



# Genetic predisposition to advanced biological ageing increases risk for childhood-onset recurrent major depressive disorder in a large UK sample

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## ABSTRACT

**Background:** Previous studies have revealed increased biological ageing amongst major depressive disorder (MDD) patients, as assayed by shorter leukocyte telomere lengths (TL). Stressors such as childhood maltreatment are more common amongst MDD patients, and it has been suggested that this might contribute to shorter TL present amongst patients. However, to our knowledge, no study has yet tested for reverse causality, i.e. whether a genetic predisposition to shorter TL might predispose to MDD or an earlier onset of MDD.

**Methods:** This study used a Mendelian randomisation design to investigate if shortened TL might increase risk for recurrent MDD in a relatively large UK sample (1628 MDD cases, 1140 controls). To achieve this, we used a subset of our sample, for which TL data was available, to identify a suitable instrumental variable. We performed single nucleotide polymorphism (SNP) genotyping on rs10936599, a SNP upstream of telomerase RNA component (*TERC*), and rs2736100, a SNP within telomerase reverse transcriptase (*hTERT*), and attempted to replicate findings which identified these SNPs as predictors of TL. After which, we performed regressions to test if genetic risk for shortened TL increased risk for MDD, childhood-onset MDD or childhood/adolescent-onset MDD.

**Results:** T-carriers of rs10936599 demonstrated shorter TL compared to CC-carriers ( $p \leq 0.05$ ; 3% of variance explained) and was subsequently used as our instrumental variable. We found that the T-allele of rs10936599 predicted increased risk for childhood-onset MDD relative to controls ( $p \leq 0.05$ ), and increased risk for childhood-onset MDD relative to adult-onset MDD cases ( $p \leq 0.001$ ), but rs10936599 did not predict adult-onset MDD risk.

**Limitations:** Limitations include a relatively small sample of early-onset cases, and the fact that age-of-onset was ascertained by retrospective recall.

**Conclusion:** Genetic predisposition to advanced biological ageing, as assayed using rs10936599, predicted a small, but significant, increased risk for childhood-onset recurrent MDD. Genetic predisposition to advanced biological ageing may be one factor driving previously reported associations (or lack of associations) between shorter TL and MDD. Our results also suggest that the telomerase enzyme may act as a potentially important drug target for the prevention of childhood-onset MDD, at least in a subset of cases. Future studies should attempt to replicate our findings in a larger cohort.

## 1. Introduction

Telomeres are capping structures of tandem TTAGGG nucleotide

repeats found at the end of chromosomes (Eitan et al., 2014). During each cell division, the ends of chromosomes shorten as part of a natural consequence of replication (Aubert and Lansdorp, 2008). Telomeres

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<http://dx.doi.org/10.1016/j.jad.2017.01.017>

Received 30 September 2016; Received in revised form 6 January 2017; Accepted 19 January 2017

Available online 16 February 2017

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function as sacrificial, non-coding DNA buffers, which degrade instead of inward, coding DNA regions (Allsopp et al., 1995). Eventually, in cells which have undergone many divisions, telomeres become so short that the coding DNA regions within the chromosome are no longer protected, and their degradation triggers the end of that cell's ability to replicate (Eitan et al., 2014). Telomere length (TL) subsequently acts as marker for 'cellular age' or 'biological age'; with shortened telomeres representing older cells, and commonly, older individuals (Benetos et al., 2001). However, unlike chronological age, biological ageing can be moderated by environmental and genetic factors (e.g. Tyrka et al., 2010; Codd et al., 2013), meaning two unrelated individuals of the same chronological age, may not be the same age biologically. Shortened leukocyte TL, relative to one's age, has been associated with an increased risk to various diseases, generally poorer physical and psychiatric health, and higher mortality (Simon et al., 2006; Fitzpatrick et al., 2007; Kao et al., 2008; Yu et al., 2008; Okereke et al., 2012; Lindqvist et al., 2015; Rode et al., 2015; Darrow et al., 2016).

Evidence suggests that an increased stress hormone response (cortisol levels), oxidative stress, and immuno-inflammatory activation, could be responsible for some of these inter-individual differences in TL observed within the population (von Zglinicki, 2002; Jurk et al., 2014; Gotlib et al., 2015). A disease which has been linked to all three of these telomere-eroding factors, is major depressive disorder (MDD; Cowen, 2002; Michel et al., 2012; Martin et al., 2015). Indeed, most previous studies (e.g. Simon et al., 2006; Lung et al., 2007; Elvsåshagen et al., 2011; Hoen et al., 2011; Garcia-Rizo et al., 2013; Verhoeven et al., 2014) but not all (e.g. Wolkowitz et al., 2011; Teyssier et al., 2012; Needham et al., 2015; Schaakxs et al., 2015), have revealed shortened leukocyte TL amongst MDD patients with some studies suggesting that shortened TLs may be observed most pervasively in recurrent depressed cases only (e.g. Elvsåshagen et al., 2011). Interestingly, a history of childhood maltreatment (a risk factor for MDD) also predicts shortened TL in adulthood (Tyrka et al., 2010; O'Donovan et al., 2011; Kananen et al., 2010; Shalev et al., 2014). This has generated hypotheses which suggest that stress may simultaneously precipitate risk for MDD, and an advancement in telomere shortening; contributing to the increased risk of comorbid ageing-related disorders present amongst MDD patients; including cardiovascular disease, obesity, and type-2 diabetes (Zhang et al., 2014). Consequently, it's been hypothesized that negative environmental factors, such as stress, are primarily responsible for shortened leukocyte TL present amongst MDD patients. However, few reports have considered the possibility of reverse causality, i.e. whether a predisposition to advanced biological ageing (i.e. genetic factors) may also predispose an individual to MDD.

