PHILOSOPHICAL TRANSACTIONS B

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Review

Cite this article: Xu H-J, Zhang C-X. 2017 Insulin receptors and wing dimorphism in rice planthoppers. *Phil. Trans. R. Soc. B* **372**: 20150489.
http://dx.doi.org/10.1098/rstb.2015.0489

Accepted: 14 June 2016

One contribution of 17 to a theme issue 'Evo-devo in the genomics era, and the origins of morphological diversity'.

Subject Areas:
developmental biology

Keywords:
wing polymorphism, insulin receptors, phenotypic plasticity, planthoppers

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Electronic supplementary material is available online at https://dx.doi.org/10.6084/m9.figshare.c.3571020.

THE ROYAL SOCIETY PUBLISHING

Insulin receptors and wing dimorphism in rice planthoppers

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Wing polymorphism contributes significantly to the success of a wide variety of insects. However, its underlying molecular mechanism is less well understood. The migratory planthopper (BPH), *Nilaparvata lugens*, is one of the most extensively studied insects for wing polymorphism, due to its natural features of short- and long-winged morphs. Using the BPH as an example, we first surveyed the environmental cues that possibly influence wing developmental plasticity. Second, we explained the molecular basis by which two insulin receptors (InR1 and InR2) act as switches to determine alternative wing morphs in the BPH. This finding provides an additional layer of regulatory mechanism underlying wing polymorphism in insects in addition to juvenile hormones. Further, based on a discrete domain structure between InR1 and InR2 across insect species, we discussed the potential roles by which they might contribute to insect polymorphism. Last, we concluded with future directions of disentangling the insulin signalling pathway in the BPH, which serves as an ideal model for studying wing developmental plasticity in insects.

This article is part of the themed issue 'Evo-devo in the genomics era, and the origins of morphological diversity'.

1. Introduction

Wing polymorphism is an evolutionarily successful feature found in a wide variety of insect species, most notably in the Coleoptera, Diptera, Heteroptera, Hymenoptera, Lepidoptera, Orthoptera, Psocoptera and Thysanoptera orders [1]. Typically, the long-winged morph (macropter) consists of developed wings and functional flight muscles, and thus is flight-capable. By contrast, the short-winged morph (brachypter) or the wingless morph (apter) has underdeveloped wings and flight muscles, and thus is obligate flightless. The proximate causes for alternate wing morphs vary between species, either resulting from different genotypes or induced by various environmental stimuli. In some cases, the macropters of some aphids, water striders and crickets can histolyse their wing muscles, and thus transform themselves into functional brachypters [1,2], but this phenotype will not be discussed herein.

Wing polymorphism contributes significantly to the ecological success of some insect species in natural and agricultural habitats. The long-winged morph is capable of long-distance dispersal, thus escaping deteriorating environments and colonizing new habitats. By contrast, the short-winged morph or wingless morph generally exhibits a fitness trade-off between flight capability and reproduction, hence this type of morph both reproduces earlier and oviposits more eggs than the long-winged morph [1,3]. Given its important ecological significance, wing polymorphism has fascinated evolutionary biologists and physiologists for decades. However, its underlying proximate mechanism remains less well understood.

Wing dimorphism in rice planthoppers (Hemiptera: Delphacidae) is one of the intensively studied and economically significant examples of wing polymorphism in insects. There are about 40 delphacid planthopper species that are able to use rice as a host plant in Asia [4], such as the most notorious species the brown planthopper (BPH, *Nilaparvata lugens*) (figure 1), the small BPH (*Laodelphax striatellus*) and

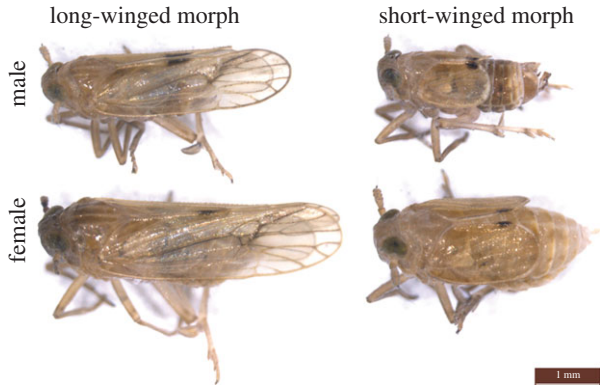

Figure 1. Wing dimorphism of the brown planthopper *Nilaparvata lugens*. (Online version in colour.)

