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Effects of SCA1, MJD, and DPRLA Triplet Repeat Polymorphisms on Cognitive Phenotypes in a Normal Population of Adolescent Twins

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The expansion of unstable trinucleotide CAG repeat polymorphisms of a number of genes causes several neurodegenerative disorders with decreased cognitive function, the severity of the disorder being related to allele length at the triplet repeat locus. While the effects of repeat length have been well studied in clinical samples, there has been little investigation of the effects of triplet repeat variation in the normal range for these genes. We have, therefore, examined linkage and association for three CAG triplet repeat markers (Spinocerebellar Ataxia Type 1, SCA1; Machado-Joseph Disease, MJD; Dentatorubro-pallidoluysian Atrophy, DRPLA) to assess their contribution to variation in cognitive ability (IQ, reading ability, processing speed) in a normal, unselected sample of adolescent twins (248 dizygotic (DZ) sibling pairs, aged 16 years). Association tests, performed in Mx and QTDT, showed a consistent positive association of SCA1 with Arithmetic ($P = 0.04$). While association was supported between SCA1 and Cambridge reading scores and between DRPLA and inspection time, results were inconsistent across software packages. Given the number of statistical tests performed, it is unlikely that trinucleotide repeat variation in the normal range for these genes influences variation in normal cognition.

KEY WORDS: association; cognition; CAG repeat polymorphisms

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INTRODUCTION

The expansion of unstable trinucleotide repeat number polymorphisms is the cause of a number of neurodegenerative disorders, such as Huntington's disease and Spinocerebellar Ataxia Type 1 (SCA1). These particular disorders are two of eight known which are caused by the expansion of one of the most common triplet repeat motifs, CAG, which encodes the amino acid glutamine [Beckmann and Weber, 1992; Stallings, 1994]. The effect of triplet repeat length in clinical samples is well characterized; generally, triplet repeat disorders display a positive relationship between number of repeats and the severity of the symptoms of the disorder [see Monckton and Caskey, 1995]. The clinical symptoms (e.g., impaired cognitive ability) of the varying triplet repeat disorders overlap and so too do the affected brain regions, which include the cerebral cortex, basal ganglia, brainstem nuclei, cerebellar dentate nucleus, Purkinje cells of the cerebellum, and spinal and bulbar motor neurons [Margolis et al., 1999; Koeppen, 2005].

The effect of triplet repeat length in the normal range on variation in psychomotor and cognitive functions has been less frequently studied. In the present study, we therefore report the association between markers for three neurodegenerative disorders: SCA1, Machado-Joseph Disease (MJD), and Dentatorubro-pallidoluysian Atrophy (DRPLA), and psychomotor and cognitive variation in an unselected sample of adolescent twins. These markers were typed for a study which investigated segregation ratio distortion in normal heterozygotes [none was found; MacMillan et al., 1999]. As IQ and other cognitive data were available for a subset of these genotyped families as part of a larger study of cognition, we had the opportunity to investigate the relationship between expansion length and a variety of indices of cognitive performance.

Spinocerebellar Ataxia Type 1 is located on chromosome 6 and the triplet repeat marker is polymorphic in the normal population (alleles in the range of 6–38 repeats), with allele length ranging from 39 to 83 repeats in clinical samples of SCA1 individuals [Margolis et al., 1999]. Animal studies have shown that ataxin-1, the protein affected in SCA1, may be involved in synaptic plasticity which is important to learning. Specifically, SCA1-null mice show poor spatial and motor learning and lower paired-pulse facilitation in a region of the hippocampus near the dentate gyrus [Matilla et al., 1998]. Chromosome 12 harbors the DRPLA gene, with the repeat length ranging from 3 to 35 in normal populations and from 49 to 88 in affected populations. The DRPLA gene product, atrophin-1, is widely expressed in neurons, but its function is not known [Wood et al., 2000]. MJD is located on chromosome 14 and the allele length of the repeat marker in normal and affected populations ranges from 12 to 40 and 55 to 84, respectively [Cummings and Zoghbi, 2000]. While its function is unknown, ataxin-3, the protein affected in MJD, is widely expressed in the brain, and in most neurons shows localization

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to cytoplasmic, dendritic, and axonal regions [Trottier et al., 1998].

