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Brief Communication

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Defining the Role of the MADS-Box Gene, *Zea Agamous-like1*, a Target of Selection During Maize Domestication

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Abstract

Genomic scans for genes that show the signature of past selection have been widely applied to a number of species and have identified a large number of selection candidate genes. In cultivated maize (*Zea mays* ssp. *mays*) selection scans have identified several hundred candidate domestication genes by comparing nucleotide diversity and differentiation between maize and its progenitor, teosinte (*Z. mays* ssp. *parviglumis*). One of these is a gene called *zea agamous-like1* (*zagl1*), a MADS-box transcription factor, that is known for its function in the control of flowering time. To determine the trait(s) controlled by *zagl1* that was (were) the target(s) of selection during maize domestication, we created a set of recombinant chromosome isogenic lines that differ for the maize versus teosinte alleles of *zagl1* and which carry cross-overs between *zagl1* and its neighbor genes. These lines were grown in a randomized trial and scored for flowering time and domestication related traits. The results indicated that the maize versus teosinte alleles of *zagl1* affect flowering time as expected, as well as multiple traits related to ear size with the maize allele conferring larger ears with more kernels. Our results suggest that *zagl1* may have been under selection during domestication to increase the size of the maize ear.

Subject areas: Genomics and gene mapping, Gene action, regulation and transmission
Key words: flowering time, kernel row number, selection scan

Genomic scans for the signature of selection in the pattern of nucleotide diversity in populations has provided insights into the frequency of selective sweeps and identified large catalogs of genes that appear to have been the targets of selection during the adaptive divergence of populations (Vitti et al. 2013). This approach has been applied in humans where it has identified selection-candidates involved in local adaptation and disease resistance (Sabeti et al. 2002; Schlötterer 2002; Storz et al. 2004; Bustamante et al. 2005; Voight et al. 2006). It has also been employed in natural populations of sunflower, whitefish, mice, and walking-stick insects to identify genes for ecological adaptation and speciation (Campbell and Bernatchez 2004; Edelist et al. 2006; Kane and Rieseberg 2008; Nosil and Sandoval 2008;

Teschke et al. 2008). Finally, genomic scans for selection have been used in crop plants to identify genes involved in domestication and crop improvement (Vigouroux et al. 2002; Casa et al. 2005; Wright et al. 2005; Yamasaki et al. 2005; Chapman et al. 2008; Hufford et al. 2012).

Once putatively selected genes have been identified, the next challenge is to link specific selected genes to the traits that they control. Some inferences in this regard can be made by relying on gene ontology and a knowledge of the phenotypes affected by loss-of-function alleles of the gene. For example, if genes known to function in amino acid biosynthesis appear as selection candidates, then one might reasonably infer that selection acted on some aspect of amino acid composition (Wright et al. 2005). However, such an exercise falls far short of proof and precludes the discovery of novel gene functions. Thus, the ultimate approach and key challenge is to contrast the phenotypic effects of the ancestral and derived ("selected") alleles of specific genes.

In maize, hundreds of putatively selected loci have been identified by either large-scale or genome-wide scans for the signature of selection due to domestication from the wild relative teosinte, *Zea mays* ssp. *parviglumis* (Vigouroux et al. 2002; Wright et al. 2005; Yamasaki et al. 2005; Hufford et al. 2012). The most thorough of these studies (Hufford et al. 2012) scanned the entire genome and identified 484 genomic regions (encompassing 1764 identified genes) that appear to have been selection targets. This analysis demonstrates that domestication was a complex process involving selection on numerous genes and traits. In fact, the genetic complexity is likely to be even greater than indicated as selection scans are tuned to detect genes that were the targets of hard sweeps and thus a considerable number of genes targeted by soft sweeps are apt to go undetected.

In this article, we examine the phenotypic effects of one of the first maize genes detected via selection scans as a target during maize domestication. The gene in questions is *zea agamous-like1* (*zagl1*; GRMZM2G026223), a MADS-box transcription factor located on the short arm of chromosome 1. *zagl1* is a homologue of the Arabidopsis gene called *SUPPRESSOR OF OVEREXPRESSION OF CO1* (*SOC1*), which plays a central role in the regulation of flowering time (Putterill et al. 1995; Samach et al. 2000; Yoo et al. 2005; Helliwell et al. 2006; Searle et al. 2006). *zagl1* was first identified as a putative target of selection in a screen of microsatellite diversity (Vigouroux et al. 2002), subsequently detected in a screen of nucleotide diversity in MADS-box genes (Zhao et al. 2011), and finally detected in the full genome scan of nucleotide diversity (Hufford et al. 2012).

