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Climatic variation and the geographical distribution of sex-determining mechanisms in the housefly

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ABSTRACT

Questions: (1) Are the geographic clines of sex-determining factors in the housefly of the northern hemisphere mirrored by similar clines on the southern hemisphere? (2) What climatic factors can best explain the geographical distribution of sex-determining factors in the housefly?

Data: Frequencies of sex-determining factors of houseflies collected in Africa and corresponding literature data on houseflies studied on other continents. Global climate data from public databases.

Results: Housefly populations on the southern hemisphere repeat the pattern earlier found on the northern hemisphere: higher frequencies of autosomal *M* and F^D factors closer to the equator. Seasonality in temperature variation is the best predictor for the distribution of the male sex-determining factor, whereas female sex-determining factors are best explained by variation in humidity and yearly mean temperature.

Keywords: cline, humidity, latitudinal variation, *Musca domestica*, seasonality, sex determination, sex ratio, temperature.

INTRODUCTION

Sex-determining mechanisms vary considerably across taxa and seem to evolve quite rapidly, for reasons that are still poorly understood (Bull, 1983, 1985; Marin and Baker, 1998; Kraak and Pen, 2002; Werren *et al.*, 2002). However, the vast majority of variation occurs above the species level. Since the housefly (*Musca domestica*) harbours several different sex-determining mechanisms, it is a particularly interesting model species for studying sex determination. All individual houseflies possess a female-determining factor (the *F* factor) that turns on the female developmental pathway, unless a so-called *M* factor is also present and blocks the action of *F*, thus triggering development into a male. In 'standard' males, the *M* factor is located on the Y chromosome (Dübendorfer *et al.*, 1992), but *M* factors can also be located on any of the five autosomes or even on the X chromosome (Table 1) (Denholm *et al.*, 1983; Dübendorfer *et al.*, 2002).

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Table 1. Relation between genotype and sexual phenotype in the housefly

Autosomes		Sex chromosomes	
4	1–5	XX	XY
F/*F*	+/+	♀	♂
F/*F*	•/*M*	♂	♂
F/F^D	•/•	♀	♀

Note: The female-determining factors (F/F^D) are located on chromosome 4; the male-determining factors (*M*) can be located on any chromosome. + = wild-type state (no *M*); • = the same phenotype will develop irrespective of the presence or absence of *M*.

In populations where autosomal *M* factors are prevalent, the Y chromosome is often absent and males are either XX or sometimes XO (Denholm *et al.*, 1985, 1990; Çakir and Kence, 1996). In some populations, males may be homozygous for an autosomal *M* factor or possess multiple *M* factors on different autosomes. In such populations, females often possess a special dominant version of the *F* factor, designated F^D, which is not blocked by *M* factors (Tomita and Wada, 1989; Hilfiker-Kleiner *et al.*, 1993).

Interestingly, the different sex-determining systems in the housefly show clear latitudinal clines and altitudinal clines. This was first reported by Franco *et al.* (1982), who examined houseflies from 53 localities in Europe, from Denmark in the north to Sicily in the south, and discovered that frequencies of autosomal *M* factors increased towards the south and decreased with higher altitude. Additional studies from England (Denholm *et al.*, 1985), Japan (Tomita and Wada, 1989), Turkey (Çakir and Kence, 1996), and the United States (Hamm *et al.*, 2005) showed similar patterns with XY males in the north or at high altitudes and males with autosomal *M* factors dominating at lower latitudes and altitudes. It is not clear whether these clines represent stable distributions or whether they are a transient phenomenon. Some authors have argued for the latter because before 1948 no study on the housefly revealed any other system than the standard XY system (Franco *et al.*, 1982; Denholm *et al.*, 1985; Tomita and Wada, 1989; Çakir and Kence, 1996).

