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Genetic Variation Shapes MECP2-Dependent Vulnerability to Stress-Related Adverse Mental Health Trajectories in Women

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Abstract

The multi-factorial origin of stress vulnerability remains incompletely understood, hampering the implementation of targeted prevention. As interplays between genes and environment lie at the basis of individual variability, epigenetic mechanisms are considered important mediators of adverse mental health trajectories following stressful experiences. We have previously demonstrated that the X-linked epigenetic factor Methyl-CpG binding protein 2 (MECP2) plays a role in stress susceptibility, with dysfunctional variants in transgenic mice and its downregulation in human populations being associated with a lower ability to cope with adverse events. By leveraging a study of the Italian Twin Registry on mental health during the COVID-19 pandemic, the present study explored whether a genetic component that accounts for individual variability in *MECP2* expression may shape risk of developing stress-related mental health deterioration. We report an association between homozygosity for the minor allele of the rs2734647, a single nucleotide polymorphism (SNP) in the *MECP2* 3′-untranslated region (UTR) that has been linked to allele-specific *MECP2* downregulation, and increased symptoms of COVID-19 pandemic-related depression, anxiety and distress in women. Our findings provide additional evidence for the emerging role of MECP2 in stress vulnerability, unveiling the contribution of genetic variation within the *MECP2 locus* to adverse mental health outcomes in women.

Keywords: stress-related disorders; SARS-CoV-2; DNA methylation; sex differences; single nucleotide polymorphisms; twins

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1. Introduction

Exposure to stressful life events (SLEs) is a common and well-recognized risk factor for poor health outcomes, including reduced mental wellbeing. The shared experience of both the direct threat of illness and indirect socioeconomic burden brought by the COVID-19 pandemic drew renewed attention to the impact of stress on mental health, and the need to implement prevention programs, as we are now facing peak cases of depression and anxiety worldwide [1].

Stress' impact changes across individuals based on multiple factors encompassing both genetic and environmental influences on the ability to cope with life's adversities. The complexity of gene-environment interactions and a limited understanding of the polygenic underpinnings of stress vulnerability, however, have hindered our ability to identify and address the needs of individuals at higher risk of adverse mental health outcomes [2].

Being at the crossroads between genes and the environment, epigenetic mechanisms have been in the spotlight of stress vulnerability research [3]. Because they can affect multiple biological pathways simultaneously, alterations in epigenetic effectors are also likely to influence complex multigenic traits. Among the multiple actors of the epigenetic machinery, the Methyl-CpG binding protein 2 (MECP2) is emerging as a compelling candidate in the regulation of susceptibility to environmental disturbances throughout life [4]. MECP2 is an X-linked environment-sensing protein, which binds to methylated DNA and performs pleiotropic functions aimed at regulating gene expression in the brain. Preclinical studies highlight that MECP2 is fundamental to successfully adapt to stress, as a reduction in MECP2 activity is sufficient to mimic the effects of exposure to early adversities [5] and treatments alleviating stress-induced behavioural impairments require functional MECP2 [6,7].

Consistently, we have shown that transgenic mice carrying a dysfunctional variant of the *MECP2* gene display an aberrant stress response and are at increased risk of developing behavioural and physiological alterations in the aftermath of traumatic experiences, featuring symptoms of post-traumatic stress disorder (PTSD) [8]. Subsequent investigations corroborated these findings in human populations, as we found that reduced blood levels of *MECP2* are associated with poorer ability to cope with stressful or traumatic experiences in both subclinical groups and psychiatric patients [9,10]. Building on this evidence, reduced *MECP2* expression emerges as a stress vulnerability factor that marks the risk of adverse mental health outcomes in response to stressful experiences. However, the source of the reduction in *MECP2* expression in human populations at risk of developing stress-related disorders remains to be determined.

As a housekeeping protein carrying out fundamental functions, *MECP2* levels are tightly regulated at both transcriptional and post-transcriptional levels, through mechanisms such as DNA methylation of cis-regulatory elements and the action of multiple trans-acting factors. Multiple noncoding elements within the *MECP2* gene were demonstrated to have important regulatory functions [11]. Of note, beyond rare mutations in functional regions leading to severe neurological outcomes such as Rett syndrome and neonatal encephalopathy, more common variants occurring in noncoding regions of the *MECP2 locus* have also been described, in association with milder phenotypic spectra [12,13]. Among these variants, the rs2734647 single nucleotide polymorphism (SNP) in the *MECP2* 3′-untranslated region (UTR) has been linked to allele-specific downregulation of *MECP2* expression in carriers of the minor allele, due to enhanced interaction with suppressing miRNAs [14], highlighting the possibility that a genetic component that accounts for individual variability in *MECP2* expression may shape the MECP2-dependent risk of developing stress-related pathologies.