the white-backed planthopper (*Sogatella furcifera*). All three species have developed the ability to migrate and track spatial changes in the quality of host plants. The BPH has five nymphal stages, and its wing buds grow gradually along with the increasing stage of the nymph, but the short- and long-winged morphs are externally indistinguishable until the adults emerge. The nymphal period varies widely depending on temperature, density during development and other environmental factors. BPHs in the tropics take about 10–18 days (3–5 days for each stadium) from the hatching of the first-instar nymph till the adult stage. The total life cycle of the BPH is about three to four weeks and a new generation may appear monthly. Long-winged morphs differ from short-winged morphs with respect to flight capability and reproduction. Besides having fully developed wings, long-winged morphs have functional flight muscles, and a slightly but significantly extended mesonotum. By contrast, short-winged morphs exhibit reduced wings and underdeveloped flight muscles. However, they have a shorter pre-oviposition period (3–4 days) than long-winged morphs (3–10 days) under cool conditions, and lay more eggs (60–500) [5].

The ability to develop into the long-winged morph enables BPHs to migrate over long distances, resulting in extensive damage to rice production across wide geographical areas. During the spring and summer, long-winged BPHs migrate northward from tropical or subtropical areas as rice becomes available in temperate areas of China, northern India, Japan and Korea. In the autumn, returning migrations (from north to south) of BPH populations have been observed across China and India [6,7]. Most adult BPHs in subsequent post-migration generations are short-winged morphs and exhibit increased fecundity [8]. Heavy BPH infestation can cause the complete drying and wilting of plants, known as 'hopper burn' [4,8]. Furthermore, the BPH also vectors several plant pathogens such as rice ragged stunt virus (RRSV) and rice grassy stunt virus (RGSV), which affect plant vigour and reduce yield [9,10]. For that reason, the BPH is the primary cause of in-field yield loss of rice throughout Asia [11].

In this review, we will limit the scope to the BPH system to shed light on the underlying mechanism of wing dimorphism in insects. The BPH system was chosen for three primary reasons. First, we have recently sequenced and assembled its genome [12], which will provide an avenue for disentangling the gene networks underpinning wing dimorphism as well as its physiology at the molecular level. Second, susceptibility of the BPH to RNA interference (RNAi) [13] allows us to interrogate gene function easily. Third, the BPH is the primary pest of rice, a major food source for more than half of the world's population [14], and thus is economically important.

First, we will briefly present general information on the environmental factors and endocrine hormones influencing wing dimorphism in the BPH. Second, we will highlight recent work on the contribution of the insulin signalling pathway to tissue developmental plasticity in several model insects. Third, we will document recent evidence revealing the mechanistic basis underlying wing dimorphism in the BPH. Lastly, we end with conclusions to address future directions on deeply exploring underlying molecular genetics by using the BPH system.

2. Environmental factors influencing wing dimorphism in the brown planthopper

Wing dimorphism contributes significantly to the success of the BPH in biological adaptation and agricultural habitats. Various environmental cues such as crowding, host plant quality, photoperiod and temperature are known to influence the development of alternative wing morphs. The long-winged morph can be promoted by overcrowding density encountered during nymphal development, and is intensified by low-quality plants [8,15–23]. Nymphs reared under the condition of short day length or low temperature were found to develop into short-winged morphs [8,24]. Additionally, the wing-morph differentiation might be influenced by the physiological status of the host rice. The percentage of the long-winged morphs that result from feeding on yellow-ripe rice is higher than that on booting-stage rice [25], while nymphs fed on the latter produce more long wings than those fed on tillering-stage rice [26]. As the short-winged morph ratio might be negatively correlated with soluble sugar, whereas it is positively correlated with nitrogen content in the host plant [24,26], it is plausible to speculate that the host nutritional status as sensed by nymphs might affect wing-morph switch. However, a recent study reported that the content of soluble protein, soluble sugar and lysine played negligible roles in wing-morph alteration [17]. In addition, of all the environmental factors relevant, population density is probably the dominant one; however, rigorous support for this premise is missing. For example, unlike planthoppers collected from the temperate region, some Philippines populations showed weak response to rearing density [18]. Currently, the effect of environmental factors on BPH wing dimorphism is controversial.