There have been a couple of studies that have reported on the relationship between triplet repeat length and IQ in non-clinical samples. Daniels et al. [1994] tested for differences in Fragile-X CGG repeat length in low, middle, and high IQ groups of children; null findings were supported in both boys and girls. In a study where Wechsler Adult Intelligence Test-Revised (WAIS-R) scores were compared in carriers and non-carriers of the Huntington's disease gene, various subtests were negatively correlated with the number of CAG repeats in expansion positive but not in expansion negative individuals [Foroud et al., 1995]. Hence, for the trinucleotide repeat disorders of Fragile X syndrome and Huntington's disease, there is no indication of a repeat length relationship to IQ in the normal population.

Various phenotypes collected in the present study measure cognitive abilities which have been shown to be affected in the polyglutamine disorders, including visual reaction time (RT) and IQ (digit symbol processing, arithmetic, spatial ability, object assembly, general knowledge, vocabulary). As the polyglutamine disorders are characterized predominantly by motor rather than cognitive dysfunction, it is reasonable to suppose that in our non-clinical sample, the measures requiring motor responses (i.e., visual RT, digit symbol substitution) will more likely be influenced by triplet repeat variation than the purely cognitive measures. To test whether normal variation in triplet repeat length of the SCA1, DRPLA, and MJD genes is related to variation in these measures, a combined linkage and association sibling-pair analysis was performed in a sample of 16-year-old twins for whom both phenotypes and triplet repeat polymorphism genotypes were available.

MATERIALS AND METHODS

Sample

The sample comprised a sub-sample of 248 twin pairs (55 monozygotic (MZ) female, 46 MZ male, 39 dizygotic (DZ) female, 36 DZ male, 72 DZ opposite sex) who were initially recruited at age 12 from schools in Brisbane and surrounding areas to participate in a study investigating melanoma risk factors [see Zhu et al., 1999]. Twins and their parents were later genotyped for three triplet repeat loci, SCA1, MJD, and DRPLA [MacMillan et al., 1999]. Four years later most of these twins completed a cognitive battery, which has been fully described in Wright et al. [2001]. Informed consent to jointly examine the cognitive and genotype data was obtained within this phase of the study. The mean age of the twins at time of cognitive testing was 16.2 years (range: 15.7–17.7 years).

Cognitive Measures

The cognitive assessments included IQ, reading, and information processing measures. The Multi-dimensional Aptitude Battery assessed IQ and consisted of five subtests: information, vocabulary, arithmetic, spatial, and object assembly subtests [Jackson, 1984, 1998]. Raw scores of the subtests and scaled scores for verbal, performance, and full IQ were examined. The digit symbol test [a subtest of the WAIS-R; Wechsler, 1981] was also administered. Reading ability tests included the Cambridge Contextual Reading Test [Nelson and Willison, 1991] and the Schonell Graded Reading Test [Schonell and Schonell, 1960] as described in Wainwright et al. [2004]. Processing speed was measured using a visual inspection time paradigm [Luciano et al., 2001a] and an eight-choice RT task [Luciano et al., 2001b].

Zygosity, Genotyping, and IBD Estimation

Blood was obtained from twins and their parents for blood grouping and DNA extraction, and all families were typed formarkers including SCA1, DRPLA, and MJD on an ABI 373 sequencer [MacMillan et al., 1999]. Zygosity was diagnosed using nine polymorphic DNA microsatellite markers and three blood groups (ABO, MNS, and Rh) in the twins and in most cases both parents. Subsequently further microsatellite markers on each of the relevant chromosomes were available [see Zhu et al., 2004] so that multipoint Identity-by-Descent (IBD) estimation of the triplet repeat markers was possible. Hence, for the respective SCA1, MJD, and DRPLA markers 38 (chromosome 6), 29 (chromosome 14), and 27 (chromosome 12) surrounding microsatellite loci had been genotyped. Multipoint IBD probabilities were estimated in Merlin using genotype data of twins and parents [Abecasis et al., 2002].