In the present study, we investigated associations between the minor allele of SNP rs2734647 and depressive and anxiety symptom clusters and pandemic-related distress. Leveraging the Italian Twin Registry (ITR) role as a reliable sentinel population for monitoring health and disease trends in Italy [15], the study was performed in individuals from the ITR enrolled to participate in a survey on the mental health consequences of the COVID-19 pandemic.

2. Results

The investigated sample consisted of 120 women and 52 men. The age range was 25–82 years, with a mean age of 52.9 (SD = 15.2 years). Participants were distributed across the country, ensuring representativeness of areas differently affected by the pandemic. Descriptive characteristics of the sample and scores on each mental health scale are reported in Table 1, separately for women and men. Men exhibited significantly lower levels of pandemic-related stress, anxiety, and depression compared to women, as measured,

respectively, by the Impact of Event Scale–Revised (IES-R, $p = 0.01$), the State-Trait Anxiety Inventory–6 (STAI-6, $p < 0.001$) and the Patient Health Questionnaire-9 (PHQ-9, $p = 0.01$) self-report measures (Table 1).

Table 1. Sociodemographic and psychological characteristics of the participants.

	Females (N = 120)		**Males (N = 52)**	
	N	**% or Mean (SD) Min–Max**	**N**	**% or Mean (SD) Min–Max**
Age, years				
N	120		52	
Mean (SD)		51.90 (14.74)		55.35 (16.07)
Min–Max		30–82		25–8
Educational level				
Primary/Secondary school	9	9.18%	4	9.30%
High school	44	44.90%	12	27.91%
Bachelor's and master's degree	36	36.73%	18	41.86%
Postgraduate master	9	9.18%	9	20.93%
Area of residence				
North	34	28.57%	17	32.69%
Centre	78	65.55%	31	59.62%
South or Islands	7	5.88%	4	7.69%
Zygosity				
Monozygotic (MZ)	81	67.50%	29	55.77%
in pairs [a]	56	-	16	-
unpaired [b]	25	-	13	-
Dizygotic (DZ)	39	32.5%	23	44.23%
in pairs (same sex) [a]	18	-	8	-
in pairs (opposite sex) [a]	7	-	7	-
unpaired (same sex) [b]	8	-	2	-
unpaired (opposite sex) [b]	6	-	6	-
Stress, IES-R Score				
N	119		51	
Mean (SD)		22.69 (13.96)		16.55 (14.50)
Min–Max	30	0–60		0–52
Symptoms of PTSD, Score ≥ 33		25.21%	7	13.73%
Depression, PHQ-9 Score				
N	120		51	
Mean (SD)		4.95 (4.68)		3.07 (4.09)
Min–Max	16	0–23		0–15
Symptoms of depression, Score ≥ 10		13.33%	5	9.80%
Anxiety, STAI-6 Score				
N	117		52	
Mean (SD)	84	46.53 (12.19)		39.44 (11.57)
Min–Max		20–80		20–80
Symptoms of anxiety, Score ≥ 40		71.79%	23	44.23%

Abbreviations: SD, Standard Deviation; IES-R, Impact of Event Scale–Revised; STAI-6, State-Trait Anxiety Inventory–6; PHQ-9, Patient Health Questionnaire-9; PTSD, Post-Traumatic Stress Disorder; MZ, monozygotic; DZ, dizygotic; Symbols: [a] individual twins from complete pairs (i.e., twins and cotwins are included in the study); [b] only one twin from the pair is included in the study.

