The Dominance Effect of the Adaptive Transposable Element Insertion *Bari-Jheh* Depends on the Genetic Background

Lain Guio and Josefa González*

Institute of Evolutionary Biology, CSIC-Universitat Pompeu Fabra, Barcelona, Spain

*Corresponding author: E-mail: josefa.gonzalez@ibe.upf-csic.es.

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Abstract

Although adaptive mutations are often considered to be dominant, it has been recently shown that a substantial proportion of adaptive mutations should display heterozygote advantage. In this work, we take advantage of a recently characterized transposable element insertion mediating oxidative stress response in *Drosophila melanogaster* to test the dominance effect of an adaptive mutation. The comparison of the survival curves of heterozygous and the two corresponding homozygous flies indicated that the dominance effect of *Bari-Jheh* depends on the genetic background. Both in homozygous and in heterozygous flies, *Bari-Jheh* was associated with upregulation of *Jheh1* (*Juvenile Hormone Epoxyde Hydrolase 1*) and/or *Jheh2* genes. Our results add to the limited number of studies in which the dominance effect of adaptive mutations has been empirically estimated and highlights the complexity of their inheritance.

Key words: adaptive mutation, selective sweep, heterozygote advantage, oxidative stress, *Drosophila*, dominance effect.

Dominance Effect of Deleterious and Adaptive Mutations

Understanding the dominance effect of mutations has consequences for several important biological processes, such as the magnitude of inbreeding depression, the evolution of mating systems, and the rate of adaptation in diploids (Charlesworth B and Charlesworth D 1998; Lynch et al. 1999; Manna et al. 2011). To date, most of our knowledge on the dominance effect of mutations comes from the study of deleterious mutations (Charlesworth B and Charlesworth D 1998; Garcia-Dorado et al. 1999; Lynch et al. 1999). These studies, mostly based on mutation-accumulation experiments in flies, showed that the majority of deleterious mutations is recessive to their wild-type allele (Simmons and Crow 1977; Wilkie 1994; Houle et al. 1997; Chavarrias et al. 2001; Fry and Nuzhdin 2003). In contrast, the study of the dominance effect of adaptive mutations has lagged behind, mostly due to the difficulty to identify adaptive mutations. However, and although few studies have empirically determined their dominance effects, adaptive mutations are often considered to be dominant (Bourguet et al. 1997; Charlesworth 1998; Orr 2010; Zhang et al. 2011; Joseph et al. 2014). This notion derives from Haldane (1927) who showed that when a mutation is rare, as it is the case of new mutations, it is more likely to be fixed if it is dominant. This is so because recessive mutations are phenotypically expressed only in homozygotes and, when the mutation is rare, the corresponding homozygotes are even rarer assuming a large outbred population. Therefore, selection has little chance of acting on recessive mutations as most of the mutant alleles are found in heterozygotes. Based on the assumption that adaptive mutations are likely to be dominant, positive selection should drive these mutations to high population frequency removing genetic variation at linked sites and thus leaving characteristic molecular signatures of complete selective sweeps. Until recently most genomic scans for positive selection were focused on identifying signatures of complete selective sweeps (Sabeti et al. 2002; Glinka et al. 2003; Voight et al. 2006). However, it has been recently shown that a substantial proportion of adaptive mutations may display heterozygote advantage (Sellis et al. 2011). Sellis et al. (2011) demonstrated that if selection is stabilizing and mutation effects are large enough to overshoot the fitness optimum, heterozygous advantage should be very common in adaptation. If adaptive mutations are overdominant, besides complete selective sweeps, we would also expect to see many incomplete selective sweeps surrounding adaptive mutations. Indeed, incomplete sweeps are common in several organisms (Clark et al. 2007; Gonzalez et al. 2008; Burke and Rose 2009; Coop et al. 2009). However, evidence of incomplete sweeps is not diagnostic of heterozygote advantage as this molecular

signature is also predicted under other scenarios, such as polygenic adaptation and adaptation to specific subhabitats (Messer and Petrov 2013). Thus, to explicitly test the hypothesis of heterozygote advantage, we need to directly measure the fitness of heterozygous individuals and compare it with the fitness of homozygous individuals for the presence and for the absence of the adaptive mutation (Sellis et al. 2011).

