAseq study are worthy of further studies aiming at investigating their central role as regulators of dispersal. We found some evidence for an involvement of genes influencing circadian rhythms in the regulation of dispersal, consistent with previous findings in common buzzards (Chakarov et al., 2013). Several genes involved in the circadian clock (*CRY2*, *KCTD21*, *DUSP26*) were found to be differentially expressed in the tissues of dispersers versus residents. The expression of genes of the circadian clock regulates long-distance migration in insects and birds (Kumar et al., 2010; Reppert & de Roode, 2018) and it is likely that dispersal and migration will rely, at least in part, on overlapping molecular pathways.

Interestingly, our results overall point towards a role of different neurotransmitters of the central nervous system in dispersal. We found that genes related to the serotonergic system were overexpressed in dispersers relative to residents. This included *TGFB2*: involved in the development of serotonergic neurons and in the synthesis of serotonin (Chleilat et al., 2019), *SLC6A4*: the serotonin transporter gene (Ramamoorthy et al., 1993), and *SLC22A3*: also a transporter of serotonin as well as of other neurotransmitters (dopamine and norepinephrine: Zhu et al., 2010). This is in line with

previous findings in rhesus macaques (Trefilov et al., 2000, see also Kaplan et al., 1995) although our study suggests that other aspects of the central nervous system might also be involved in dispersal. We also found a higher expression in dispersers of *NOS1*, the nitric oxide synthase 1 gene which synthesizes the neurotransmitter *NO* (Alderton et al., 2001). Moreover, our genomic scan suggested that dispersal in common lizards associates to variation around *CA10*, which encodes a ligand of the neurexin proteins involved in neurotransmitter release from the presynapses (Reissner et al., 2013; Sterky et al., 2017). Other genes differentially expressed between dispersers and residents such as *KCTD21*, *TRIM27*, *MXRA5*, as well as *SLC6A4* have been previously link to autism spectrum disorder in humans, which reinforces the idea that neurological differences underlie dispersal behaviour (Al-Mubarak et al., 2017; Nava et al., 2012; St Pourcain et al., 2013; Warrier et al., 2015), see also (Crespi, 2017).

Neurotransmitters such as serotonin and *NO* regulate locomotor behaviour by acting on motoneurons (Foster et al., 2014; Perrier et al., 2013) but they also regulate other phenotypic aspects that often integrate dispersal syndromes (e.g., social behaviour; Donaldson et al., 2014, aggressiveness; Krackow & König, 2008, immune and inflammatory responses; Wu et al., 2019, or reproduction; Prasad et al., 2015). Actually, recent theoretical work predicts that the genetic integration between dispersal and social behaviour are a consequence of their likely coevolution (owing to the evolutionary feedback between aspects such dispersal propensity and social interactions; Mullon et al., 2018). We thus believe that placing the focus on neurotransmitters is promising not only for understanding how dispersal decisions are controlled but also how dispersal syndromes develop and evolve.

In conclusion, here, we followed a holistic approach to unravel the genetic basis of dispersal in a vertebrate model. We showed that dispersal propensity has a genetic basis and we identified some genetic pathways that might underlie the regulation of dispersal and potentially, dispersal syndromes. Despite the challenges of studying the genetics of behaviour in nonmodel species (Walton et al., 2020), further work is needed to identify the genetics of dispersal to better understand how a trait of such relevance for a species' population and evolutionary dynamics evolves. In our GWAS, we could only find a single SNP in association to dispersal, despite an expected polygenic basis. Certainly, RAD markers are not sufficiently powerful to detect genetic variants underlying traits of limited heritability, given their low genome coverage and its indirect capture of causal-variant effects through linkage (Kardos et al., 2016). Increasing power using whole-genome approaches will help in clarify the genetic structure of dispersal (although see Kardos et al., 2016). Yet, we discuss that potential epistatic and genotype-per-environment effects probably mask genetic variation of dispersal. Thus, the combination of whole genomic tools with experimental approaches (e.g., artificial selection for dispersal propensity or the assessment of dispersal propensity while manipulating main dispersal drivers: absence vs. presence of predators or relatives, for instance) seems a promising approach to achieve deeper insights. Alongside molecular analyses, substantial knowledge may also be gained by conducting physiological studies to test the role that different neurotransmitters and the circadian clock play in dispersal decisions. Manipulation of serotonin levels or the photoperiod are common and can be applied to different species (e.g., Ossenkopp et al., 2005), opening avenues to integrate the genetic and the physiological causes underlying dispersal behaviour.

AUTHOR CONTRIBUTIONS

Julien Cote, Delphine Legrand, Camille Bonneaud and Jean Clobert designed the study, Julien Cote, Elvire Bestion, Félix Pellerin, Olivier Guillaume, Lucie Di Gesu, and Laurane Winandy collected dispersal data and tissue samples, Olivier Guillaume and Olivier Calvez managed the experimental system and provided ethical advice, Kathryn R. Elmer, Andrey A. Yurchenko, and Hans Recknagel provided the reference genome sequence, Murielle Richard and Jordi Salmona extracted the DNA for RAD-seq, Elvire Bestion conducted RNA extractions and Jordi Salmona preliminary analysis of RNAseq data, Luis M. San-Jose conducted the statistical analysis, Luis M. San-Jose and Julien Cote wrote the manuscript with contributions of all authors.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that no competing interests exist.

DATA AVAILABILITY STATEMENT

RNAseq and RADseq raw reads are available at the European Nucleotide Archive (https://www.ebi.ac.uk/ena/about/data-repositories - on-going submission). Data used for quantitative genetics and gene counts are available at Zenodo: https://zenodo.org/record/7774046#.ZCFrVTe67T4.

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SUPPORTING INFORMATION

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