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Failure to Replicate an Association of a LINE-1 Element in ERI1 Exoribonuclease Family Member 3 (*ERI3*) with Schizophrenia

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We reported previously that a LINE-1 element in the *ERI3* gene was more common among lymphoblastoid blood DNA samples from European-American patients diagnosed with schizophrenia (PDS) than those from controls (Doyle *et al*, 2017).

We sought to replicate our original finding in a second set of blood DNA samples from PDS and controls. De-identified DNA from EBV-transformed lymphoblastoid cell lines of European-American subjects who met DSM-IV criteria for schizophrenia ($n = 1665$) and controls ($n = 997$) were acquired from the Rutgers University Cell and DNA Repository (Infinite Biologics, Piscataway, NJ, USA). Two microliters of DNA at 20 ng/μl in sterile water were used in genotyping experiments. A Taqman-based allelic discrimination assay was used, as described (Doyle *et al*, 2017), to genotype these additional PDS and control samples for the presence or absence of the LINE-1 element within *ERI3*.

This analysis revealed 44 PDS and 37 controls heterozygous for the LINE-1 element, corresponding to minor allele frequencies (MAF) of ~1.3% in the PDS population and ~1.86% in the control population ($X^2 = 2.376$, $p = 0.123$). Notably, the MAFs for these data were in the opposite direction from our original analysis in which PDS had a MAF of ~1.9% and controls had a MAF of ~1.3% ($X^2 = 4.323$, $p = 0.0376$; Doyle *et al*, 2017). When data from the two sample sets were combined (PDS, $n = 2950$; controls, $n = 3302$), the MAFs were ~1.6% for the PDS population and ~1.4% for the control population ($X^2 = 0.309$, $p = 0.578$).

There is currently no evidence to suspect population stratification or study collection bias between the control or PDS samples employed in our original or replication studies because both the control and PDS populations were collected through the NIMH genetics initiative from European-American individuals across the USA. All PDS samples came from individuals diagnosed by the DSM-IV criteria, and controls were from individuals who screened negative for psychiatric disorders by self-report questionnaires. Despite the relatively large sample sizes studied, it is more likely that the low MAF of the genotyped *ERI3* LINE-1 element resulted in skewed outcomes in the original and replication studies. Therefore, in contrast to our original finding (Doyle *et al*, 2017), we conclude that this particular LINE-1 element within the *ERI3* gene does not associate with the schizophrenia phenotype in European-Americans.

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