The Dominance Effect of *Bari-Jheh* Depends on the Genetic Background

Bari-Jheh is a full-length transposable element insertion located on chromosomal arm 2R in *Drosophila melanogaster*. *Bari-Jheh* is a good candidate to empirically evaluate the dominance effect of an adaptive mutation: It mediates resistance to oxidative stress and it is polymorphic in natural populations (Gonzalez et al. 2009; Guio et al. 2014). Thus, it is possible to measure the survival of heterozygous flies and compare it with the survival of the two corresponding homozygous (Gonzalez et al. 2008, 2009).

To determine the dominance effect of *Bari-Jheh* on oxidative stress resistance, we compared the survival of homozygous flies for the presence of *Bari-Jheh*, homozygous flies for the absence of *Bari-Jheh,* and heterozygous flies obtained from reciprocal crosses of the two homozygous strains. We first analyzed flies from outbred populations previously created in our lab (Guio et al. 2014). As expected, both male and female flies homozygous for the presence of *Bari-Jheh* were more resistant to oxidative stress compared with flies homozygous for the absence of *Bari-Jheh* (fig. 1*A* and table 1; Guio et al. 2014). Because we did not find differences in the survival curves of heterozygous flies from reciprocal crosses, we did not take into account the direction of the cross in our analyses (table 1). We found that survival curves of heterozygous flies were statistically different from survival curves of homozygous flies without *Bari-Jheh* (table 1 and fig. 1*A*). However, we found that survival curves of heterozygous flies were not statistically different from survival curves of homozygous flies with *Bari-Jheh* suggesting that the effect of this adaptive mutation on oxidative stress resistance is dominant (table 1 and fig. 1*A*).

Because the dominance effect of mutations can be affected by the genetic background (Mukai et al. 1966; Simmons and Crow 1977), we repeated the oxidative stress survival experiment with introgressed flies also previously created in our lab (Gonzalez et al. 2009; Guio et al. 2014). We found that both male and female flies homozygous for the presence of *Bari-Jheh* were more resistant to oxidative stress than homozygous flies for the absence of *Bari-Jheh* (fig. 1*B* and table 1), as we have previously reported (Guio et al. 2014). For females, we did not find differences in the survival curves between the heterozygous flies from reciprocal crosses (table 1). However, we found differences in the survival curves of males and thus we analyzed the two crosses separately for males (table 1). We found that heterozygous female flies and males from one of the reciprocal crosses were more resistant to oxidative stress compared with flies without the insertion and showed no differences compared with flies with the insertion suggesting that *Bari-Jheh* is dominant (fig. 1*B*). On the other hand, males from the other reciprocal cross were more resistant to paraquat compared with flies with and without the insertion suggesting that in this particular background *Bari-Jheh* is overdominant (table 1 and fig. 1*B*). To confirm these results, we repeated the experiments with another pair of introgressed flies (see Materials and Methods). We obtained similar results: Heterozygous female flies and males from one of the reciprocal crosses were more resistant to paraquat compared with flies without the insertion and showed no differences compared with flies with the insertion, whereas males from the other reciprocal cross were more resistant compared with flies with and without the insertion (table 1 and fig. 1*C*).

Overall, we found that *Bari-Jheh* dominance effect depended on the genetic background. In outbred populations, *Bari-Jheh* is a dominant mutation. In introgressed strains, *Bari-Jheh* is a dominant mutation in females whereas in males *Bari-Jheh* is dominant or overdominant depending on the reciprocal cross.

Bari-Jheh Is Associated with Upregulation of *Juvenile Hormone Epoxyde Hydrolase 1* and/or *2* in Homozygous and Heterozygous Flies

Bari-Jheh is located in the intergenic region between *Juvenile Hormone Epoxyde Hydrolase 2* (*Jheh2*) and *Jheh3* and 3.2 kb upstream of *Jheh1*. We have previously reported the expression level of these three genes in flies homozygous for the presence and for the absence of *Bari-Jheh* (Guio et al. 2014). In this work, we have analyzed the expression level of these three genes in heterozygous male flies.