In this study, we addressed whether flowering time or any domestication-related traits are affected by a maize versus teosinte allele at *zagl1*. We used a series of recombinant isogenic lines with either a teosinte allele or maize allele of *zagl1* introgressed into a predominately maize background. We observed that the number of kernel rows in the ear was affected, with the maize allele conferring a higher kernel row number. Our results suggest that *zagl1* was selected to cause an increase in ear size and the number of kernel rows during maize domestication.

Materials and Methods

To identify traits controlled by *zagl1*, we selected a single heterozygous inbred family (HIF) from a set of 866 maize-teosinte BC_2S_3 lines constructed for Quantitative Trait Locus (QTL) mapping (Shannon 2013). This quantitative trait mapping population used the maize inbred line W22 as the recurrent parent, and a *Z. mays* ssp. *parviglumis* individual from the Balsas region of southwestern Mexico (CIMMYT accession 8759) (Shannon 2013). These lines are on average 87.5% W22. The HIF (number MR0388) was segregating for a 1.35 Mbp teosinte segment (Chr 1: 3,851,753–5,202,733 AGP v4) containing 99 genes, including *zagl1*. To test the effect of *zagl1* on domestication traits independently from the effects of flanking loci in the interval, recombinant chromosome nearly isogenic lines (RC-NILs) were created by selfing individuals that were heterozygous for the teosinte introgression and identifying offspring with recombination events between *zagl1* and the 2 flanking genes. In addition, lines which were homozygous for the entire maize and the entire teosinte chromosomal segment were created (Supplementary Figure 1).

To create the RC-NILs, 1710 plants from MR0388 were genotyped. First, 950 seeds from MR0388 family were genotyped via seed chips. A fragment of each seed was removed from the opposite side from the embryo and DNA was extracted from the fragment using the Sigma Extract–N-Amp Seed kits. Seeds were genotyped at *zagl1* and the 2 flanking loci as described below. Seeds with recombination events between the 2 flanking markers were then germinated in trays and transplanted into pots and grown in the greenhouse. Approximately 1 month after transplanting in the greenhouse, the plants were then transplanted in the field at the West Madison Agricultural Research Station. An additional 760 MR0388 seeds were sown in the field. DNA was extracted from leaf tissue of these plants following a modified cTAB extraction protocol, and genotyped to identify individuals with crossovers. All individuals with recombinant chromosomes were selfed. The following winter, the offspring that were homozygous for the recombinant chromosome were identified by genotyping and then selfed to create a set of RC-NILs.

We identified the adjacent genes on each side of *zagl1* from the maize filtered gene set. GRMZM2G475380 is located upstream of *zagl1* on the negative strand and we identified a 4 bp indel at 4,914,411 (AGP v4) as a marker within this gene (Table 1). GRMZM2G475380 contains an oxoglutarate/iron-dependent dioxygenase domain with homology to *downy mildew resistant 6* (DMR6) of Arabidopsis. GRMZM2G070047 is downstream of *zagl1* on the positive strand and we identified a 65 bp indel at 5,088,141 (AGP v4) for a marker in this gene. GRMZM2G070047 encodes an ubiquitin-conjugating enzyme with homology to *Arabidopsis thaliana SUMO-conjugating enzyme* 1 (*At*SCE1). For genotyping, fluorescently labeled forward primers were created for the indels in GRMZM2G475380 and GRMZM2G070047 as well as an SSR (AI737167) in *zagl1*. Multiplex PCR was then performed to amplify the 3 fragments which were then analyzed using ABI 3730 XL DNA Autosequencer.