The genotype and allele frequencies of the rs2734647 *MECP2* SNP are in line with those observed in the literature [14]: CC = 60.8%, N = 73, of which 46 are twins in pairs

and 27 independent twins; CT = 34.2%, N = 41, 24 in pairs and 17 independent twins; TT = 5%, N = 6, 2 in a pair, 4 independent twins in women; C = 80.8%, N = 42, 22 in pairs and 20 independent twins, T = 19.2%, N = 10, 2 in a pair, 8 independent twins in men. The socio-demographic characteristics of the sample, stratified by sex, did not significantly differ according to genotype. Women carrying the TT genotype showed higher scores across all mental health scales, compared to the CC genotype (IES-R 37.24 vs. 22.60, $p = 0.01$; PHQ-9 11.33 vs. 4.75, $p = 0.001$; STAI-6 56.67 vs. 47.29, $p = 0.05$). In particular, regression models (Table 2), adjusted for age and accounting for the non-independence of observations, showed that women homozygous for the T variant have an average increase of about 14 points on the IES-R scale ($\beta = 14.49$, $p = 0.04$), 7 points on the PHQ-9 scale ($\beta = 6.90$, $p = 0.02$), and 10 points on the STAI-6 scale ($\beta = 10.08$, $p = 0.007$). The T variant in heterozygosity (CT) did not appear to influence the mean scores of the three scales. In contrast, regression models in men did not reveal significant associations between the T allele and psychological outcomes (Table 2). Compared with carriers of the C allele, men carrying the T allele showed no significant differences in IES-R ($\beta = -4.79$, $p = 0.38$), PHQ-9 ($\beta = -0.38$, $p = 0.80$), or STAI-6 ($\beta = -3.70$, $p = 0.35$) scores. Sensitivity analyses showed no major differences in the results when randomly excluding individual twins or pairs from the analysis.

Table 2. Linear regression models estimating the association between *rs2734647* genotypes and psychological scale scores in women and men.

Sex	Model/Genotype	Beta Coefficient	Robust SE	*p*-Value	95% Confidence Interval
FEMALE	MODEL 1–Stress (IES-R Score)				
	CC (Reference group)	—	—	—	—
	CT	−1.87	2.95	0.53	−7.74; 4.00
	TT	14.49	7.05	0.04	0.47; 28.52
	Intercept	21.75	4.91	<0.001	11.98; 31.52
	MODEL 2–Depression (PHQ-9 Score)				
	CC (Reference group)	—	—	—	—
	CT	−0.43	0.73	0.56	−1.88; 1.02
	TT	6.90	2.98	0.02	0.97; 12.82
	Intercept	6.70	1.40	<0.001	3.91; 9.49
	MODEL 3–Anxiety (STAI-6 Score)				
	CC (Reference group)	—	—	—	—
	CT	−3.70	2.56	0.15	−8.81; 1.40
	TT	10.08	3.64	0.007	2.84; 17.31
	Intercept	51.26	4.33	<0.001	42.63; 59.88
MALE	MODEL 1–Stress (IES-R Score)				
	C (Reference group)	—	—	—	—
	T	−4.79	5.45	0.38	−15.82; 6.24
	Intercept	−0.37	7.81	0.96	−16.19; 15.44
	MODEL 2–Depression (PHQ-9 Score)				
	C (Reference group)	—	—	—	—
	T	−0.38	1.52	0.80	−3.45; 2.69
	Intercept	2.07	2.45	0.40	−2.90; 7.04
	MODEL 3–Anxiety (STAI-6 Score)				
	C (Reference group)	—	—	—	—
	T	−3.70	3.89	0.35	−11.56; 4.16
	Intercept	37.57	6.86	<0.001	23.69; 51.46

All models were adjusted by age; regression models account for the non-independence of observations (twin pairs); Abbreviations: SE, Standard Error.