As with many reports on aphids and crickets [1,2,27–30], the level of juvenile hormones (JH) has long been thought to control wing-morph switch in planthoppers. Topical application of JHs or JH agonists on the BPHs at sensitive developmental stages induced short-winged morphs [20,31], whereas treatment with JH antagonists induced long-winged morphs [32–34]. Nevertheless, the most convincing evidence via measuring the JH levels in alternative wing morphs is missing [30].

3. Insulin/insulin-like growth factor signalling pathway and developmental plasticity

The insulin/insulin-like growth factor (IGF) signalling (IIS) pathway is an evolutionarily conserved nutrient-sensing pathway that modulates growth and development in metazoans

[35–44]. Emerging evidence indicated that the IIS pathway plays a key role in determining the developmental plasticity of tissue or organs in insects [39,45]. In *Drosophila*, selective dysfunction of the insulin receptor (InR) in the eye resulted in a dramatic reduction in eye tissue and in the head capsule, whereas the other body parts were of wild-type size. Conversely, overexpression of InR in the eye led to hyperproliferation [46]. In a follow-up study, Puig and his colleages eye-specifically overexpressed *Drosophila* FOXO protein, a negative transcription factor downstream from the insulin signalling pathway, and found that the eye size of the mutant flies was significantly smaller than that of wild-type flies [47]. More recently, Tang *et al.* [48] documented that organ-autonomous changes in FOXO expression are sufficient to autonomously alter an organ's nutritional plasticity and insulin sensitivity in *Drosophila*. More relevant evidence that links the IIS pathway with polyphenism has been derived from studies on male rhinoceros beetles. Horn size in the male beetles is hyper-variable, ranging from tiny bumps to exaggerated structures in accordance with the available nutrients. Mechanistic analysis showed that the horns exert enhanced tissue-specific sensitivity to the IIS pathway compared with other tissues, and as a result, knockdown of the InR disproportionately and significantly reduced horn size [49]. Taken together, this evidence implies that certain tissues or organs in some insects are capable of adjusting their size based on organ-specific insulin sensitivity in accordance with developmental nutrition.

4. Insulin/insulin-like growth factor signalling pathway and wing dimorphism in the brown planthopper

(a) Two insulin receptors determine wing morphs in planthoppers

In contrast with the single InR found in *Drosophila*, two putative InRs have been identified in the BPH, designated *Nl*InR1 and *Nl*InR2, respectively. *Nl*InR1 and *Nl*InR2 closely resemble each other as well as their *Drosophila* counterpart with respect to amino acid identity and domain architecture [50]. Surprisingly, *Nl*InR1 and *Nl*InR2 play fully opposite roles in wing-morph determination in the BPH. Nymphal knockdown of *Nl*InR2 led to a strong bias towards long-winged adults; by contrast, dysfunction of *Nl*InR1 resulted in the development of short-winged BPHs. In other words, production of long-winged morphs is positively related to the activity of *Nl*InR1, but is inversely related to the activity of *Nl*InR2. Morphologically, perturbation of either *Nl*InR resulted in correct wing veins, indicating that both InRs mainly constrain their functions to modulate wing size instead of its developmental pattern. Besides, both genetic and biochemical analyses suggested that *Nl*InR1 resembles the well-established canonical function of InR as with the *Drosophila* InR, whereas *Nl*InR2 acted more probably as a negative regulator of the *Nl*InR1 signalling cascade, and shares the same signalling cascade downstream from *Nl*InR1. Additional evidence shows that the wing tissue in the BPH is highly susceptible to insulin signalling activity relative to other body parts, and that *Nl*InR2 regulates wing-morph development in a tissue-specific manner rather than through a systemic effect on growth and metabolism. These breakthrough findings suggest that the BPH employs the same suit of genes to generate different wing morphs in different environments by alternating their expressional levels. Further, functional studies on insulin receptors from additional two planthopper species, *L. striatellus* and *S. furcifera*, indicated that the planthopper family might share a common regulatory mechanism underlying wing dimorphism [50]. Thus, we refer to the wing-morph plasticity in planthoppers as wing polyphenism instead of wing polymorphism, as alternative wing morphs are caused by redeployment of the existing developmental pathways, but are not genetically determined.