In addition to the introgression of interest on the short arm of chromosome 1, other heterozygous regions of the genome remained in the HIF MR0388: one on chromosome 1 (Chr 1: 300,856,757 – 303,633,741 AGP v4), 2 on chromosome 2 (Chr 2: 187,452,391–189,706,233 and 236,393,775–240,483,550 AGP v4), one on chromosome 6 (Chr 6: 108,479,288–108,844,298 AGP v4), and 4 on chromosome 7 (Chr 7: 720,319–6,965,661, 147,952,424–148,807,875, 169,297,960–169,449,625 and 173,942,988–179,012,026 AGP v4). Our attempt to develop PCR-based markers for these other regions yielded only 4 additional markers which we used to genotyped the RC-NILs and control lines: umc1331 on the long arm of chromosome 1, umc1642 and umc1426 on the short arm of chromosome 7, and TIDP3050 on the long arm of chromosome 7. Genotyping was performed as described above. Genotypes in these regions were incorporated into our statistical analysis to discern if they affected trait values.

Table 1. List of markers used in the screen for cross-overs in the interval of *zagl1* and the flanking genes

Marker	M129610	*zagl1* (AI737167)	M70259
Gene	GRMZM2G475380	GRMZM2G026223	GRMZM2G070047
Marker type	Indel	SSR	Indel
AGP_v4 Position	4,914,411	4,979,584	5,088,141
Amplicon size polymorphism (Maize/ Teosinte)	158/154 bp	89/84 bp	919/854 bp
Forward primer	CTTCCAGGTGGGCACACAG	AAAATTATTCTCTGCACTGCTGGC	TGCAATCATTCTGTAGTCCCGTGTG
Reverse primer	GAGAGGGTCGGAATTGTGTT	GATTTCCGCTCAAACAACAAAAAC	CACCATGGCTGCTGTTTGTCCG

In the summer of 2013, the 13 RC-NILs along with 3 maize and 4 teosinte control lines were grown at the West Madison Agricultural Research Station. The lines were grown in 4 randomized blocks with 20 plants per plot. For each plot, 10 plants were selected for phenotyping excluding the 2 end plants. The plants were scored for days to anthesis (DTA), days to silk (DTS), plant height (PLHT), and the average length of internodes in the shank subtending the ear (LBIL) in the field. The ears for the 10 selected plants were collected at harvest, dried down, and scored for cupules per rank (CUPR), ear length (EARL), ear diameter (EARD) and number of kernel rows (KRN).

Raw data were checked to identify outlier phenotypes. One plant with unusually low EARL, CUPR, and KRN was set to missing data. Mixed models were fitted using the lmer function in R package lme4 (Bates et al. 2015) to estimate the significance of *zagl1* and 2 flanking markers. An initial full model was:

$$Y \sim \mu + \text{Block} + \text{Class} + F_2 - \text{by} - \text{Class} + \text{Seed lot} + \text{Plot} + \text{within plot residual variation}$$

Class was the combination of genotypes at *zagl1* and its flanking loci, and was the only fixed effect in this model. F_2 refers to the individual ancestral F_2 plant from which a NIL was derived. Most F_2 ancestors were represented by only a single genotypic class, F_2 ancestor effects are mostly confounded with the interaction between F_2 ancestor and Class. Therefore, we fit a single term F_2-by-Class in the full model to capture variation due to F_2 ancestor main effects and their interaction with Class combined. Seed lot refers to the source of the seed used to plant each plot and was fit as nested within F_2-by-Class. Plot is nested within F_2-by-Class-by-Block. The residual term from this model is plant-to-plant variation within a plot.

We first tested the random effects and dropped the terms if they were unimportant (P value > 0.10). We used the exactRLRT function in R package RLRsim (Scheipl et al. 2008) to test the significance of random effects. Having chosen the appropriate set of random effects, we then dropped Class from the model and tested each marker, including background markers, one at a time. We used the function KRmodcomp in R package pbkrtest (Halekoh and Højsgaard 2014) to test the significance of marker fixed effects in the mixed model. This function computes an F-test with the Kenward-Roger approximation for degrees of freedom (Kenward and Roger 1997). If any markers had $P < 0.05$, we selected the marker with lowest P value and added it to the model. Then we retested all other markers for significance when added to the updated model. The process of forward model selection was continued until no additional markers had $P < 0.05$. Marker effects (the difference between homozygous teosinte and homozygous maize allele classes) and P values were estimated from the final model.