Structural Equation Modeling

Combined tests of linkage and association were performed using maximum-likelihood based structural equation modeling in the Mx software package [Neale et al., 1999]. Within this framework, a variance components model was specified to include the effect of the QTL (linkage) and a means model was specified to include the fixed effect of association as well as sex and age effects [Fulker et al., 1999; Zhu et al., 1999]. Hence, observed variances and covariances for MZ and DZ twins were partitioned into four components: additive genetic variance (A), common environmental variance (C), unique environmental variance (E), and QTL variance (Q). The expected covariance structure for MZ twins was $A + C + Q$, and for DZ twins was $0.5A + C + \hat{\pi}Q$, where $\hat{\pi}$ (pi-hat) is the estimated proportion of genes shared identical by descent at the marker locus. Pi-hat is equivalent to the probability of sharing two genes IBD plus half the probability of sharing one gene IBD, that is, $p(IBD2) + 0.5\ p(IBD1)$ [Amos, 1994; Boomsma, 1996; Eaves et al., 1996]. To test for linkage, Q was fixed to zero and the fit of this reduced model was compared to the fit of the saturated model using the χ^2 likelihood ratio test. In this test the difference in minus two times the log likelihood (-2 LL) between the saturated and reduced model is compared to the critical value of a χ^2 distribution, with degrees of freedom equal to the difference in degrees of freedom between the models. In the univariate case, this likelihood ratio statistic is a mixture of a χ^2 on 1 df and a point mass of 0, so the probability related to the χ^2 should be halved. To determine whether a cognitive measure was associated with triplet repeat length at any of the three loci, the phenotype was linearly regressed onto mean allele length (r_{allele}) at the relevant locus. The test of association was considered under an ACE model by fixing the allele-length regression coefficient to zero. A significance level of 0.05 was used for our test of association (r_{allele}), corresponding to a critical value of 3.84 with 1 df.

As family-based data were used, we further tested for effects of population stratification and within family effects using QTDT [Abecasis et al., 2000]. The binned allele length for each marker was re-coded into three categories representing short, medium, and long allele length. This was done to avoid QTDT combining low frequency alleles (<5%) of differing repeat length. Significant associations were inspected for linearity of triplet repeat size by re-coding each of the three categories into a binary trait (presence vs. absence of allele) and checking whether the chi-squares (obtained from the association test's *P*-value on 1 df) form a linear relationship between the ordinal categories.

RESULTS

Preliminary

Outlier screening and transformations of data distributions followed the procedures adopted throughout our previous studies, which were based on larger sample sizes [see Luciano et al., 2001a, 2004a; Wainwright et al., 2004]. Post hoc examination of inspection time data indicated that 24 participants did not perform the task properly and their measurements were excluded. Following $\log_{10}$ transformation of inspection time, 16 outlying cases were removed. Choice RT was considered for an 8-choice condition, with the index measure calculated as the mean of log RT across 96 trials. A significant correlation between mean log RT and accuracy ($r = 0.49$) indicated the presence of a speed-accuracy trade-off effect, so a regression term for accuracy was included in the means model of the ensuing genetic analysis. The Schonell reading variable was reverse $\log_{10}$ transformed due to negative skewness in the data.

Prior to genetic analysis, assumptions about equality of means and variances across birth-order, sex, and zygosity were tested for each variable. The means of 7 of the 13 variables differed significantly between males and females, necessitating the inclusion of an additional term to adjust the means model for the genetic analyses. Also taken into account in the genetic analyses performed in Mx were the significantly different variances between males and females for three variables: IQ subtests, information and spatial, and inspection time. A difference in means across birth-order was detected for verbal IQ, but with no other IQ variables showing this trend—in particular vocabulary, information, and arithmetic (subtests of verbal IQ)—this was assumed to be a type I error and was not corrected for in the genetic analysis of this variable.

The means and variances of the cognitive variables are presented in Table I separately for males and females. Similar sex effects have been observed in our previous studies of these measures which have used larger sample sizes [Luciano et al., 2001a, 2004a; Wainwright et al., 2004]. However, our larger studies show no sex differences in the variance of IQ subtests and no mean difference between males and females for the reading tests; additionally, sex effects for all MAB IQ subtests and inspection time are significant, with increased performance by males. The observation of higher than average mean IQ scores in our sample may be an artefact of using non-Australian norms. As the digit symbol mean score is consistent with the average normative WAIS-R score, this indicates that the finding is MAB-specific.