We have evidence (Kozielska *et al.*, 2008) that frequencies of autosomal *M* factors have not changed much for several decades in Europe. This is not entirely unexpected, since recent theoretical models have shown that multiple *M* factors may stably co-exist (Kozielska *et al.*, 2006). However, it is still unclear why the clines exist in the first place. Some authors have suggested that autosomal *M* factors 'hitchhike' with insecticide resistant genes (Kerr, 1970; Franco *et al.*, 1982; Tomita and Wada, 1989), but more recent studies did not find evidence to support this (Shono and Scott, 1990; Hamm *et al.*, 2005). Obviously, any factor that shows pronounced clinal variation could in principle be involved in causing the clinal distribution of sex-determining mechanisms. The most obvious factor that varies predictably with both latitude and altitude is temperature, and temperature variation has been invoked as a possible explanation by several authors (Franco *et al.*, 1982; Çakir and Kence, 1996). However, other climatic variables might also explain geographic variation, as shown in studies on clinal variation in body size. For example, wing length in birds as a measure of body size correlates with humidity and

temperature (James, 1970). Seasonality, on the other hand, seems to explain best body size in muskrats (Boyce, 1978), and seasonality in resource availability might explain the body size pattern in several insect species (Chown and Klok, 2003; Blanckenhorn and Demont, 2004). Recently, it has been shown that body size variation in a seed-feeding beetle (*Stator limbatus*) is explained best by host plant size, humidity, and seasonality (Stillwell *et al.*, 2007).

No systematic quantitative analysis has yet been performed to determine to what extent variation in temperature or other climatic factors can explain the distribution of sex-determining mechanisms in the housefly. In this paper, we present such an analysis, based on previously published data and on newly collected data. All previous studies of geographical distributions of sex-determining mechanisms in the housefly have been carried out on populations in the northern hemisphere. If temperature or other climatic factors are important in determining the distributions, we would expect to find the opposite pattern in the southern hemisphere – that is, relatively more autosomal *M* factors in the north than in the south. To test this prediction, we additionally collected houseflies from several subequatorial populations in Africa and examined them for the presence of autosomal *M* factors and F^D factors.

MATERIALS AND METHODS

Sampling and analyses of African housefly populations

We collected houseflies at farms, horse stables, and markets at five locations in Tanzania and six locations in South Africa. At every location, approximately 100 adult flies were caught with a sweeping net and stored in boxes supplied with water, milk powder, and egg-laying medium [according to the protocol of Hilfiker-Kleiner *et al.* (1994)]. For transport to our laboratory in the Netherlands, 150–200 larvae from each sampling location were stored in 50-ml tubes that contained medium. In the laboratory, larvae, flies, and eggs were grown under conditions as described by Hilfiker-Kleiner *et al.* (1994) with the following modifications of their protocol: ambient temperature was set at 20°C, relative humidity at 60%, and flies were kept under constant light.

For each sampling location, 15 males were crossed with virgin females from a mutant strain recessive for visible traits on each autosome [*ali curly* (*ac*) on linkage group 1; *aristapedia* (*ar*) on 2; *brown body* (*bwb*) on 3; *yellow eyes* (*ye*) on 4; *snip wings* (*snp*) on 5]. Since mutant females have the standard *F* factor, they only get sons when crossed with males homozygous for an *M* factor, and mixed-sex offspring when crossed with males heterozygous for *M* factors. Thus, by inspecting the F1 sex ratio of each male, we could estimate the frequency of homozygous males. For 10 of the 15 males for each location, we selected 3 male F1 offspring and crossed each of them with a mutant virgin female to determine on what chromosomes male-determining *M* factors were located [see Franco *et al.* (1982) for a more detailed description of this technique].

To determine whether females were carriers of a dominant female-determining factor F^D, for each sampling location up to 15 females were crossed with males of a laboratory strain that were homozygous for an autosomal *M* factor. Female offspring of such crosses necessarily carried an F^D factor, since F^D overrides the male-determining effects of up to three simultaneously present *M* factors (McDonald *et al.*, 1978, Franco *et al.*, 1982).

Compilation of published studies

We compiled relative frequencies of males with autosomal *M* factors and females with F^D from four additional published studies (see Table 2 and Fig. 1). These studies used either cytological techniques to determine the presence/absence of the Y chromosome, or used crosses similar to those described above. In the cytological studies (Denholm *et al.*, 1985; Çakir and Kence, 1996), autosomal *M* factors were inferred from the absence of Y chromosomes. This procedure can obviously underestimate the frequencies of autosomal *M* factors, since males with Y chromosomes can also have autosomal *M* factors. For the studies relying on crosses (Tomita and Wada, 1989; Hamm *et al.*, 2005), we also regarded males to be 'autosomal' only in the absence of a Y chromosome, so as to make these studies comparable with the cytological studies.

