Data Supplement for O'Connell et al., Antidepressant Outcomes Predicted by Genetic Variation in Corticotropin-Releasing Hormone Binding Protein. Am J Psychiatry (doi: 10.1176/appi.ajp.2017.17020172)

Supplementary Methods

Trial

The PReDICT study recruited 344 subjects through the Mood and Anxiety Disorders Program at Emory University. The study design has been published previously (Dunlop et al., 2012). Ethical approval was given by The Emory Institutional Review Board and the Grady Hospital Research Oversight Committee and the study was registered at ClinicalTrials.gov (NCT00360399).

Participants

PReDICT enrolled treatment-naïve participants ages 18-65 years with primary diagnosis of non-psychotic depression, meeting DSM-IV criteria for current major depressive disorder (HDRS score ≥ 18 at screening and ≥ 15 at baseline). The current study included subjects from the per-protocol completer dataset (N = 234) (Dunlop et al., 2017); patients who completed 12 weeks of treatment, met all inclusion/exclusion criteria, had no major protocol violations, and whose end-of-treatment antidepressant medication (ADM) corresponded with the baseline assigned treatment.

Treatment

Participants were randomly assigned to one of three possible treatments: CBT delivered as 16 one-hour individual sessions; duloxetine 30-60 mg/day or escitalopram 10-20 mg/day. Only individuals randomized to either duloxetine or escitalopram were considered in further analyses (N=151).

Genotyping, quality control and imputation

Genome-wide genotypes (Illumina OmniExpress array) were measured in peripheral blood DNA drawn at baseline randomization. All relatives of individual subjects (N = 3, Pihat ≥ 0.125) were excluded, as well as those with low genotyping (N = 5). From the per-protocol completer participants who agreed to provide DNA; five did not pass genotyping-QC and three were removed for relatedness based on identity by descent (IBD). A total of 215 genotyped individuals remained after initial quality control (QC).

Participant genotype data were imputed against the 1000 Genomes Project Phase 3 reference haplotypes with IMPUTE2 (Howie et al., 2009) and pre-phased with SHAPEIT2 (Delaneau et al., 2012). We retained only SNPs with Hardy–Weinberg equilibrium P value $\geq 1 \times 10^{-6}$, and imputation info scores of ≥ 0.8. After QC 8,621,204 SNPs remained. The SNP of interest (rs2865143) was extracted from the imputed data and only individuals with complete imputed genotypes for rs28365143 (N = 141) were included in the replication analyses. The best-guess genotype call rate in full sample was 0.933775.

Treatment Outcome Measures
Symptoms severity was assessed weekly by blinded raters for the first 6 weeks, then every two weeks for the second 6 weeks. Identically to the discovery sample, remission was defined as an HDRS score ≤ 7 at week eight and response as an HDRS score improvement of ≥50% from baseline to week eight.

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Extended Discussion

CRHBP is a 322 amino acid protein that is widely conserved across vertebrates and humans (Westphal & Seasholtz, 2006). In humans, CRHBP is expressed not only in a variety of brain regions (including amygdala, hippocampus, and lateral septal nucleus), and also in the body, particularly the liver and placenta (Chan et al., 2000). Between 65 and 90% of all CRH exists as part of a complex with CRHBP, and formation of this complex is thought to regulate levels of free CRH available for receptor binding and downstream cortisol release (Behan et al., 1997). In mouse models, levels of CRHBP increase in response to stress, which in turn may also directly inhibit cortisol release (Seasholz et al., 2001; Herringa et al, 2004; Stinnett et al., 2015).

References

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FIGURE S1. Consort Diagram for the iSPOT-D Trial