3. Discussion

In the present work, we explored possible genetic contributions to the emerging connection between MECP2, a key reader of the epigenetic machinery, and risk of mental deterioration following stressors. We report an association between homozygosity for the minor allele of SNP rs2734647 and increased symptoms of COVID-19 pandemic-related depression, anxiety and distress in women, suggesting that genetic variation within the *MECP2 locus* may shape differential vulnerability to stress exposure. By evidencing a genetic association between a common variant in the *MECP2 locus* and vulnerability to the detrimental effects of stress, the present study offers a novel genetic marker that could be exploited for population stratification to predict risk before symptoms appear [16]. The present results are in line with our previous studies linking reduced *MECP2* expression to stress vulnerability in clinical and non-clinical populations [9,10]. Indeed, the minor allele (T) of the rs2734647 *MECP2* variant is known to determine preferential miRNA binding and has been associated with *MECP2* expression downregulation [14]. It cannot be ruled out, however, that more than one variant in this genomic region contributes to *MECP2* expression, as rs2734647 is in tight linkage disequilibrium with other SNPs in the *MECP2* gene [12]. Of note, since MECP2 acts as a master experience-dependent regulator [4], environmental stimuli are also important contributors to lasting modulation of *MECP2* expression via stable epigenetic modifications at the *MECP2 locus*. For instance, we previously outlined that exposure to childhood adversities influences the association between *MECP2* downregulation and stress susceptibility [9,10], suggesting MECP2 as a key player in shaping the long-term effects of early life experiences. Additional studies examining further genetic and environmental impacts on *MECP2* levels are thus likely to expand present results and reveal novel scenarios for MECP2-dependent vulnerability. In line with our previous findings that MECP2-dependent vulnerability to stressors may vary by sex [9,10], we observed that men carrying the T allele did not display higher levels of psychological distress compared to C carriers. Sex differences in heritability of stress-related disorders could explain the blunted phenotypic manifestation of the T allele in men, as genetic factors account for a higher proportion of risk in females [17]. Furthermore, as emerging evidence implicates MECP2 involvement in neuroimmune regulation and dysregulated HPA axis reactivity [8,18], two mechanisms thought to contribute to the greater female vulnerability to stress-related disorders [19], common genetic variants determining minor alterations in MECP2 function may have more pronounced consequences in women than in men. However, as we previously observed that men exposed to traumatic experiences display increased levels of *MECP2* [10], the possibility that the stress caused by the pandemic might have triggered *MECP2* upregulation via sex-dependent mechanisms cannot be excluded. Beyond these considerations, it should be noted that, in line with the sex bias underlying vulnerability to stress-related disorders, males experienced a smaller pandemic-related mental health impact compared to females [20], which may have reduced the likelihood of detecting significant differences in males. Further studies aimed at investigating the interplay between *MECP2* genetic variability, its downstream molecular effects and stress-related psychological outcomes in both sexes may help clarify whether MECP2 contributes to stress susceptibility through shared or sex-specific mechanisms, thereby advancing our understanding of interindividual differences in stress responses [16].

Interestingly, zygosity appears to play a pivotal role in MECP2-dependent vulnerability to stressors. Indeed, as we previously outlined in transgenic mouse studies [8], phenotypic expression is observed when the T allele is present in homozygosity, as heterozygous women displayed similar levels of psychological distress compared to women homozygous for the C allelic variant. Preferential silencing of the T allele due to skewed X chromosome inactivation (XCI) or somatic selection of C allele-expressing cells might explain the phenotype

of heterozygous women [21]. Alternatively, the C allele may be in linkage disequilibrium with other genetic variants [12] exerting protective effects against stress-related psychological disturbances, potentially contributing to the absence of a detectable association in heterozygous women. Whether the rs2734647 polymorphism is implicated in one of these processes remains to be elucidated.

Overall, the present findings highlight a novel association between a functional X-linked *MECP2* SNP and adverse mental health outcomes in women. As gene association studies comprising the X chromosome are still limited [22], the present work underlies the importance of addressing X chromosome-related genes to fully disclose the profound genetic complexity of stress vulnerability. Of note, our study was performed on a general population cohort of twins from the Italian Twin Registry [15], who were easily and rapidly contacted to investigate the mental health effects of the pandemic. Because twins have by definition shared environments, this design has the advantage of allowing the detection of true genetic link with increased confidence, reducing the chance of evidencing only spurious associations emerging from population stratification. Also, the pandemic-related public health emergency, in which data collection occurred, likely amplified the variability in mental health outcomes among individuals [23], increasing the penetrance and expressivity of risk gene variants. This exceptional context may thus have contributed to revealing genotype-dependent differences in psychological response that would otherwise have remained less detectable, thereby advancing our understanding of the multifactorial mechanisms underlying interindividual differences in vulnerability to stress-related disorders [16]. Importantly, the limited precision coming from smaller sample sizes of the male subgroup and of TT women warrants cautious data interpretation, and validation in independent cohorts is needed to confirm the robustness and generalizability of the present results. Nevertheless, the replication of the genetic association across three distinct symptom measures and consistency with previous findings of a sex-stratified link between MECP2 and increased symptoms of anxiety, depression and PTSD across different human cohorts strengthens confidence in the findings.

The present results contribute additional evidence to the emerging role of MECP2 in vulnerability to stress-related disorders, unveiling a possible contribution of genetic variability to pro-risk *MECP2* downregulation. Future studies devoted to dissecting the interaction between MECP2-related molecular mechanisms and environmental factors in both females and males could help in better understanding the pathomechanisms underlying stress-related disorders and their sex bias, hopefully contributing to allow timely access to targeted preventive programs.

