Published in final edited form as:
Mol Psychiatry. 2012 March ; 17(3): 236–237. doi:10.1038/mp.2011.132.

Therapygenetics: The *5HTTLPR* and response to psychological therapy

Thalia C Eley[1], **Jennifer L Hudson**[2], **Cathy Creswell**[3], **Maria Tropeano**[1], **Kathryn J Lester**[1], **Peter Cooper**[3], **Anne Farmer**[1], **Cathryn M. Lewis**[1], **Heidi J Lyneham**[2], **Ronald M Rapee**[2], **Rudolf Uher**[1], **Helena MS Zavos**[1], and **David A Collier**[1]

[1]King's College London, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, London UK

[2]Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, Australia

[3]Winnicott Research Unit, School of Psychology and Clinical Language Sciences, University of Reading, Reading, UK

Whilst pharmacogenetic research thrives[1], genetic determinants of response to purely psychotherapeutic treatments remain unexplored. In a sample of children undergoing Cognitive Behavior Therapy (CBT) for an anxiety disorder, we tested whether treatment response is associated with the serotonin transporter gene promoter region (*5HTTLPR*), previously shown to moderate environmental influences on depression. Children with the short-short genotype were significantly more likely to respond to CBT than those carrying a long allele.

There is considerable evidence of association between anxiety/depression and the *5HTTLPR*, particularly in response to stress[2]. Moreover, the low expression S allele, typically associated with *poorer* outcomes following stress, is also associated with *better* outcomes under low stress and may reflect sensitivity to the environment[3]. We hypothesized that this allele would be associated with enhanced response to psychological therapies[4].

We collected DNA from 584 anxiety-disordered children aged 6-13 years, undergoing manual-based CBT[5] at research clinics in Sydney, Australia and Reading, UK. We focus on 359 children with 4 white European grandparents (entire sample findings similar; see Supplementary Information). Families provided data pre-treatment, post-treatment and at follow-up (usually 6-months, for detailed methods see Supplementary Information).

Parental DNA was obtained for 389 children (267 white), and parents self-rated depression, anxiety and stress[6]. Parents provided informed consent, children assent. Genomic DNA was extracted from buccal and blood samples using established procedures. The *5HTTLPR* genotypes were in Hardy-Weinberg Equilibrium. There was no significant difference in genotypic frequencies between cases and 459 white European psychiatrically well controls[7] ($\chi^2_2 = 0.40$, $p = .82$).

Treatment response was considered as the absence of the primary ("primary anxiety response"), or *any* ("all anxiety response") anxiety disorder. As all analyses test the same

Correspondence: thalia.eley@kcl.ac.uk.

The authors declare no conflict of interest

Supplementary information is available at *Molecular Psychiatry's* website.

Europe PMC Funders Author Manuscripts

core hypothesis, we did not correct for multiple testing. The *5HTTLPR* was significantly associated with both "primary" and "all" anxiety response at *follow-up* (Figure 1i); a recessive model was indicated. Positive "primary" ("all") anxiety response at follow-up was seen in 20.0% (18.8%) more children with the SS than the SL/LL genotypes; 78.4% vs. 58.4%, $p < .01$ (60.8% vs. 42.0%, $p < .02$). The influence of *5HTTLPR* remained significant even after controlling for significant clinical predictors of treatment response (mood disorders, pre-treatment symptom severity and maternal psychopathology), and time (to follow-up), age, gender and treatment site. The odds ratios for *5HTTLPR-SS* were .39, $p = .02$ (.44, $p = .03$) for "primary" ("all") anxiety response. Furthermore, the *5HTTLPR* also significantly predicted change in symptom severity from pre-treatment to follow-up (Figure 1ii) even after controlling for significant clinical covariates ($\beta = -.17$, $p < .01$). For full results see Supplementary Information.