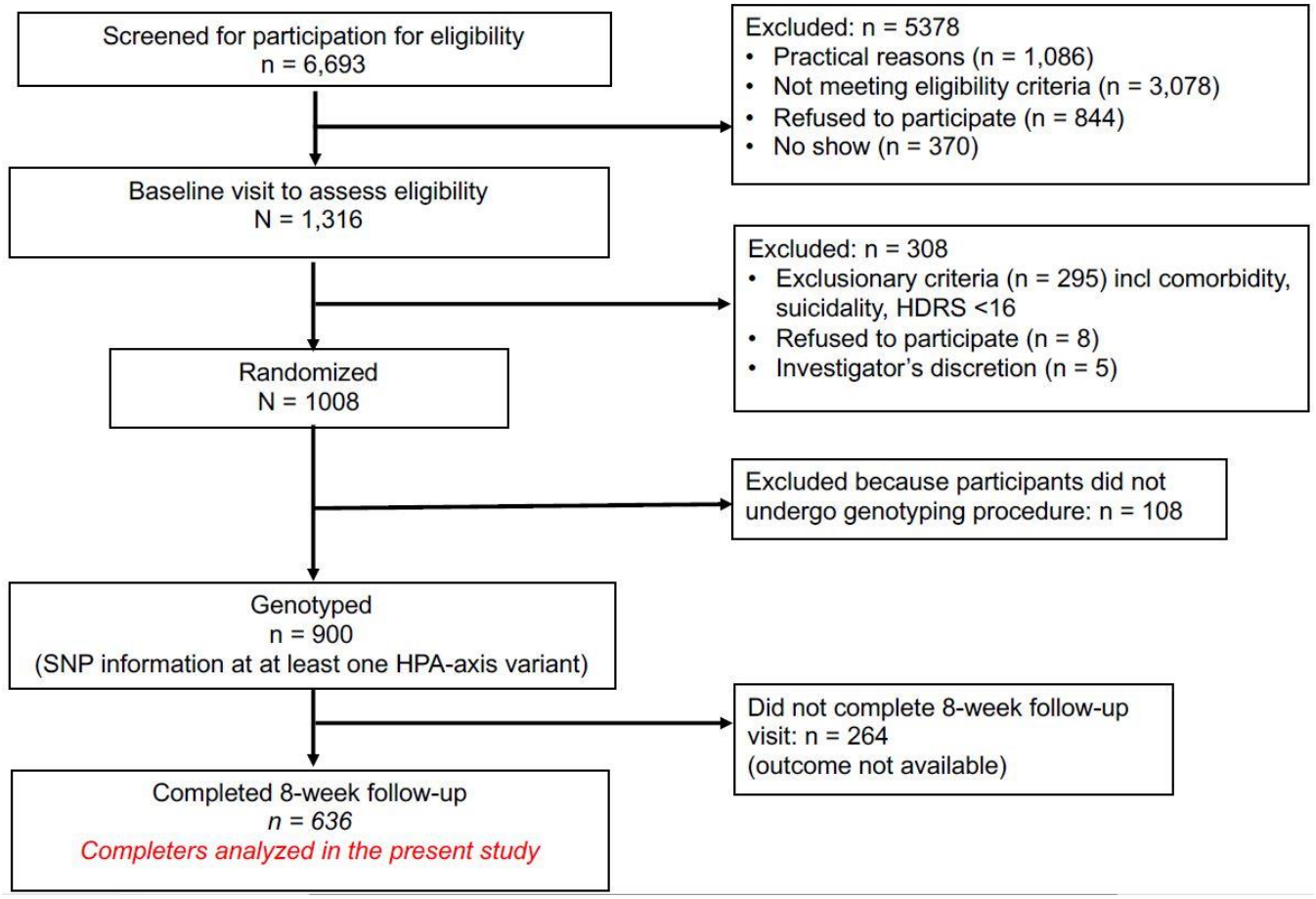

TABLE S1. Genotypes of completers vs. full genotyped sample at all candidate SNPs (iSPOT-D cohort only)

		Completers only (N)			All genotyped (N)			
Gene	SNP	Ref/Ref	Ref/Alt	Alt/Alt	Ref/Ref	Ref/Alt	Alt/Alt	Chi-sq or Fisher's exact p-value Completers vs. full genotyped sample
CRH	rs3176921	455	143	38	650	194	56	0.88
	rs5030875	569	64	2	811	84	4	0.82
CRHBP	rs10055255	201	272	159	293	374	26	0.90
	rs28365143	547	84	5	786	108	6	0.75
CRHR1	rs110402	191	298	144	264	424	209	0.94
	rs1876828	428	174	30	631	228	37	0.54
	rs242924	194	289	145	267	414	211	0.92
	rs242939	518	107	8	727	159	10	0.91
	rs4076452	449	170	17	639	238	23	0.98
	rs6472257	495	130	11	703	181	16	0.98
CRHR2	rs2267712	436	176	21	611	263	23	0.60
	rs2270007	432	175	26	606	257	34	0.88
	rs2284216	503	115	12	705	173	16	0.86
	rs4723003	511	114	11	713	171	16	0.86
NR3C1	rs6918	470	157	9	660	227	13	0.97
	rs2963156	418	192	26	584	282	34	0.87