Table 2. Studies of the geographical distribution of housefly sex-determining mechanisms used in our pooled analyses

Study	No. of locations	No. of males	No. of females
1. Denholm *et al.* (1985): UK	6	430	–
2. Tomita and Wada (1989): Japan	18	1105	739
3. Çakir and Kence (1996): Turkey	34	1050	–
4. Hamm *et al.* (2005): USA	4	308	–
5. Present study: Africa	11	99	126

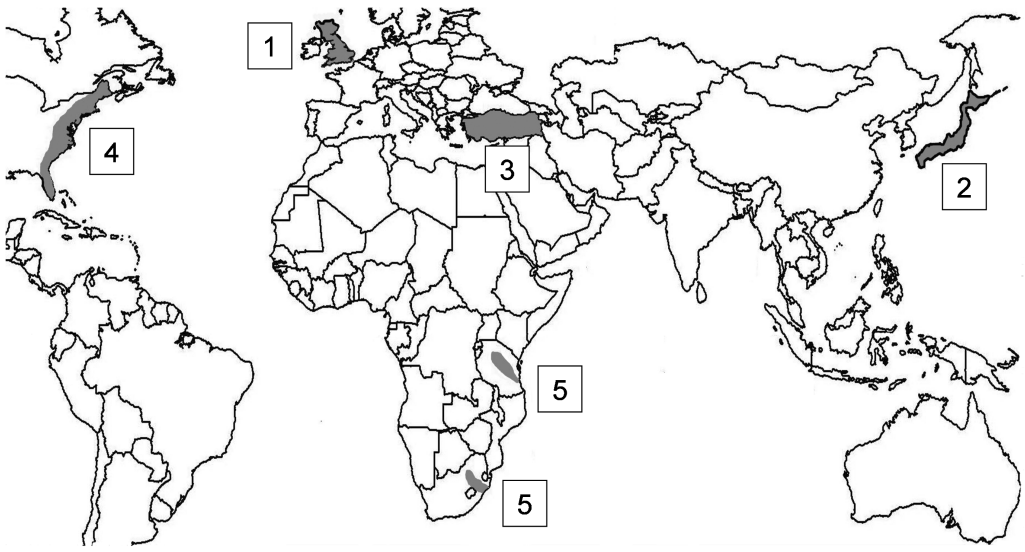

Fig. 1. Geographical locations and references (see Table 2) of housefly studies that were used in the analysis.

Sources of geographical and climatic data

In our study of African houseflies, we used GPS to estimate the latitude and altitude of the study locations. For the published studies, latitudes and altitudes were either explicitly provided in the original study [Turkey (Çakir and Kence, 1996); USA, latitude only (Hamm *et al.*, 2005)], or we estimated latitude and/or altitude based on the description of the sampling location provided in the original study [Japan (Tomita and Wada, 1989); UK (Denholm *et al.*, 1985)] with Google Earth (www.earth.google.com). To correct for idiosyncratic differences between countries, for each sampling location we used latitude relative to the mean latitude of the sampling locations per country/study as a predictor variable, rather than absolute latitude.

For each study location we obtained estimates of annual mean temperature, annual relative humidity, annual daily temperature range, annual number of days with ground frost, and annual percentage of sunshine hours during daylight from the World Water and Climate Atlas of the International Water Management Institute (www.iwmi.cgiar.org/WAtlas). More detailed information on monthly averages of minimum and maximum temperatures were obtained from WORLDCLIM [www.worldclim.org (see Hijmans *et al.*, 2005)], which provides global estimates at a spatial resolution of one square kilometre.

We derived two proxies for seasonality as predictor variables in the statistical analysis (Table 3). The first estimate (Season1) was calculated as the (dimensionless) coefficient of variation of the average monthly temperatures. The second estimate (Season2) was calculated as the average of the difference between the highest and lowest monthly maximum temperature and the difference between the highest and lowest monthly minimum temperature. As proxy that might reflect temperature during the active season, we included the highest monthly mean temperature (Tactive).

Table 3. Abbreviations and explanations of predictor variables used in the analysis

Abbreviation	Description
Alt	Altitude
Lat	Latitude relative to mean latitude per study
Tmean	Annual mean average daily temperature
Tmin	Annual mean minimum daily temperature
Tmax	Annual mean maximum daily temperature
Tactive	Mean temperature of warmest month
DailyTR	Annual mean daily temperature range
Humidity	Annual mean relative humidity
Frost	Annual number of days with ground frost
Sunshine	Annual percentage of sunshine hours
Season1	Coefficient of variation of average monthly temperatures
Season2	Average of difference between highest and lowest monthly maximum temperature and difference between highest and lowest monthly minimum temperature

Statistical analysis

Relative frequencies of autosomal *M* males and F^D females were modelled as proportions with logistic regression in R (R Development Core Team, 2006), using the glm procedure with the 'family = binomial' option.