In outbred populations, we found that male flies homozygous for the presence of *Bari-Jheh* are associated with upregulation of *Jheh1* and *Jheh2* and downregulation of *Jheh3* genes, as previously described (*t*-test P value = 0.0004, 0.0080, and 0.0033, respectively; fig. 2*A*; Guio et al. 2014). We compared the expression of the three genes in heterozygous males from the two reciprocal crosses and we did not find significant differences (*t*-test P value > 0.05; supplementary fig. S1*A*, Supplementary Material online). Thus, we combined the expression results for the two crosses (fig. 2*A*). Flies heterozygous for *Bari-Jheh* mutation are associated with *Jheh1* upregulation (*t*-test P value = 0.0325; fig. 2*A*). Because flies heterozygous for *Bari-Jheh* are resistant to oxidative stress, these results suggested that upregulation of one of the two genes, *Jheh1* or *Jheh2* may be enough to confer resistance to oxidative stress. Consistent with this hypothesis, in the

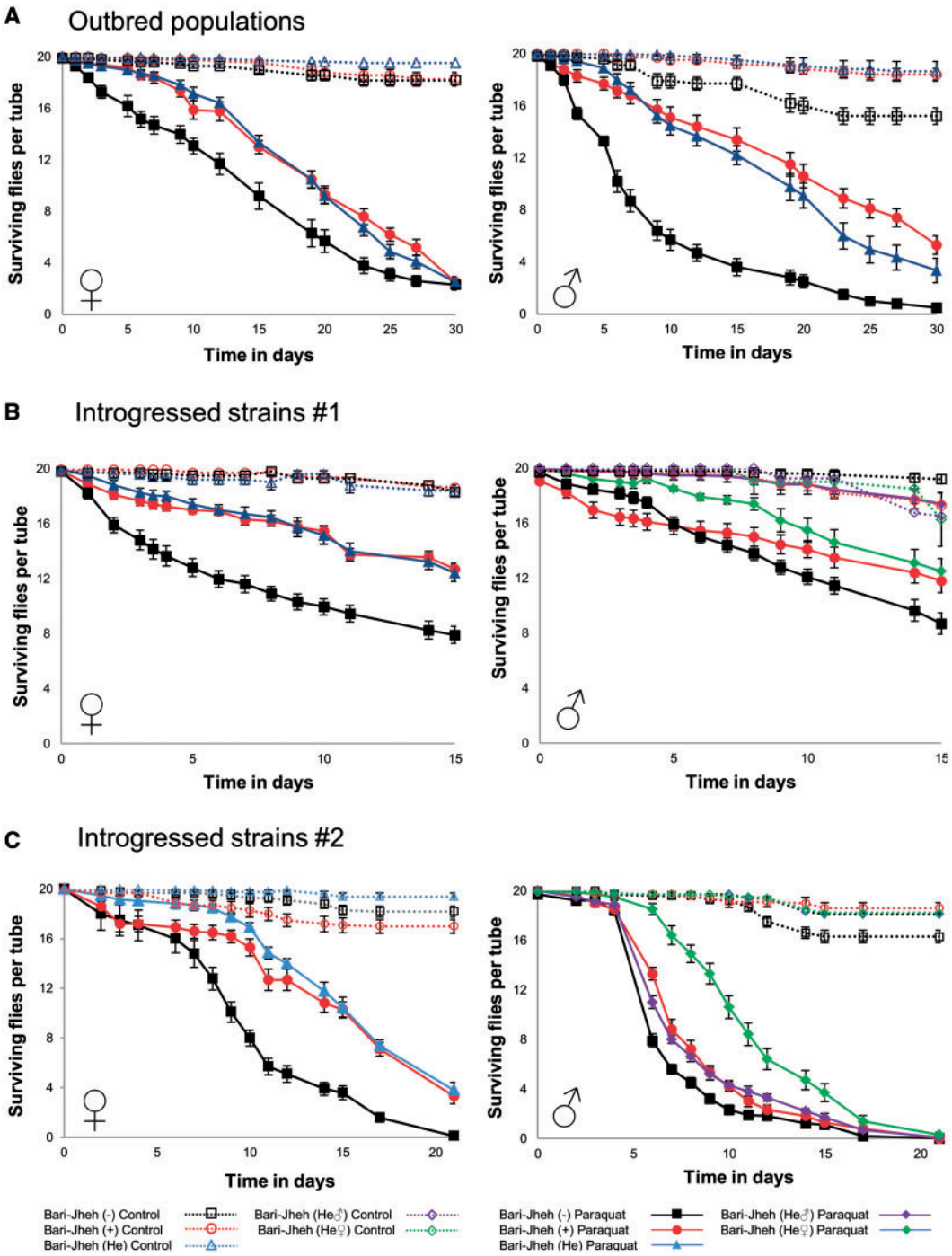

Fig. 1.—Dominance effect of *Bari-Jheh* on oxidate stress resistance in outbred populations (A) and in introgressed strains (B) and (C). Survival curves of homozygous flies with *Bari-Jheh* insertion (*Bari-Jheh* (+)), homozygous flies without *Bari-Jheh* insertion (*Bari-Jheh* (−)), heterozygous flies from crosses in which the father carried the insertion (*Bari-Jheh* (He♂)), heterozygous flies from crosses in which the mother carried the insertion (*Bari-Jheh* (He♀)), and heterozygous flies from the two reciprocal crosses considered together (*Bari-Jheh* (He)).

introgressed strains, flies homozygous for the presence of *Bari-Jheh* are associated with upregulation of *Jheh2* (*t*-test *P* value = 0.0020; fig. 2*B*) and flies heterozygous for *Bari-Jheh* showed upregulation of both *Jheh1* (*t*-test *P* value = 0.0294; fig. 2*B*) and *Jheh2* genes (*t*-test *P* value = 0.0001 and 0.0211 for the two reciprocal crosses; fig. 2*B*).

In introgressed strains, heterozygous flies from the two reciprocal crosses differed in the level of expression of *Jheh2* and