Table 2. Significant additive effects of the teosinte allele at the markers on traits assayed with *P* values in parentheses below each effect

		Markers	
Traits	umc1331	M129610	*zagl1*
DTA	−0.531	—	1.835
days	(0.016)	—	(0.000)
DTS	−0.177	—	2.012
days	(0.006)	—	(0.000)
EARD	—	—	−0.350
mm	—	—	(0.034)
EARL	—	—	−0.826
cm	—	—	(0.039)
KRN	—	—	−0.600
count	—	—	(0.020)
LBIL	0.049	−0.325	0.123
cm	(0.008)	(0.000)	(0.008)
PLHT	—	—	7.455
cm	—	—	(0.004)

Units of measurement are shown beneath the traits. Supplementary Table 1 lists of all effects on all traits whether significant or not.

Results and Discussion

Molecular evidence for a selective sweep on *zagl1* during domestication has been observed in multiple studies (Vigouroux et al. 2002; Zhao et al. 2011; Hufford et al. 2012); however, the phenotype that was the target of the observed selection is unknown. To determine the trait(s) that provided a selective advantage, we investigated the effects of a maize versus teosinte allele of *zagl1* on flowering-time and domestication traits using a set of RC-NILs. Since our RC-NILs have cross-overs between *zagl1* and the nearest upstream and downstream genes, we have sufficient resolution to estimate the genetic effects of allelic substitution specifically at *zagl1* free from the confounding effects of linked genes.

Using a mixed linear model analysis of the RC-NILs, we tested for effects on 8 traits associated with *zagl1*, its 2 flanking genes and 4 unlinked markers (Table 2). Of the 4 unlinked markers, only umc1331 shows significant associations with any traits, explaining some variation for DTA, DTS and LBIL, indicating that there is a gene other than *zagl1* affecting flowering time and branch length on the long of chromosome 1 near umc1331. The results also indicate that the 2 introgressions on chromosome 7 tagged by markers umc1642, umc1426, and TIDP3050 do not harbor genes affecting the traits we assayed. For all traits except CUPR, the *zagl1* marker had a significant effect on phenotype. Of all 7 markers, *zagl1* affects the most traits, indicating that it accounts for most of the trait variation among the RC-NILs. The RC-NILs separate into non-overlapping

groups for their *zagl1* genotype by principal components analysis (Supplementary Figure 2). In addition to *zagl1*, the flanking marker (M129610) has an effect on LBIL, suggesting that there may be a gene linked to *zagl1* affecting this trait.

Since DTA and DTS are direct measures of flowering time and *zagl1* is a known flowering time gene in Arabidopsis (Putterill et al. 1995), the association of *zagl1* with these traits was anticipated. PLHT is typically highly correlated with flowering time since later-flowering lines grow taller, and thus the association of PLHT with *zagl1* was anticipated as well. Notably, whereas *zagl1* has a significant association with each of these 3 traits, neither of its 2 flanking loci do. This result shows that variation for these traits among the RC-NILs is controlled by *zagl1* itself rather than a linked gene. Thus, our data demonstrate that *zagl1* acts as a flowering time gene in *Zea*. Substitution of both teosinte alleles of *zagl1* for maize alleles causes an approximately 2-day delay in both pollen shedding and silking and increases plant height by 7.5 cm (Table 2; Supplementary Figure 3). These are relatively large effects, considering the effects of 98% flowering-time alleles within maize are very small (<2 days) (Buckler et al. 2009).

Flowering time seems unlikely to have been a target of selection during domestication as the incipient domesticated maize would have been under selection in the same environment as its progenitor, teosinte, and thus subjected to the same environmental exigencies. However, an argument could be made that selection for earlier flowering during domestication was a factor as distinct flowering regimes would reduce gene flow between incipient maize and teosinte and thereby facilitate the domestication process. Accordingly, it is possible that *zagl1* was under selection during domestication to enable earlier flowering in maize.