This is the first study to explore the association between a genetic marker and response to a purely psychological treatment. One previous pilot study (N = 69) found an association between COMTval158met and CBT response in adult panic disorder, but many subjects were also medicated[8]. A naturalistic study (N = 111) of adult bulimia found that those with the *5HTTLPR* S allele were *less* likely to respond to treatment, be it CBT, medication or both[9]. We found that in anxiety-disordered children, those with the *5HTTLPR* SS genotype were 20% more likely to be disorder-free by follow-up than those with SL/LL genotypes. Whilst these findings hold true in the white subset and the entire dataset, the sample is relatively small and there is no independent replication so they must be considered preliminary. Furthermore, the association with *5HTTLPR* was only seen at follow-up. The period between post-treatment and follow-up is typically characterised by continued improvement as the child applies the skills learnt[10], thus it is possible that the genotype influences capacity for continued benefit from the intervention.

These findings are important both clinically and conceptually. First, our data suggest that "therapygenetics", like pharmacogenetics[1], may have the potential to inform treatment choices. Second, the possibility that the *5HTTLPR* influences responsivity to psychological treatment[4], is in keeping with the hypothesis that this marker reflects environmental sensitivity[3]. In conclusion, if replicated, these results may provide a tool that could help decide whether an individual is likely to benefit from standard CBT alone or whether enhanced treatment is required.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Keers R, Aitchison KJ. Expert Review of Neurotherapeutics. 2011; 11:101–125. [PubMed: 21158559]
2. Karg K, Burmeister M, Shedden K, Sen S. Arch Gen Psychiatry. Jan 3.2011 2010.
3. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Mol Psychiatry. 2009; 14:746–754. [PubMed: 19455150]
4. Uher R. Mol Psychiatry. 2008; 13:1070–1078. [PubMed: 18679406]
5. Lyneham, HJ.; Abbott, MJ.; Wignall, A.; Rapee, RM. The Cool Kids Anxiety Treatment Programme. MUARU, Macquarie University; Sydney: 2003.
6. Lovibond PF, Lovibond SH. Behav Res Ther. 1995; 33:335–343. [PubMed: 7726811]
7. Schosser A, Gaysina D, Cohen-Woods S, Chow PC, Martucci L, Craddock N, et al. Mol Psychiatry. Aug.2010 15:844–849. [PubMed: 19255581]

8. Lonsdorf TB, Ruck C, Bergstrom J, Andersson G, Ohman A, Lindefors N, et al. Bmc Psychiatry. Nov.2010 10:9. [PubMed: 20105311]
9. Steiger H, Joober R, Gauvin L, Bruce KR, Richardson J, Israel M, et al. J Clin Psychiatr. 2008; 69:1565–1571. [PubMed: 19192439]
10. James, A.; Soler, A.; Weatherall, R. Cochrane review: Cognitive behavioural therapy for anxiety disorders in children and adolescents. John Wiley & Sons, Ltd.; 2007. p. 1248-1275.

Europe PMC Funders Author Manuscripts

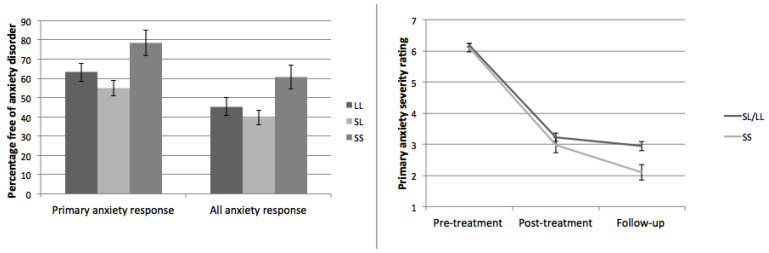

Figure 1. Proportion of children free of (a) their primary anxiety disorder and (b) all anxiety disorders at follow-up by *5HTTLPR* genotype

Note. 1(i). There were significant associations at follow-up between both "primary anxiety response" and "all anxiety response" respectively, using either a genotypic ($\chi^2_2 = 8.61$, $p = .01$; $\chi^2_2 = 6.60$, $p = .04$) or recessive ($\chi^2_1 = 7.03$, $p = <.008$; $\chi^2_1 = 5.88$, $p = .02$) model. 1(ii) Children with the SS genotype showed significantly greater reduction in symptom severity from pre-treatment to follow-up ($\beta = -.15$, $p < .01$). At post-treatment the difference was not significant ($\beta = -.03$, $p = .55$).

Europe PMC Funders Author Manuscripts