Table 1
Statistical Analyses of the Survival Curves

Genetic Background	Strains Compared[a]	Sex	Logrank Test *P* Value	Odds Ratio (Confidence Interval)
Outbred	*Bari-Jheh* (−) versus *Bari-Jheh* (+)	Females	**1.62×10^{-4}**	2.18 (1.46–3.32)
	Bari-Jheh (He♂) versus *Bari-Jheh* (He♀)		0.285	—
	Bari-Jheh (−) versus *Bari-Jheh* (He)		**1.59×10^{-5}**	2.38 (1.59–3.57)
	Bari-Jheh (+) versus *Bari-Jheh* (He)		0.637	—
	Bari-Jheh (−) versus *Bari-Jheh* (+)	Males	**1.06×10^{-27}**	5.66 (3.50–9.17)
	Bari-Jheh (He♂) versus *Bari-Jheh* (He♀)		0.433	—
	Bari-Jheh (−) versus *Bari-Jheh* (He)		**1.68×10^{-32}**	8.19 (4.81–13.91)
	Bari-Jheh (+) versus *Bari-Jheh* (He)		**0.0044**	1.44 (0.79–2.63)
Introgressed #1	*Bari-Jheh* (−) versus *Bari-Jheh* (+)	Females	**1.17×10^{-13}**	3.43 (2.53–4.65)
	Bari-Jheh (He♂) versus *Bari-Jheh* (He♀)		0.124	—
	Bari-Jheh (−) versus *Bari-Jheh* (He)		**1.79×10^{-13}**	3.15 (2.33–4.26)
	Bari-Jheh (+) versus *Bari-Jheh* (He)		0.771	—
	Bari-Jheh (−) versus *Bari-Jheh* (+)	Males	**2.50×10^{-4}**	1.75 (1.32–2.32)
	Bari-Jheh (He♂) versus *Bari-Jheh* (He♀)		**4.15×10^{-4}**	2.50 (1.64–3.79)
	Bari-Jheh (−) versus *Bari-Jheh* (He♂)		**2.84×10^{-15}**	4.29 (2.88–6.39)
	Bari-Jheh (+) versus *Bari-Jheh* (He♂)		**8.24×10^{-7}**	2.24 (1.54–3.27)
	Bari-Jheh (−) versus *Bari-Jheh* (He♀)		**7.66×10^{-6}**	2.03 (1.43–2.89)
	Bari-Jheh (+) versus *Bari-Jheh* (He♀)		0.194	—
Introgressed #2	*Bari-Jheh* (−) versus *Bari-Jheh* (+)	Females	**7.99×10^{-18}**	4.17 (2.66–6.54)
	Bari-Jheh (He♂) versus *Bari-Jheh* (He♀)		**0.013**	1.35 (0.91–2.00)
	Bari-Jheh (−) versus *Bari-Jheh* (He)		**5.73×10^{-18}**	8.82 (5.14–15.11)
	Bari-Jheh (+) versus *Bari-Jheh* (He)		0.252	—
	Bari-Jheh (−) versus *Bari-Jheh* (+)	Males	**0.001**	3.04 (2.02–4.57)
	Bari-Jheh (He♂) versus *Bari-Jheh* (He♀)		**7.90×10^{-11}**	10.09 (5.56–18.3)
	Bari-Jheh (−) versus *Bari-Jheh* (He♂)		**0.003**	1.87 (1.25–2.78)
	Bari-Jheh (+) versus *Bari-Jheh* (He♂)		0.942	—
	Bari-Jheh (−) versus *Bari-Jheh* (He♀)		**4.61×10^{-23}**	18.89 (10.4–34.3)
	Bari-Jheh (+) versus *Bari-Jheh* (He♀)		**1.29×10^{-12}**	5.79 (3.67–9.14)