A recent genome-wide association study (GWAS) revealed single nucleotide polymorphisms (SNPs) predictive of relative TL; with the two most significant SNPs rs10936599 and rs2736100, located upstream or within the telomerase encoding genes telomerase RNA component (*TERC*) and telomerase reverse transcriptase (*hTERT*), respectively (Codd et al., 2013). These SNPs are hypothesized to affect the functionality of telomerase, an enzyme with the ability to reverse telomere shortening, by adding TTAGGG sequences to the existing telomere ends (Codd et al., 2013). Thus, SNPs coding for this enzyme represent functionally discrete factors with pervasive effects on long-term TL maintenance. They also represent a means by which we can test if inherent genetic factors influencing TL maintenance predict risk for MDD.

Mendelian randomisation is an 'instrumental variable analysis' and is the formal term used to describe a situation where we test whether genetic factors (a 'instrumental variable') contributing to a biological factor correlating with a disease (e.g. shortened telomere lengths) directly predicts the disease itself (e.g. MDD; Sheehan et al., 2008; Smith and Hermani, 2014). If it does, this would suggest that the biological correlate may be involved in causing the disease, but if it does not, it may indicate it is an effect of having the disease, or that an

independent factor impacts upon both the biological correlate and the disease.

Within this study we adopted a Mendelian randomisation design to investigate whether a genetic predisposition to advanced biological ageing (via rs10936599, rs2736100) predicted an increased risk of recurrent MDD in a large UK sample. As MDD is generally an adult-onset disorder (Kessler et al., 2001) and has been repeatedly associated with biological ageing and risk for ageing-related disease (Zhang et al., 2014), we also tested whether a genetic predisposition to advanced biological ageing might shorten the time it takes for MDD to present itself, i.e. increase risk for childhood ( $\leq 12$  years old) or childhood/adolescent-onset ( $\leq 17$  years old) MDD. These earlier-onset time points were chosen because they represent key, well-characterised, developmental milestones and times during which there are increased rates of cellular division, relative to adulthood. Therefore, phenotypes which result from particular cell populations having a limited proliferative potential (as a result of advanced biological ageing), may begin to precipitate at these earlier time points.

To achieve our aims effectively, we first attempted to replicate Codd and colleagues' findings using relative TL data from an independent cohort (and a subset of our genetic cohort), and to determine the best genetic model and/or combination of the two SNPs (rs10936599 and rs2736100) to use as our 'instrumental variable'. Secondly, using a large UK cohort of 1628 recurrent MDD cases and 1140 control subjects, we tested whether the relative frequency of risk alleles for shorter TL was greater amongst MDD cases, or early-onset MDD cases.

## 2. Methods

### 2.1. Subject information

Recurrent MDD cases were recruited from the UK component of RADIANT, described previously (Lewis et al., 2010). Controls (n=1140) were recruited from the Depression case-control study (n=1040; Cohen-Woods et al., 2009), and from the South East London Community Health Study (SELCoH, n=100; Hatch et al., 2011). For a full break down, see Table 1.

### 2.2. Recurrent MDD cases

RADIANT is an umbrella term for three studies which sought to understand genetic risk for MDD and factors affecting response to treatment; this comprised of the Depression Network (DeNT) study (Farmer et al., 2004), the Depression Case-Control (DeCC) study (Cohen-Woods et al., 2009) and the Genome-Based Therapeutic Drugs for Depression (GENDEP) study (Uher et al., 2009). Within these multi-centre clinical studies, we selected only those recruited from the UK who had at least two episodes of major depression of at least moderate severity, in order to create a homogeneous sample. Diagnosis of MDD was ascertained using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview in all three studies

**Table 1**

Descriptive statistics of case/control subjects within study; including total number of participants, mean age at interview (with Standard Deviation) and numbers within each gender.

Study	N	Age	Males	Females
DeCC cases	1248	47 (SD = 12.34)	380	868
GENDEP cases	83	46 (SD = 12.3)	29	54
DeNT cases	297	46 (SD = 10.9)	71	226
Total Cases	1628	46.26 (SD = 10.8)	480	1148
DeCC controls	1040	45 (SD = 9.8)	429	611
SELCoH controls	100	51 (SD = 16.9)	49	51
Total Controls	1140	46 (SD = 10.8)	481	669
Total	2768	46 (SD = 11.6)	958	1811

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