TABLE S2. Associations between all candidate SNPs and depression outcome measures in the iSPOT-D sample

		Response		Remission		Absolute Reduction		% Reduction	
Gene	SNP ID	β	p	β	p	β	p	β	p
CRH	rs3176921	–0.18	0.21	–0.14	0.33	–0.66	0.11	0.0287	0.13
	rs5030875	0.25	0.38	0.0013	1.00	0.25	0.75	–0.0279	0.44
CRHBP	rs10055255	–0.022	0.85	0.0083	0.94	–0.03	0.93	0.0002	0.99
	rs28365143	–0.77	0.0017*	–1.02	0.00016*	–2.51	0.000254*	0.12	0.00010*
CRHR1	rs110402	0.21	0.07	0.17	0.16	0.47	0.15	–0.02	0.13
	rs1876828	–0.13	0.38	–0.16	0.31	–0.11	0.80	0.01	0.47
	rs242924	0.22	0.06	0.16	0.17	0.51	0.12	–0.03	0.09
	rs242939	0.34	0.13	0.38	0.08	1.17	0.06	–0.05	0.06
	rs4076452	–0.13	0.49	–0.05	0.80	–0.37	0.48	0.01	0.67
	rs6472257	–0.10	0.62	–0.26	0.21	–0.63	0.27	0.03	0.30
CRHR2	rs2267712	–0.09	0.57	–0.09	0.55	–0.11	0.79	0.01	0.69
	rs2270007	–0.19	0.21	–0.16	0.31	–0.30	0.48	0.02	0.40
	rs2284216	–0.25	0.24	–0.02	0.94	–0.77	0.20	0.02	0.37
	rs4723003	–0.11	0.60	0.10	0.64	–0.39	0.51	0.01	0.62
NR3C1	rs6918	0.13	0.50	–0.15	0.45	0.19	0.72	0.00	0.98
	rs2963156	0.04	0.80	0.02	0.89	0.21	0.62	–0.01	0.63

* $p < 0.003938$, Bonferroni-corrected threshold for 13 hypotheses.

TABLE S3. Regression coefficients with SNP*drug class interaction term. The effect of SNP within each drug class was assessed by re-fitting the regression model with each drug class as the reference category, and assessing the effect of the alternate "A" allele within that drug class. The overall significance of the interaction term is also reported here. The effect of SNP within individual drug arms was assessed by fitting a linear regression model including drug as a categorical predictor and an interaction term between drug and SNP.

		β	p
% Reduction	SSRI: A allele	–0.17	5.02×10^{-6} *
	Escitalopram	–0.18	5.81×10^{-4} *
	Sertraline	–0.16	0.0020*
	SNRI: A allele	–0.01	0.89
	Venlafaxine		
	SSRI/SNRI-genotype interaction	0.16	0.019
Absolute Reduction	SSRI: A allele	–3.46	1.89×10^{-5} *
	Escitalopram	–3.49	0.0022*
	Sertraline	–3.46	0.0022*
	SNRI: A allele	–0.25	0.843
	Venlafaxine		
	SSRI/SNRI-genotype interaction	3.21	0.031
Response	SSRI: A allele	–1.21	4.32×10^{-5} *
	Escitalopram	–0.37	4.97×10^{-5} *
	Sertraline	–0.16	0.066
	SNRI: A allele	0.27	0.55
	Venlafaxine		
	SSRI/SNRI-genotype interaction	–1.48	0.0066
Remission	SSRI: A allele	–1.33	4.47×10^{-5} *
	Escitalopram	–1.30	0.0032*
	Sertraline	–1.38	0.0036*
	SNRI: A allele	–0.29	0.54
	Venlafaxine		
	SSRI/SNRI-genotype interaction	–1.03	0.071

* $p<0.003938$, Bonferroni-corrected threshold for 13 hypotheses.

TABLE S4. Association of genotype with treatment response after stratification by Caucasian vs. non-Caucasian participants in the iSPOT-D cohort

		Caucasian		Non-Caucasian	
		β	p	β	p
% Reduction	Genotype (A allele)	–0.11	0.009	–0.12	0.011
Linear Reduction	Genotype (A allele)	–2.15	0.018	–2.58	0.018
Response	Genotype (A allele)	–0.63	0.061	–0.85	0.021
Remission	Genotype (A allele)	–1.12	0.0033	–0.88	0.024