Linkage and Association

The distribution of alleles for each triplet repeat locus in the twin sample (includes both DZ co-twins and a single MZ co-twin) is shown in Figure 1. These frequency distributions were similar to those reported in other studies focusing on healthy individuals of Caucasian descent [e.g., Watkins et al., 1995; Takano et al., 1998]. MJD was shown to have the most variation with 21 alleles and a heterozygosity of 0.84, while SCA1 and DRPLA had 13 and 17 alleles, respectively, with heterozygosities of 0.75 and 0.80.

Tests of the significance of the QTL variance component and the association effect (mean regression) are presented in Table II. Linkage results were non-significant for all measures, except arithmetic, which demonstrated significant linkage to SCA1 ($P = 0.03$); although this result would not withstand correction for multiple testing. The lack of power for this analysis is evidenced by the wide confidence interval on the estimate of QTL variance of 32% (95% confidence intervals ranging 0–64%).

Tests of population stratification were significant for digit symbol (MJD, $P = 0.005$), vocabulary (DRPLA, $P = 0.03$), and verbal IQ (DRPLA, $P = 0.047$), but the within family tests of association for these measures were not significant. The QTDT total association results were consistent with Mx results for the association of SCA1 with arithmetic ($P < 0.05$), the combined alleles explaining 2.1% of variance (estimate derived from Mx). The direction of the effect was positive, so that longer repeats were associated with higher IQs. QTDT results also supported this linear effect with the linear trend line fitted to the chi-square values (from association analyses of the short, medium, and long allele binary categories) giving an R^2 of 0.92. Marginal

TABLE I. Means and Variances for the Cognitive Measures Separately for Males (N Range: 193–236) and Females (N Range: 234–260)

	Means		Variances	
	Female	Male	Female	Male
IQ raw scores				
Information	21.14	21.06	**23.06**	**34.22**
Vocabulary	17.60	17.18	25.85	23.62
Arithmetic	**12.06**	**12.58**	7.46	7.44
Spatial	**29.52**	**32.12**	**91.20**	**63.68**
Object assembly	12.62	13.24	13.98	14.36
Digit symbol	**65.34**	**55.28**	96.46	118.63
IQ scaled scores				
Verbal IQ	110.28	111.27	116.74	126.83
Performance IQ	**110.27**	**114.48**	279.66	245.43
Full-scale IQ	**111.04**	**113.76**	168.04	157.41
Reading				
Cambridge	**31.59**	**29.68**	63.37	57.99
Schonell[a]	**10.39**	**11.06**	11.61	11.95
Speed				
Choice RT[b]	27.47	27.43	0.47	0.59
Inspection time[c]	19.02	18.85	**2.93**	**4.35**

Significant differences between the sexes (P-value of 0.05) are indicated in bold.
Inspection time and RT variables have been multiplied by 10 to facilitate maximum-likelihood estimation.
[a]Reverse $\log_{10}$ transformed.
[b]Choice RT is the mean of $\log_{10}$ transformed RT trials.
[c]Log_{10} transformed.

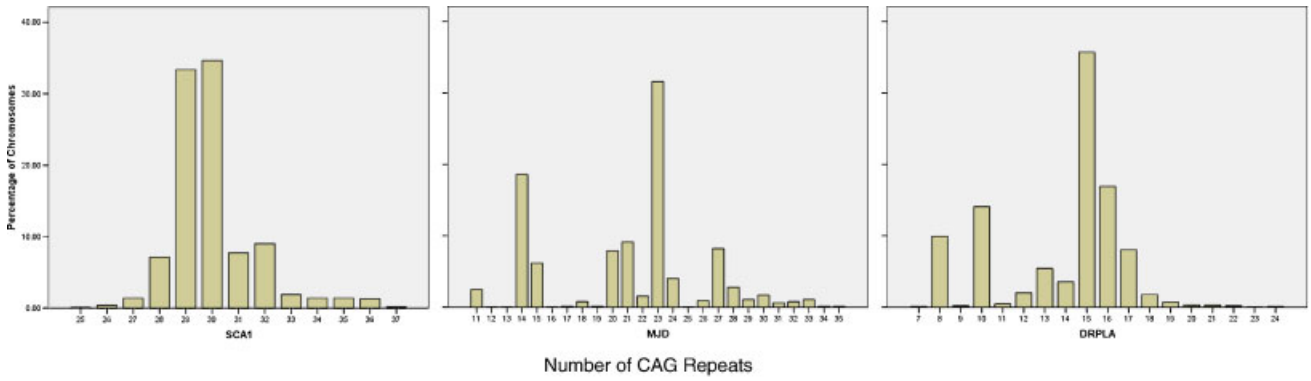

Fig. 1. Distribution of CAG repeat numbers in the SCA1, MJD, and DRPLA genotype data.