NOTE.—Nomenclature of the strains is the same as in figure 1. Significant *P* values after correcting for multiple testing are given in bold (Benjamini and Hochberg 1995).

were considered separately (*t*-test *P* value = 0.0164; supplementary fig. S1*B*, Supplementary Material online). Heterozygous males from one of the reciprocal crosses showed differences in the level of expression of *Jheh2* compared with the two homozygous strains (*t*-test *P* value = 0.0191 and 0.0211 compared with homozygous for the presence and for the absence, respectively; fig. 2*B*). These heterozygous males also showed differences in survival compared with homozygous flies with and without the insertion (fig. 1*C*). Heterozygous males from the other reciprocal cross only showed differences in expression compared with flies without the insertion (*t*-test *P* value = 0.0001; fig. 2*B*), which is also consistent with these heterozygous flies showing survival differences only with flies without the insertion (fig. 1*C*).

Bari-Jheh: A Case Study on the Dominance Effect of Adaptive Mutations

In this work, we found that the dominance effect of the adaptive transposable element insertion *Bari-Jheh* on oxidative stress resistance depended on the genetic background (fig. 1). The dominance effect of a mutation on a particular trait is influenced by environmental conditions and genetic background (Wool et al. 1982; Bourguet et al. 1996, 1997, 2000). Changes in dominance may arise because of alleles at linked or unlinked loci. This seems to be the case of *Bari-Jheh* mutation that is dominant in one of the backgrounds investigated (outbred populations; fig. 1*A*) and overdominant in males of one of the two reciprocal crosses in the other background (introgressed strains; fig. 1*B* and *C*). Our results highlight the complexity of the inheritance of adaptive mutations.

Our results add to the limited number of studies in which the dominance effect of adaptive mutations has been estimated. Previous empirical evidence focused on mutations conferring resistance to insecticides that most commonly occur through target-inactivation or metabolic detoxification (Ffrench-Constant 2013). *Bari-Jheh* mediates resistance to oxidative stress most likely through increase enzymatic activity of *JHEH2* (Taniai et al. 2003) as well as through changes in juvenile hormone titer (Campbell et al. 1992; Rauschenbach et al. 1996; Taniai et al. 2003; Flatt et al. 2005; Guio et al. 2014). As