In addition to flowering time, we observed significant associations between *zagl1* and multiple traits related to ear size including EARD, EARL, and KRN (Table 2; Supplementary Figure 2). In each case, the maize allele is associated with an increase in ear size. Importantly, these associations are specifically with *zagl1* and neither flanking genes show a significant effect, indicating that *zagl1* is the causative gene. The effect of the teosinte allele on KRN is to reduce the number of kernel rows by 0.6 (Table 2). As a rough estimate of the effect on kernel production, our lines have about 14 kernel rows and about 30 kernels from the base to the tip of the ear, resulting in about 420 kernels per ear. A reduction from 14 to 13.4 kernel rows would translate into 18 fewer kernels per ear with the teosinte allele. Since an increase in ear size is one of the major changes during maize domestication, our data indicate that *zagl1* was likely one of the genes under selection for this change.

The effects of *zagl1* that we report on flowering time and kernel row number should be interpreted with caution, given that our assay has clear limitations. First, we identified the 2 genes that flank *zagl1* based on the B73 reference genome. It is possible that additional genes lie between these 2 genes and *zagl1* in W22 and/or our teosinte parent. If such genes exist they could explain the phenotypic effects we observed. Second, we assessed the effects of a teosinte allele of *zagl1* in a largely maize genetic background that is unlikely to represent the genetic background in which selection on *zagl1* occurred during domestication. Finally, our field experiment was performed in the long summer days of central Wisconsin which may have potentiated genotype-by-environment interactions quite distinct from those in central Mexico where maize was domesticated.

To understand the nature of the difference in gene function between maize and teosinte, we examined available DNA sequence diversity data (Vigouroux et al. 2002) and RNAseq allele specific expression data (Lemmon et al. 2014). First, the DNA sequence diversity data included 15 teosinte and 16 maize landrace sequences that covered a 87 bp segment of Exon 6 in *zagl1* in Genbank GeneID: 100279630 – protein isoform X3 (Figure 1). Even in this small region, there is an amino acid substitution for which 14 of 15 teosintes are tyrosine (Y) and all maize plus one teosinte are cysteine (C). This nearly fixed difference is a candidate for the causal substitution. Second, expression data for ear tissue in 17 maize-teosinte F_1 hybrids involving 6 different maize and 6 different teosinte parents show a read depth ratio 2200 maize/1469 teosinte or 1.50 expression ratio of maize to teosinte. This ratio differs significantly from equal expression of the maize and teosinte alleles by a binomial test ($P = 1.17 \times 10^{-33}$), suggesting *zagl1* expression may have been upregulated during domestication. Given that there are data for both an amino acid substitution and expression change, either a protein functional or regulatory change may underlie the effect on kernel row number we observed.

An association mapping study showed a significant association of *zagl1* with ear shattering in teosinte, a key domestication trait (Weber et al. 2008), however, we saw no variation for ear shattering among our *zagl1* RC-NILs that could be tested to confirm this prior report. The failure to observe a shattering phenotype may indicate either that 1) *zagl1* does not affect that trait and the reported association was a false-positive, 2) *zagl1* does affect shattering but the shattering variant that segregates in teosinte was not involved in maize domestication, or 3) the genetic background of our RC-NILs obscures the effects of *zagl1* on shattering.

Evidence for selection on flowering time genes like *zagl1* during domestication is not unique to maize, there are multiple cases for which genes in the flowering time pathway have been identified as players in domestication or subsequent crop improvement (Olsen and Wendel 2013). Some of these cases involve changes in flowering time but others relate to changes in inflorescence size or structure such as we have seen with *zagl1* in maize. Blackman et al. (2010, 2011a, 2011b) identified *Helianthus annuus Flowering Locus T1* (*HaFT1*) as a gene under selection during sunflower domestication that colocalizes with a QTL for flowering time. Domesticated sunflower carries an allele with a frame-shift mutation in *HaFT1* that is rare in its wild ancestor.

Genomic scans for genes that were the targets of selection during domestication have been applied in a variety of crop species, and they have identified hundreds of candidate domestication loci (Casa et al. 2005; Wright et al. 2005; Yamasaki et al. 2005; Chapman et al. 2008; Hufford et al. 2012). Few attempts have been made to identify the traits that provided the selective advantage and show that the crop and progenitor alleles confer different phenotypic effects on that trait. Indeed, other than the present study, the only other attempt to determine the phenotypic effects of the progenitor versus crop allele for a gene identified by a selection scan was a study of the prolamine binding factor (*pbf1*) in maize and teosinte (Lang et al. 2014). *pbf1* is a transcription factor that regulates expression of a family of genes encoding prolamine seed storage proteins. Lang et al. had essentially negative results. They could not associate any difference in prolamine composition or protein content with the maize versus teosinte allele of *pbf1*. Moreover, the teosinte *pbf1* allele showed higher expression than the maize allele, and the teosinte allele was associated with a higher kernel weight. The latter result is opposite of expectations, given that maize kernels weigh substantially more than teosinte kernels.