We used a model selection approach to find the 'best' (most parsimonious) collections of explanatory variables, employing a modified version of Akaike's information criterion, corrected for over-dispersion and small sample sizes (Burnham and Anderson, 2002):

$$\mathrm{QAIC_c} = 2k - 2L/\hat{C} + 2k(k+1)/(n-k-1)$$

where k is the number of estimated model parameters, L the log-likelihood of the model, n the number of data points, and $\hat{C} = \chi^2_{\mathrm{GOF}}/\mathrm{df_{full}}$ is a variance inflation factor to adjust for over-dispersion of the model, χ^2_{GOF} being the chi-squared goodness-of-fit statistic and $\mathrm{df_{full}}$ the residual degrees of freedom of the full model. The final term on the right-hand side of the $\mathrm{QAIC_c}$ equation corrects for small sample sizes.

Given the number of predictor variables, an all-subset selection approach starting with all predictors was computationally infeasible. We therefore started our model selection algorithm with all one-variable models and all possible additive two-variable models and selected the models with the lowest $\mathrm{QAIC_c}$ values. In cases where a two-variable model had a lower $\mathrm{QAIC_c}$ value than any of the one-variable models, we tested for both variables of the two-variable model separately whether they could be deleted without significantly increasing the residual deviance, using F-tests [$F = (\Delta\mathrm{deviance}/\Delta\mathrm{df})/(\mathrm{deviance_{full}}/\mathrm{df_{full}})$ with $\mathrm{df_{full}}$ numerator and Δdf denominator degrees of freedom]. If neither of the variables could be removed, we then selected the best model from all possible models with three predictors. Again we tested whether one or more of the predictors could be sequentially removed from the model without significantly reducing the fit of the model. If three predictors remained, we went on to test all models with four variables, and so on. However, it turned out that in all analyses the best three-variable models were always reducible, thus terminating our model selection algorithm.

RESULTS

New African data

In Tanzania, in three of the five sampled populations, all males had autosomal *M* factors and no Y chromosome, while in the remaining two populations 80% of the males had autosomal *M* factors. The autosomal *M* factors were always located on chromosome 2. In South Africa, the overall frequency of males with autosomal *M* factors was about the same as in Tanzania (see Table 4), but the *M* factors were found on all chromosomes except chromosome 4. However, males from Tanzania were significantly more often homozygous for *M* factors than males from South Africa (Tanzania 62%; South Africa 26%; logistic regression: $P = 0.02$). Females with F^D were found in all populations (Table 4). However, in South Africa the frequency of F^D was significantly lower than in Tanzania, where all females carried the F^D factor in all but one population.

Model selection showed that the distribution of African autosomal *M* males is most parsimoniously explained by yearly mean temperature alone (Table 5, Fig. 2). The distribution of F^D females on the other hand was best explained by temperature during the warmest month of the year (Table 5, Fig. 2).

Table 4. Frequencies of males with autosomal *M* factors and females with F^D in Tanzanian and South African sampling locations

Location	Chrom *M*	% Auto *M* (*n*)	% F^D (*n*)
Tanzania			
Same	2	100 (10)	100 (13)
Moshi	2	100 (10)	100 (11)
Makuiuny	2, Y	80 (10)	100 (13)
Arusha	2	100 (10)	100 (14)
Karatu	2, Y	80 (10)	85 (13)
South Africa			
Zinkwazi Beach	2, 3	100 (9)	29 (7)
Umhlali	1, 2, 3, 5	100 (10)	79 (14)
Hammarsdale	2, 3	100 (9)	92 (13)
Ashburton	1, 2, 3	100 (5)	13 (8)
Mooi River	2, 3	100 (6)	29 (7)
Warden	3, Y	70 (10)	15 (13)

Note: Chrom *M* = chromosomes on which *M* factors were found; % Auto *M* = percentage of males carrying the *M* factor exclusively on autosomes (all other males had *M* on the Y chromosome but also on an autosome); % F^D = percentage of females carrying the F^D factor; *n* = number of individuals tested.