association of SCA1 repeat length with Cambridge Reading test scores ($P = 0.054$) was found in Mx but not QTDT, with the direction of the effect also being positive. While association of DRPLA and inspection time was supported in the QTDT analyses ($P = 0.01$), this result may be less reliable than that from Mx where unequal variances between males and females were explicitly modeled. The relationship between repeat length and IT was quadratic so that those with medium length alleles had faster IT scores.

DISCUSSION

This is the first report to characterize the relationship of trinucleotide repeat length of the markers predisposing to SCA1, MJD, and DRPLA disorders with cognitive phenotypes in a large, non-clinical sample. With a maximum number of 229 DZ twin pairs for SCA1, our power to detect linkage at any of the triplet repeat marker loci was low, though the sample size was reasonable for detecting association [Risch and Teng, 1998]. Linkage of SCA1 to arithmetic was nominally significant, but no other linkage effects for the other markers or measures approached significance. Association of the CAG repeat loci with the measures was tested using a linear regression on number of CAG repeats. The only significant association—consistent across Mx and QTDT software packages—was for SCA1 and arithmetic. Interestingly, this relationship was positive which contrasts the findings in clinical samples that increased repeat length predicts increased severity of symptoms (i.e., poorer cognitive function). The significant association component of our joint linkage and association results suggests that either SCA1 or one or more variants in linkage disequilibrium with SCA1 influences arithmetic performance.

There is existing evidence implicating the region on 6p in which SCA1 lies in influencing cognition. For instance, a QTL for dyslexia has been mapped to 6p21 [Cardon et al., 1994] and association of the succinate-semialdehyde dehydrogenase gene (on 6p22) to IQ has been reported [Plomin et al., 2004]. The present study uncovered weak evidence for linkage to SCA1, but as the linkage was modeled in the presence of association it is unlikely that SCA1 is the causative gene. A genome-wide study conducted in a sample which partly includes participants from the present study shows suggestive linkage in a region near the SCA1 marker to arithmetic [Luciano et al., 2006], strengthening support that a marker in close proximity to SCA1 influences arithmetic. Unlike the linkage, the statistical power of our association tests was reasonable. If the positive association of SCA1 repeat length with arithmetic is a true effect, this suggests that a threshold exists at which having larger repeats becomes detrimental to cognitive performance. SCA1 disease genes show a CAG repeat range of 39–82, while the largest repeat length observed in our sample was 37. Obviously, this association requires replication in an independent sample to exclude spurious associations and given that we performed a large number of statistical tests, it is possible that the positive findings reflect type 1 error, especially in view of the counterintuitive direction of the association.

Our combined tests of linkage and association generally indicated that variation at the triplet repeat markers for SCA1, MJD, and DRPLA diseases did not influence measures of IQ, reading ability, or processing speed in a non-clinical population. The exception was arithmetic which showed a positive association with SCA1. While Cambridge reading and inspection time showed significant associations with SCA1 and DRPLA, respectively, the association results were quite inconsistent between software packages. Our results, then, suggest that length of the CAG repeats investigated do not influence variation in cognitive function when the expansion length is in the normal range. The CAG triplet repeat disorders show various clinicopathologies, and while we focused on cognitive function, it is possible that trinucleotide expansion length in the normal range or in other genes does influence other behavioral functions, symptoms of psychopathology, or motor function. Some research [e.g., Wang et al., 1996; Ritsner et al., 2002; Medland et al., 2005; Swift-Scanlan et al., 2005] supports the association between CAG repeats and risk of schizophrenia, bipolar disorder, and left-handedness, although these effects, like those found in the present study, require replication and further study.