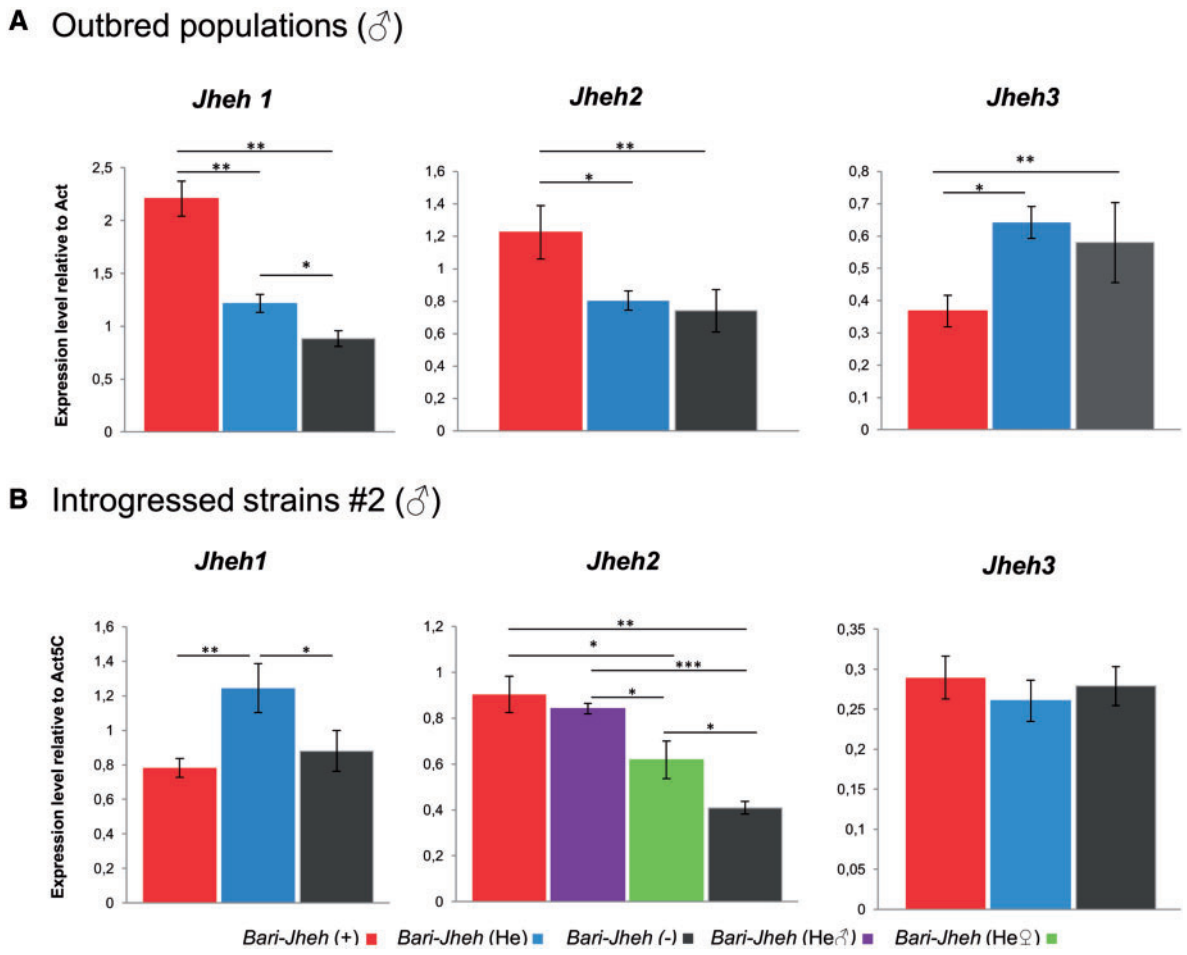

Fig. 2.—Expression level of *Jheh1*, *Jheh2*, and *Jheh3* genes in flies heterozygous for *Bari-Jheh* and in the two corresponding homozygous. Normalized expression level under oxidative stress conditions of male flies from outbred populations (*A*) and from introgressed strains #2 (*B*). In red, expression level of flies homozygous for *Bari-Jheh* insertion. In gray, expression level of flies homozygous for the absence. In blue, expression level of heterozygous flies from the two reciprocal crosses considered together. In purple, expression level of heterozygous flies from crosses in which the father carried *Bari-Jheh* insertion. In green, expression level of heterozygous flies from crosses in which the mother carried the insertion. Error bars indicate standard error of the mean based on the three biological replicas performed.

such, *Bari-Jheh* is an adaptive mutation with a more complex molecular mechanism and phenotypic effect than the other adaptive mutations previously characterized.

To try to shed light on the molecular mechanism behind the dominance effect of *Bari-Jheh*, we compared the expression of *Jheh* genes between heterozygous and homozygous flies. *Bari-Jheh* is associated with upregulation of *Jheh1* and/or *Jheh2* in homozygous flies and heterozygous flies suggesting that upregulation of one of these two genes may be enough to confer resistance to oxidative stress. Interestingly, heterozygous flies that showed overdominance differed in the level of expression of *Jheh2* compared with the two corresponding homozygous. Further experiments are needed in order to get a comprehensive understanding of the molecular mechanism of this adaptive insertion.

The scarcity of empirical studies testing the dominance effect of adaptive mutations is mostly due to the difficulty of identifying adaptive mutations and their fitness effects. However, the availability of technologies such as next generation sequencing has proven useful for the identification of adaptive mutations at an unprecedented scale (Turner et al. 2010; Jones et al. 2012). Future studies of a comprehensive set of adaptive mutations should help provide a more general view of the dominance effect of adaptive mutations.