Table 5. Logistic regression model selection for autosomal *M* frequencies (males) and F^D frequencies (females) in African houseflies

Model	d.f.	$QAIC_c$	*F*	*P*	Model	d.f.	$QAIC_c$	*F*	*P*
Males					*Females*				
Tmean		16.22			**Tactive**		13.16		
NullModel		16.50			Tmin		15.34		
Tmax		17.17			NullModel		15.59		
Season1		17.91			Tmean		15.66		
Frost		17.94			DailyTR		15.69		
Tmean + Tactive	9	18.17	0.3	0.86	Tactive + Tmax	9	15.70	0.06	0.82

Note: Depicted are the five one-variable models with the lowest $QAIC_c$ values plus the two-variable model with the lowest $QAIC_c$. *F*-tests refer to deletion of a single variable. d.f. = residual degrees of freedom; **bold** = final model. See Table 3 for an explanation of variables.

Analysis including data from previous studies

The analysis of the combined data is presented in Table 6 (see also Fig. 3). The most parsimonious model for the frequency of autosomal *M* males contained the single seasonality variable Season2 (described in Table 3). Model selection showed that the distribution of F^D in females is most parsimoniously explained by a two-variable model with the predictors humidity and yearly mean temperature.

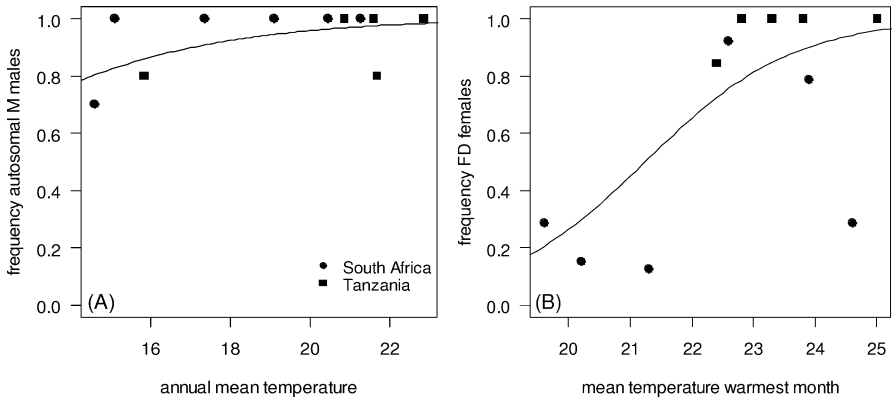

Fig. 2. Best predictors of frequencies of sex-determining factors in African houseflies. Relationship between the single variables of the most parsimonious logistic regression models and the frequencies of (A) males with autosomal *M* factors and (B) females with F^D factors.

Table 6. Logistic regression model selection for autosomal *M* frequencies (males) and F^D frequencies (females) for pooled data

Model	d.f.	$QAIC_c$	*F*	*P*	Model	d.f.	$QAIC_c$	*F*	*P*
Males					*Females*				
Season2		92.24			Humidity		23.63		
Season2 + DailyTR	71	88.17	1.09	0.30	**Humidity + Tmean**	26	18.65	6.82	0.02
Season2 + Sunshine	71	89.16	0.50	0.48	Humidity + Sunshine	26	19.35	0.54	0.47
Season2 + Humidity	71	92.16	0.05	0.83	Humidity + Frost	26	20.17	7.41	0.01
					Humidity + Tmean + Sunshine	25	17.74	0.29	0.59
					Humidity + Tmean + DailyTR	25	18.06	0.57	0.46
					Humidity + Tmean + Season2	25	18.28	0.00	0.97

Note: Depicted are the one-variable models with the lowest $QAIC_c$, three of the best two-variable models, and three three-variable models and the results of *F*-tests by deleting the right-most variable. Note that the two-variable models have lower $QAIC_c$ values than the one-variable models, but for males the second variable can be removed without significantly affecting the model. The same holds true for the two-variable and three-variable models in females. d.f. = residual degrees of freedom; **bold** = final model. See Table 3 for explanation of variables.

DISCUSSION

In this study, we sought to address two main questions regarding the geographical distribution of sex-determining factors in the housefly. The first question was whether the increasing frequency of autosomal *M* factors towards the equator on the northern hemisphere would be matched by a similar pattern on the southern hemisphere. The second question was which of a number of climatic and spatial variables could best explain the observed distributions of sex-determining factors.