Recently, we found that the short-winged and the long-winged morph could be switched up to the fifth-instar nymph (the final nymphal stadium) (W-H Xue, Y-Q Jiang, J-L Zhang, N Xu, C-X Zhang, H-J Xu 2016 unpublished data). Prior to the fifth-instar stage, the short- and the long-winged morphs could be reversible depending on the activities of *Nl*InR1 and *Nl*InR2, respectively. The advantage of wing-morph commitment at their final stadium allows planthoppers to respond to environmental variability more flexibly and economically, as the building of wings and musculature is energetically expensive [1,8]. This finding of binary control of insulin signalling activity will facilitate a deep understanding of the mechanistic basis of wing polyphenism in insects.

(b) Conservation of the second insulin receptor across insects

The distinct physiological roles defined by *Nl*InR1 and *Nl*InR2 lead to questions on the structural difference between them and the extent to which the function of these two InRs are conserved across insects. Genomic sequencing of selected insect species advances bioinformatic mining to identify homologous genes in diverse insect species. By examining 42 species in the orders of Anoplura, Blattodea, Coleoptera, Diptera, Hemiptera, Hymenoptera and Lepidoptera, we found two putative InRs in 24 species belonging to five orders, except for in Anoplura and Blattodea (electronic supplementary material, table S1). In the order Blattodea, the dampwood termite *Zootermopsis nevadensis* has three InRs. However, in the order Anoplura, an orphan InR was identified, as in the majority of Diptera species. Conversely, in the order Hymenoptera (i.e. ants, bees and wasps), two putative InRs were identified in 17 of 19 species examined (electronic supplementary material, table S1). Considering complex social life traits of most Hymenoptera species, it would be interesting to investigate whether InR2 plays any roles in their social castes. Although the data are limited, we speculate that more insects encoding two or more InRs will be revealed as more genomic sequences become available.

By examining the structural difference between *Nl*InR1 and *Nl*InR2 in the BPH, we found that the second InR (*Nl*InR2) lacks four cysteine residues adjacent to the amino-terminal part of the furin-like cysteine-rich region (Fu) domain [50] that plays an important functional role in the interaction of the receptor with insulin [51,52]. Especially, only one cysteine at position 550 (C^{550}), numbered after the *Drosophila* counterpart, is found within the amino-terminal portion of the Fu domain in the *Nl*InR2, whereas concatenate residues of two cysteines ($C^{549}C^{550}$) are present in the corresponding position in *Nl*InR1 (figure 2). Intriguingly, this pattern is exclusively conserved in another 37 insect species examined, and even in the human InR. Herein, we propose the InRs containing $C^{549}C^{550}$ residues in the Fu domain as the first InR (InR1),

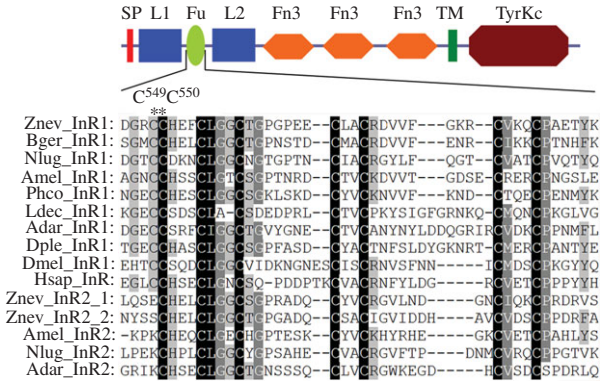

Figure 2. Alignment of the furin-like cysteine-rich (Fu) domains of insect InRs. The insect InR contains a typical domain architecture that consists of a signal peptide (SP), two ligand-binding loops (L1 and L2), a Fu region, three fibronectin type 3 domains (Fn3), a single transmembrane (TM) and a tyrosine kinase (TyrKc). Amino acid sequences of the Fu domain are selected from nine insect species that represent orders of Anoplura, Blattodea, Coleoptera, Diptera, Hemiptera, Hymenoptera and Lepidoptera, respectively. Concatenate residues of two cysteines ($C^{549}C^{550}$) are indicated with stars. Znev: *Zootermopsis nevadensis*; Bger: *Blattella germanica*; Nlug: *Nilaparvata lugens*; Amel: *Apis mellifera*; Phco: *Pediculus humanus corporis*; Ldec: *Leptinotarsa decemlineata*; Adar: *Anopheles darlingi*; Dple: *Danaus plexippus*; Dmel: *Drosophila melanogaster*; Hsap: *Homo sapiens*. (Online version in colour.)

whereas those with one cysteine residue are the second InR (InR2). More interestingly, a maximum-likelihood phylogenetic tree based on the tyrosine kinase domain of InRs is fully congruent with this premise. The InR group was apparently separated from the anaplastic lymphoma kinase (Alk) that also belongs to the receptor tyrosine kinase family. However, InR1 and InR2 further form separate clades in the InR group (figure 3). Notably, the placement of human InR in the InR1 clade is consistent with findings of how *Nl*InR1 functions as a typical InR [49].