In this study, we report evidence that a maize and a teosinte allele of *zagl1* have significant effects on both flowering time and kernel

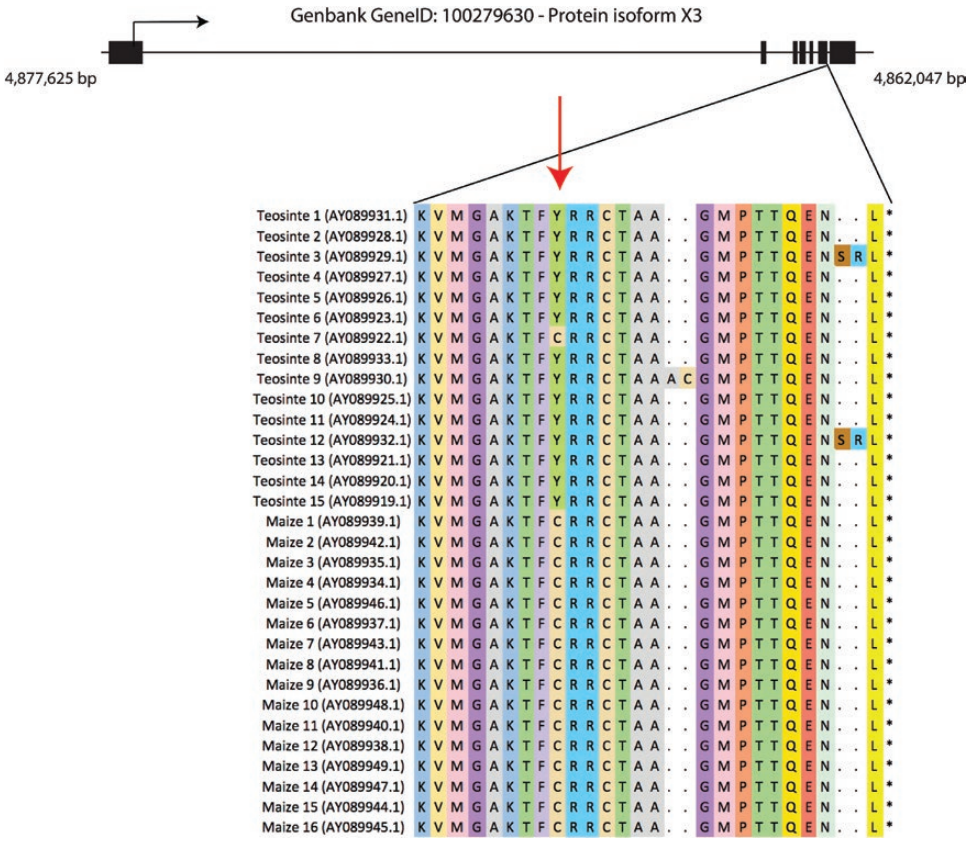

Figure 1. Partial amino acid alignment for Exon 6 in *zagl1* in Genbank GeneID: 100279630 – protein isoform X3 for sequences of maize and teosinte (*Z. mays* ssp. *parviglumis*) from Vigouroux et al. (2002). Genbank accession numbers for each sequence are shown. Arrow points to Y > C substitution that distinguishes most maize and teosinte.

row number. The effects on kernel row number are in the expected direction with the maize allele conferring more rows of grain. The change from small ears with 2 rows of grain in teosinte to large ears with 8 to 20 (or more) rows of grain in maize was one of the major changes in morphology during domestication. Our results show that *zagl1*, which was the target of a hard selective sweep during domestication, likely contributed to this change.

Supplementary Material

Supplementary data are found at *Journal of Heredity* online.

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Conflict of Interest

The authors do not have any conflict of interest.

Data Availability

The genotype-phenotype data set is available at Dryad (doi:10.5061/dryad.420k8).

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