4. Materials and Methods

4.1. Study Design and Participants

The study included twins from the population-based ITR, who were contacted during the most critical phase of the COVID-19 emergency in Italy, to evaluate the impact of the pandemic on mental health. Data were collected between June and December 2020 through the LimeSurvey online platform. For the purposes of this study, we included in the analysis only individuals aged 18 years or older who participated in the COVID Survey [24] and for whom genotyping data were available in the ITR database.

4.2. Psychological Assessment

To assess depressive and anxiety symptom clusters and distress related to the SARS-CoV-2 health emergency, self-report instruments were employed. In particular, the subjective distress experienced during the past seven days was scored through the IES-R [25], a questionnaire that includes 22 items rated on a 5-point scale from 0 = “not at all” to

4 = "extremely" (range 0–88). To anchor the IES-R scale within the context of the pandemic, the items were modified to refer specifically to the COVID-19 pandemic. State anxiety was evaluated in the same subjects with the STAI-6 [26,27], which includes 6 items rated on a 4-point scale from 1 = "not at all" to 4 = "very much" (this scale was appropriately converted to the score range 20–80 as in the full 20-item scale). Depressive traits were measured using the PHQ-9 [28,29], which includes 9 items rated on a 4-point scale from 0 = "never" to 3 = "almost every day" (range 0–27) assessing symptom severity over the previous two weeks. For all three instruments, higher scores indicate greater symptom severity. Missing values at specific items were replaced with the mean values of the items when missingness did not exceed 10% of total items in a scale (i.e., 2 missing for IES-R, 1 missing for both STAI-6 and PHQ-9). According to established cut-offs, participants scoring ≥33 on the IES-R, ≥40 on the STAI-6 or ≥10 on the PHQ-9 are considered to be at risk of post-traumatic stress, anxiety or depression, respectively.

4.3. DNA Collection, Genotyping and Quality Control

Genotyping data for rs2734647 were obtained using the Global Screening Array (GSA-24 v3.0 + Multi-Disease) BeadChip (Illumina, San Diego, CA, USA), performed on genomic DNA extracted from saliva samples collected using Oragene kits (DNA Genotek, Ottawa, ON, Canada). Genomic coordinates and allele annotations were based on the human reference genome GRCh37/hg19, forward orientation, with C designated as the reference allele for rs2734647. The GenTrain 3.0 algorithm of GenomeStudio 2.0 software was used for genotyping calling with a 0.15 no-call threshold. No subjects had a missing rs2734647 genotype. Given the X-linked location of *MECP2*, the observed genotype frequencies were compared, by chi-square tests, with those expected under Hardy–Weinberg equilibrium (HWE) only in female participants, considering one twin per pair. No significant deviations from HWE were observed ($p = 0.27$). Male participants, being hemizygous, were considered only for allele frequency calculations.

4.4. Statistical Analysis

All analyses were conducted, treating twins as individual participants. Sociodemographic characteristics and mental health scores were compared across genotype groups using chi-square tests for categorical variables and Student's *t*-tests for continuous variables. Subsequently, separate linear regression models were fitted to examine the association between participants' genotypes (independent variable) and each of the three mental health measures (dependent variables). All regression models were adjusted for age and used robust estimators to account for the non-independence of twin observations within pairs. Moreover, sensitivity analyses were performed by using a leave-one-family-out approach; this allowed us to assess whether the findings were particularly sensitive to individual participants or twin pairs. Sex was self-reported by participants and used to stratify the analyses.

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Data Availability Statement: Due to ethical and confidentiality restrictions, the data are not publicly available. Data may be made available upon reasonable request to the corresponding author, subject to institutional approval and a data-sharing agreement.

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Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

The following abbreviations are used in this manuscript:

MECP2	Methyl-CpG Binding Protein 2
SNP	Single Nucleotide Polymorphism
UTR	Untranslated Region
SLEs	Stressful Life Events
PTSD	Post-Traumatic Stress Disorder
ITR	Italian Twin Registry
IES-R	Impact of Event Scale–Revised
STAI-6	State-Trait Anxiety Inventory–6
PHQ-9	Patient Health Questionnaire-9
GSA	Global Screening Array
HWE	Hardy–Weinberg Equilibrium
XCI	X-Chromosome Inactivation
SD	Standard Deviation
SE	Standard Error
DNA	Deoxyribonucleic Acid
miRNA/miRNAs	microRNA/microRNAs

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