The phylogenetic tree also led to questions whether InR2 was a novel evolved gene or a redundant gene that was lost during the evolutionary process in some insect species. Phylogenomic analyses based on 1478 protein-coding genes from 103 insect species showed that the origins of Hemiptera and Hymenoptera insects dated back to the Carboniferous and Permian periods [53], respectively. Both orders originated earlier than the Diptera insects that originated in the Triassic period. Given that Hemiptera and most Hymenoptera insects contain both InR1 and InR2, and the majority of Diptera insects only have InR1, we assume that InR2 might be an ancestral gene that was lost during the evolutionary process in some species. For those species containing two insulin receptors, InR2 might be necessary for their adaption to special ecological niches. For example, as aforementioned, the function of InR2 in the BPH is likely to leverage InR1 activity to produce alternative wing morphs, and as a result balances trade-offs between dispersal and reproduction in response to environmental heterogeneity. Consequently, further analysis based on comparative genomics is needed to elucidate how evolution has modified the InR2 outcome.

5. Conclusion and prospects

The proximate molecular mechanisms of wing polymorphism have been extensively studied in some insect species, such as

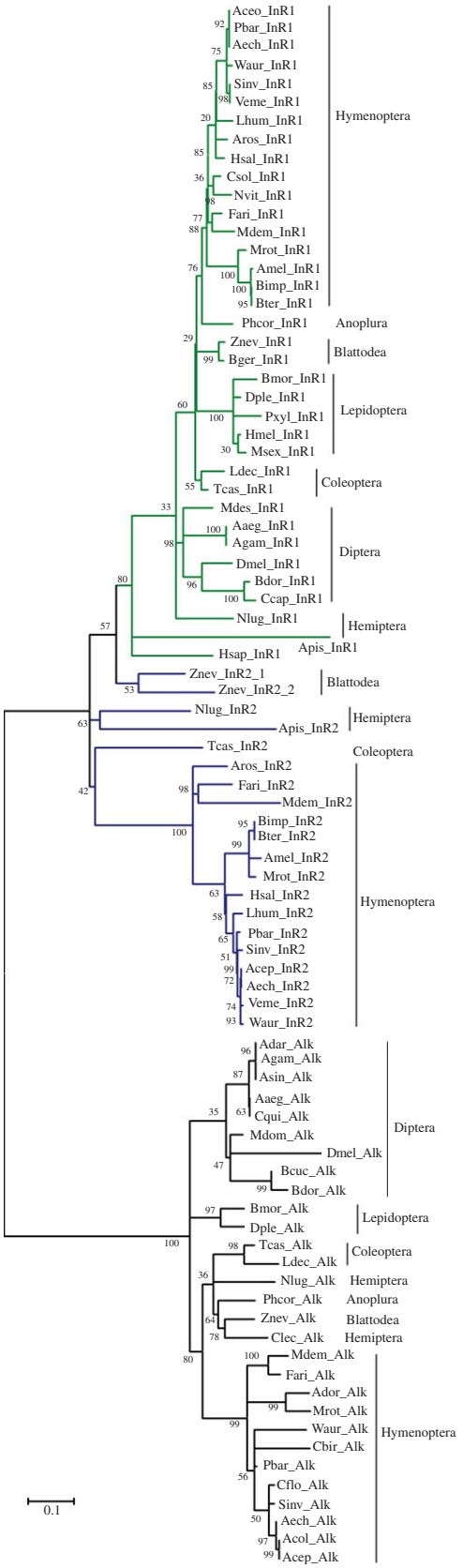

Figure 3. (*Caption overleaf.*)

aphids, crickets and planthoppers, in which JH have long been considered to play critical roles [54]. Generally, the classical model proposed that the JH level above a threshold value at critical stadia represses wing development, and thus short-winged morphs emerge, and vice versa. In this review, we introduced another layer of regulatory mechanism that regulates wing plasticity in planthoppers. Aided by genomic resources and the recently developed RNAi technique, we