Materials and Methods

Fly Stocks

Outbred Populations

Outbred populations were previously created in our laboratory (Guio et al. 2014). Briefly, we used flies from the Drosophila Genetics Reference Panel (Mackay et al. 2012) obtained from the Bloomington Stock Centre. We used lines RAL-21,

RAL-405, RAL-911, RAL-502, and RAL-138 to create an outbred population homozygous for the presence of *Bari-Jheh* element. We collected ten virgin females and ten males from each strain and we placed them in one large fly chamber. After the first generation, the siblings were randomly mated during ten generations before performing the experiments. The population size was ≈800 individuals per generation. We repeated the procedure with five strains homozygous for the absence of *Bari-Jheh* element to create an outbred population without this insertion: RAL-40, RAL-461, RAL-822, RAL-439, and RAL-908 (Guio et al. 2014).

Introgressed Strains

Introgressed strains were previously created in Dr Petrov laboratory at Stanford University (Gonzalez et al. 2009). Briefly, female flies with the element *Bari-Jheh* (*Wi3* strain) were crossed with males homozygous for the absence of the element *Bari-Jheh* (*Wi1* strain). Virgin females from F_1 were crossed with males from *Wi1* strain. F_2 virgin females were also crossed with Wi1 males and after egg laying females were analyzed for the presence of *Bari-Jheh* element. Only crosses in which females carried the element were kept to produce the next generation. The procedure was repeated up to eight generations. After eight generations sibling crosses were performed until homozygous strains were established for the presence and the absence of *Bari-Jheh* (Gonzalez et al. 2009). In this work, we used four different strains obtained after this procedure: Two pairs of strains with and without *Bari-Jheh*.

Heterozygous Strains

To create the heterozygous flies, we collected 100 virgin females homozygous for the presence of *Bari-Jheh* and we crossed them with 100 males homozygous for the absence of the element. We performed the crosses in large fly chambers. We kept the flies 72 h to ensure that females were inseminated and we collected eggs during an interval of 24 h. We repeated the same procedure with 100 females homozygous for the absence of the element *Bari-Jheh* and crossed them with 100 males homozygous for the presence of the element in a different chamber. We performed these reciprocal crosses for the outbred populations and for the introgressed strains.

We synchronized the egg laying period of the heterozygous crosses and the homozygous crosses so that the F_1 could be analyzed when all the flies were 5 days old.

Oxidative Stress Resistance Experiments

We used paraquat (methyl viologen dichloride hydrate; Sigma-Aldrich) as an oxidative stress agent. Paraquat is one of the most widely used herbicides in agricultural settings including tree plantation areas, a natural habitat for *D. melanogaster* (http://www.epa.gov).

To induce oxidative stress, we added paraquat to the regular fly food containing 4.5% (w/v) glucose, 6% (w/v) yeast, 0.7% (w/v) agar, and 3% (w/v) wheat flour. The final concentration of paraquat was 3 mM. For control conditions, we used regular fly food without paraquat (for more details, see Guio et al. 2014). For outbred populations, we analyzed 10 tubes containing 20 flies each, per sex, per strain, and per condition. For introgressed strains, we analyzed 20 tubes for homozygous strains and 10 tubes for each heterozygous cross. Survival was monitored every 24 h.

To analyze the data, we used logrank test. When differences between the strains being compared were significant, we estimated the size of the effect and its confidence intervals. When the differences between reciprocal crosses for heterozygous flies were not significant, we considered both crosses together.

Reverse Transcription Polymerase Chain Reaction Expression Analysis

We quantified the expression of *Jheh1*, *Jheh2*, and *Jheh3* in oxidative stress conditions. To induce oxidative stress, we exposed 5-day-old male flies to food containing 10 mM paraquat during 8 h. After the exposure, we freeze flies with liquid N_2. We purified total RNA using Trizol reagent and we synthesized cDNA using 1 μg of RNA after treatment with DNase. Then, we used the cDNA for quantitative polymerase chain reaction analysis using *Act5C* as a housekeeping gene. Expression assays were performed with three biological replicas. Results were analyzed using dCT method. Primers used were described in Guio et al. (2014)

Supplementary Material

Supplementary figure S1 is available at *Genome Biology and Evolution* online (http://www.gbe.oxfordjournals.org/).

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