Our results show that unlike in studies of European, North American, and Asian housefly populations, where males without autosomal *M* factors are common, all males carried at

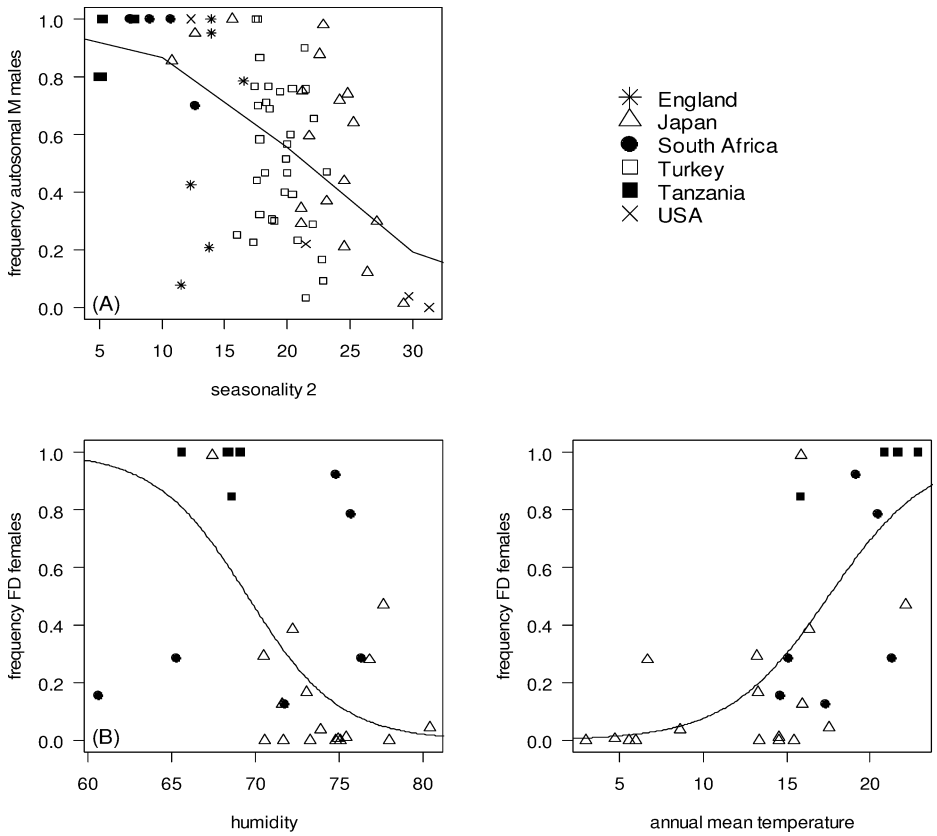

Fig. 3. Best predictors of frequencies of sex-determining factors in houseflies, pooled data. Relationship between the single variables of the most parsimonious logistic regression models and the frequencies of (A) males with autosomal *M* factors and (B) females with F^D factors.

least one autosomal *M* factor in the Tanzanian and South African populations, and the frequency of Y chromosomes was very low (Table 4). Nevertheless, the frequency of males homozygous for autosomal *M* factors was considerably higher in Tanzania than in South Africa, indicating that in African populations autosomal *M* factors are more frequent towards the equator, just like they are in populations on the northern hemisphere. Similarly, the frequency of F^D factors in females was much higher in Tanzania than in South Africa (Table 4). Thus, the answer to the first question, whether the increasing frequency of autosomal *M* factors towards the equator on the northern hemisphere would be matched by a similar pattern on the southern hemisphere, is 'yes'.

Our analysis further showed that neither latitude nor altitude *per se* was a good predictor, but that climatic factors had more explanatory power. The analysis suggests that autosomal *M* and F^D distributions are affected by different climatic factors (Tables 4 and 5). The distribution of autosomal *M* males is best explained by a measure of seasonality (the average of the differences between the minimum and maximum values of the monthly minimum and maximum temperatures), whereas the distribution of F^D females is best explained by humidity and annual mean temperature.

Because our study was entirely correlational, we have not established a causal link between climatic factors and the distribution of male and female sex-determining factors. We therefore discuss and speculate about plausible mechanisms that might be responsible for the clinal distribution of autosomal *M* and F^D, and what might be investigated further.