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TABLE II. Chi-Squares (and *P*-values) for the Tests of Linkage (QTL) and Allelic Association (Mx: $r_{allele;}$) of the Triplet Repeat Markers to the Cognitive Measures

	SCA1				MJD				DRPLA			
	Mx		QTDT[a]		Mx		QTDT[a]		Mx		QTDT[a]	
	QTL (*P*)	r_{allele} (*P*)	r_{allele} (*P*)	%Var	QTL (*P*)	r_{allele} (*P*)	r_{allele} (*P*)	%Var	QTL (*P*)	r_{allele} (*P*)	r_{allele} (*P*)	%Var
IQ												
Information	0.73 (0.19)	1.36 (0.24)	0.78 (0.68)	0	0 (0.50)	0.09 (0.76)	0.05 (0.97)	0	0 (0.50)	0.28 (0.59)	1.86 (0.39)	0
Vocabulary	0 (0.50)	2.76 (0.10)	4.74 (0.09)	1	0 (0.50)	0.02 (0.90)	0.05 (0.97)	0.02	0 (0.50)	0.24 (0.62)	0.61 (0.74)	0.13
Arithmetic	**3.79 (0.03)**	**4.02 (0.04)**	**7.18 (0.03)**	2.1	0.70 (0.20)	.00 (0.95)	0.30 (0.86)	0.02	0 (0.50)	0.89 (0.34)	2.36 (0.31)	0.18
Object assembly	0 (0.50)	0.01 (0.92)	2.29 (0.32)	0	0 (0.50)	1.28 (0.26)	2.23 (0.33)	0.46	0 (0.50)	0.34 (0.56)	0.94 (0.62)	0.07
Spatial	0 (0.50)	1.98 (0.16)	1.71 (0.42)	0.25	0 (0.50)	1.22 (0.27)	1.38 (0.50)	0.66	0.27 (0.30)	0.81 (0.37)	3.81 (0.15)	0.07
Verbal IQ	1.97 (0.08)	2.42 (0.12)	4.91 (0.09)	1.31	0 (0.50)	0.02 (0.90)	0.11 (0.95)	0.05	0 (0.50)	0.85 (0.35)	1.15 (0.56)	0.11
Performance IQ	0 (0.50	0.12 (0.73)	0.07 (0.97)	0.07	0 (0.50)	1.71 (0.19)	1.94 (0.38)	0.70	0.25 (0.31)	0.01 (0.93)	2.82 (0.24)	0
Full-scale IQ	1.67 (0.10)	0.91 (0.34)	1.79 (0.41)	0.50	0 (0.50)	0.67 (0.41)	0.66 (0.72)	0.16	0 (0.50)	0.46 (0.50)	2.47 (0.29)	0.02
Digit symbol	0 (0.50)	0.38 (0.54)	0.79 (0.67)	0.04	0.07 (0.39)	1.02 (0.31)	1.15 (0.56)	0.44	0 (0.50)	0 (0.95)	1.67 (0.43)	0.01
Reading												
Cambridge	0 (0.50)	**3.70 (0.05)***	3.34 (0.19)	1.58	0 (0.50)	0.23 (0.63)	0.13 (0.94)	0.04	0 (0.50)	0.03 (0.86)	0.17 (0.92)	0
Schonell	0.04 (0.42)	1.97 (0.16)	2.33 (0.31)	0.76	0.67 (0.20)	0.01 (0.93)	0.37 (0.83)	0.03	0 (0.50)	1 (0.32)	2.97 (0.23)	0.36
Speed												
Inspection time	0 (0.50)	0.27 (0.60)	0.12 (0.94)	0	0.13 (0.36)	0.01 (0.92)	2.81 (0.24)	0	0.09 (0.38)	0.17 (0.68)	8.47 (0.01)	0
Choice RT	0 (0.50)	0.05 (0.81)	2.55 (0.28)	0	1.79 (0.09)	1.29 (0.25)	1.16 (0.56)	0.34	0 (0.50)	2.47 (0.12)	0.78 (0.68)	0.81

The percentage of variance (%Var) in the trait explained by joint allele effects was estimated from Mx. Significant effects indicated in bold.
[a]2 df test.
*0.054

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