Figure 3. (*Overleaf*.) Phylogenetic analysis of InRs from 37 insect species. A maximum-likelihood phylogenetic tree (bootstraps with 1000 replications) is created using the full-length sequences of the tyrosine kinase domains of InRs and anaplastic lymphoma kinase (Alk). The GenBank accession numbers of InRs are indicated in electronic supplementary material, table S1. The InR1 and InR2 branches are at the upper clade (shown in green and blue lines, respectively), and orders are listed on the right. Sinv: Solenopsis invicta; Veme: Vollenhovia emeryi; Waur: Wasmannia auropunctata; Acep: Atta cephalotes; Aech: Acromyrmex echinatior; Pbar: Pogonomyrmex barbatus; Lhum: Linepithema humile; Csol: Ceratosolen solmsi marchali; Nvit: Nasonia vitripennis; Aros: Athalia rosae; Hsal: Harpegnathos saltator; Fari: Fopius arisanus; Mdem: Microplitis demolitor; Mrot: Megachile rotundata; Amel: Apis mellifera; Bimp: Bombus impatiens; Bter: Bombus terrestris; Phcor: Pediculus humanus corporis; Znev: Zootermopsis nevadensis; Bger: Blattella germanica; Ldec: Leptinotarsa decemlineata; Tcas: Tribolium castaneum; Bmor: Bombyx mori; Dple: Danaus plexippus; Hmel: Heliconius melpomene; Msex: Manduca sexta; Pxyl: Plutella xylostella; Mdes: Mayetiola destructor; Aaeg: Aedes aegypti; Agam: Anopheles gambiae; Dmel: Drosophila melanogaster; Bdor: Bactrocera dorsalis; Ccap: Ceratitis capitata; Nlug: Nilaparvata lugens; Apis: Acyrthosiphon pisum; Cflo: Camponotus floridanus; Clec: Cimex lectularius; Acol: Atta colombica; Hsap: Homo sapiens. (Online version in colour.)

found that two InRs appear to act as switches to determine alternative wing morphs in planthoppers. Although we are still a long way from understanding the mechanisms underlying wing polyphenism in insects, this finding provides the first insights into the genetic network underpinning alternative wing morphs.

It is noteworthy that the molecular genetics underlying wing plasticity in planthoppers cannot fully account for the proximate causes of wing polymorphism in other insect species. For example, with regard to aphid species, they have complex life cycles showing cyclic parthenogenesis with alternating asexual and sexual generations, which has been intensively studied and reviewed elsewhere [2,3,55–57]. Instead of the short- and long-winged morphs, wingless and winged morphs were produced in most aphid species. By contrast, wing buds in the BPH intrinsically maintain the capability of developing into short or long wings, indicating that the BPH constrains the function of the insulin signalling pathway on wing size, but not on its developmental pattern. Considering the diverse evolutionary process of wing polymorphism, comprehensive studies on different insect species are warranted to answer the fundamental question of this phenotypic variation. For example, comparative analysis of wing polymorphism in aphids and crickets within the context of the accumulated knowledge of *Drosophila* might help reveal its intrinsic regulatory mechanism.

Given that the BPH system appears to be an ideal model for studying developmental plasticity of wing size in insects, future research should be explored to resolve questions as to how environmental cues are translated into the molecular mechanism that regulates InR2 activity, whether wing polyphenism is co-regulated by the insulin signalling pathway and JH as well as the interplay between them, and what is the precise mechanism by which InR2 modulates InR1 signalling activity.

Data accessibility. The datasets supporting this article have been uploaded as part of the electronic supplementary material.

Authors' contributions. H.-J.X. and C.-X.Z. conceived of the study. H.-J.X. carried out data analysis and drafted the manuscript. All authors gave their final approval for publication.

Competing interests. We have no competing interests.

Funding. This work was supported by the National Science Fund for Excellent Young Scholars (no. 31522047, to H.-J.X.), Zhejiang Provincial Natural Science Fund for Distinguished Young Scholars (no. LR16C140001, to H.-J.X.) and Fundamental Research Funds for the Central Universities (no. 2015XZZX004-34, to H.-J.X.).

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