Seasonality – that is, within-year changes in climatic factors – is an important determinant when it comes to adaptation of organisms to their environment (Danks, 2006). Seasonal responses (e.g. diapause, cold hardiness, and reproductive pattern) have to go in line with a variety of climatic conditions (Danks, 2006). In the housefly, there is evidence of a seasonal trend in the frequency of intersexes, which are more frequent in winter than in summer (Milani, 1967). In this paper, we have shown that the frequencies of autosomal *M* factors are explained best by variation in a measure of seasonality. It is conceivable that these two observations are somehow connected. Autosomal *M* factors might confer higher fitness at high temperatures but at the same time cause greater developmental instability with respect to fluctuations in temperature. Although there is no direct evidence that autosomal *M* factors are temperature sensitive, two housefly laboratory strains have been discovered with temperature-dependent expression of sex-determining factors. One strain carries a maternal effect mutation, *Arrhenogenic* (*Ag*) (Vanossi Este and Rovati, 1982; Dübendorfer *et al.*, 2002). If the mother is heterozygous for *Ag* she produces mostly sons and intersexes at lower temperatures and mostly daughters at higher temperatures, whereas females without *Ag* only produce daughters (Schmidt *et al.*, 1997a). In a second strain, the mutation *masculinizer* (*man*) occurs, which has the properties of a null allele of *F* (Schmidt *et al.*, 1997b). All individuals homozygous for *man* develop into males, whereas all individuals heterozygous for *man* develop into females at low temperatures and into males and intersexes at high temperatures. Thus, in these strains temperature acts directly on the sex-determining system but, to date, these variants have only been found in the laboratory. Whether autosomal *M* factors are also temperature sensitive, albeit perhaps to a lesser degree, remains to be investigated.

It is also conceivable that *M* changes chromosomes via translocation (e.g. via transposable elements). This mechanism is plausible, since it has been demonstrated in the scuttle fly *Megaselia scalaris*, where the *M* factor resides within a transposable element (Traut and Willhoeft, 1990). Theoretical models show that the fixation probability of transposable elements in a population not only depends on the transposition rate but also correlates negatively with generation time (Le Rouzic and Capy, 2005). In the case of the housefly, this would imply that autosomal *M* is more frequent in warmer regions as more generation cycles are possible per population. Over time one would expect the autosomal *M* factor to spread into colder regions. However, Kozielska *et al.* (2008) found that the distribution of autosomal *M* in Europe has not changed over the last 50 years. This suggests that generation time *per se* cannot be the sole explanation and there has to be an additional mechanism.

An alternative mechanism could be temperature-induced segregation distortion by *M* factors. It is well known theoretically that segregation distorters can increase in frequency even at the expense of individual fitness (Haig and Bergstrom, 1995; Weissing and van Boven, 2001). Jayakar (1987) has shown that sex-determining factors linked to segregation distorters may lead to a shift in sex-determining mechanisms. In *Drosophila melanogaster*, segregation distorters have been found that are temperature sensitive (Mange, 1968; Hartl, 1975; Hiraizumi, 1993); in some strains, a temperature of 25°C was associated with strongly aberrant segregation ratios, while the degree of distortion was lower at both higher and lower temperatures. There is weak evidence that segregation distortion sometimes occurs in the housefly (Clark, 1999), but this has not been linked to temperature.

Adult houseflies have an optimal humidity/temperature range in which they are most active (West, 1951). Both humidity and temperature extremes do have lethal effects on adult houseflies, as well as on any other developmental stage (Hewitt, 1908; West, 1951). Humidity has a strong effect on eggs and larvae, as they dry out if there is not enough moisture, whereas too much humidity leads to drowning. Larvae in a later stage however need a less moist environment to be able to pupate (Hewitt, 1908). It is possible that F^D, besides being non-susceptible towards *M*, could also lead to increased viability of any of the fly developmental stages in warmer and less humid places.

The main goal of this study was to determine whether the distribution of male and female sex-determining factors in the housefly can be explained by variation in climatic variables. As previously suggested by Stillwell *et al.* (2007) for body size, mean temperature should not be the only variable taken into consideration when studying latitudinal clines. We find that seasonality and humidity in addition to mean temperature explain the clines in male and female sex-determining factors. How this association comes about at the mechanistic level remains to be elucidated.

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