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Linkage Disequilibrium Mapping of a Chromosome 15q25–26 Major Depression Linkage Region and Sequencing of *NTRK3*

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Abstract

Background—We reported genome-wide significant linkage on chromosome 15q25.3–26.2 to recurrent early-onset major depressive disorder (MDD-RE). Here we present initial linkage-disequilibrium (LD) fine-mapping of this signal and sequence analysis of *NTRK3* (neurotrophic receptor kinase-3), a biologically plausible candidate gene.

Methods—In 300 pedigrees informative for family-based association, 1195 individuals were genotyped for 795 SNPs. We resequenced 21 exons and seven highly conserved *NTRK3* regions in 176 MDD-RE cases to test for an excess of rare functional variants, and in 176 controls for case-control analysis of common variants.

Results—LD mapping showed nominally significant association in nine genes–*NTRK3*, *FLJ12484*, RHCG, DKFZp547K1113, VPS33B, SV2B, SLCO3A1, RGMA and MCTP2–with MDD-RE. In *NTRK3*, five SNPs had nominally significant *p*-values (0.035–0.001). Sequence analysis revealed 35 variants (24 novel, including nine rare exonic); the number of rare variants did not exceed chance expectation. Case-control analysis of 13 common variants showed modest nominal association of MDD-RE with rs4887379, rs6496463 and rs3825882 ($p = 0.008$, 0.048, and 0.034), which were in partial LD with four of five associated SNPs from the family-based experiment.

Conclusions—Common variants in *NTRK3* or one of the other genes identified might play a role in MDD-RE. However, much larger studies will be required for full evaluation of this region.

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Keywords

NTRK3; *TRKC*; Neurotrophin; tag SNPs; Association; Major Depression

Introduction

In our Genetics of Recurrent Early-Onset Depression (GenRED) project, the 15q25.3–26.2 region produced the greatest linkage evidence to recurrent early-onset major depressive disorder MDD-RE) in preliminary (1) and final (2) genome scan analyses. Linkage fine-mapping of this region with single nucleotide polymorphisms (SNPs) in 631 European-ancestry families produced genome-wide significant evidence for linkage (3). Here we present initial linkage disequilibrium (LD) mapping of this signal--the first LD mapping study of a linkage candidate region for MDD--which suggested nine possible candidate genes, including *NTRK3* (neurotrophic receptor kinase 3).

We also present here further study of *NTRK3*, which encodes a receptor that binds neurotrophin 3 (NT3) (4). Antidepressants are neuroprotective in the hippocampus (5) and alterations in neurotrophins, particularly BDNF and possibly also NT3, could influence MDD through loss of neuroprotective effects (6). In post-mortem MDD brain, there is evidence for upregulation of *NTRK3* (7). A transgenic mouse model over-expressing *ntrk3* showed increased anxiety-like behaviors (8). No MDD genetic association studies have been published for *NT3* or *NTRK3*. We therefore carried out a resequencing experiment of *NTRK3* in 176 GenRED MDD-RE cases and 176 controls.

Methods and Materials

Clinical methods have been described elsewhere (2); MDD-RE was defined as two or more episodes of DSM-IV MDD with onset before age 31 in probands or 41 in relatives, as suggested by previous family studies (9). Subjects gave written informed consent under IRB-approved protocols. Two partially overlapping samples were selected for LD mapping and resequencing, respectively, in the current study. LD mapping analyses were performed in 300 families informative for family-based association analysis by virtue of having parents and/or unaffected siblings available (813 affected/382 unaffected genotyped individuals, see Supplementary Table S1). For resequencing, from the 176 families with the greatest evidence for 15q25–26 linkage (including 98 from the LD mapping sample), we selected the case with the highest IBD sharing with affected relatives. European-American controls (N=176) selected from the NIMH repository (http://zork.wustl.edu/nimh/home/d_controls.html#) had no MDD-RE (nor bipolar disorder, schizophrenia, or other psychotic disorder) by self-report (10).

Initially, 1,056 SNPs with adequate Illumina design scores (≥ 0.6) were selected from HapMap, ABI, Celera and dbSNP (Build 34) to cover the linkage peak from rs1822237 to rs727896 (85,776,199 to 94,499,478 on build 36.2). SNP density was 5–6 kb within 78 genes and predicted genes, and 10–12 kb in intergenic regions. 795 SNPs were successfully genotyped by the Center for Inherited Disease Research using the Illumina GoldenGate assay. Of these, 11 were excluded for minor allele frequencies < 0.01, and three for deviations from Hardy-Weinberg equilibrium, computed using unrelated unaffecteds, at $p \leq 0.001$, so that results for 781 SNPs are presented here. Quality control results were excellent: of 1,615,890 attempted genotypes, 99.89% were called and 0.04% were inconsistent with family structure. There were 0.011% discordances among 52,960 duplicate genotypes, and 0.011% inconsistencies in parent-child controls. For either parent-child pairs or trios, when the rate of errors or inconsistencies exceeded 2%, these were excluded. Three families surpassed this threshold.

Thirty primer sets were used to resequence ~16 kb of *NTRK3* in 176 MDD cases, including all exons and flanking intronic regions, as well as highly conserved regions, on an ABI 3100 Genetic Analyzer. We covered 21 exons from three alternative transcripts (Figure 1), and the seven most conserved (LOD value: 173–292; size: 172–465 bp) non-exonic regions from the UCSC Genome Browser "most conserved region" track (11). The resequenced regions in which we identified non-synonymous variants or common (MAF > 0.05) polymorphisms in cases were also resequenced in 176 controls to determine whether these were unique to or over-represented in cases.

Family-based association analyses were carried out using TRANSMIT (12), using the robust variance estimator to correct for prior linkage and the use of multiple siblings in the families (see Supplementary Methods). Power was evaluated by simulating 1,000 replicates of the sample under a multiplicative model (Table 1). For a threshold of $p = 0.001$ (in the range of the best results observed here), power was reasonable for RR = 1.5, but low for RR = 1.3. Larger samples will be required to achieve sufficient power to detect significant association after correction for multiple testing.

For the case-control resequencing experiment, we determined whether the number of variants identified in cases was significantly higher than would be expected in this length of sequence, using a population genetics-based method (13). This method compares the number of variations detected to the number expected in a particular sequence, taking into account sequence length and differing rates of variation in exons vs. introns. For more common variants, allelic case-control association was tested using Fisher's exact test statistic.

Results

Results of association tests for all 781 SNPs are shown in Supplementary Table S2. The 43 tests with nominal $p < 0.05$ are shown in Table 2. There were not more such tests than would be expected by chance, and no *p*-value would be considered significant after correction for multiple testing. Nominally positive results were observed for SNPs in nine known genes–*NTRK3, FLJ12484, RHCG, DKFZp547K1113, VPS33B, SV2B, SLCO3A1, RGMA* and *MCTP2*.

Two long genes contained multiple nominally significant SNPs: *NTRK3* and *SLCO3A1*. Resequencing of *SLCO3A1* is ongoing. Resequencing of *NTRK3* revealed 35 sequence variations. The 24 novel variants we identified did not exceed the number expected by chance (N = 40). Rarer variants (frequency < 5%) are listed in Table 3 along with the number of cases who were carriers. There were nine rare variants in exons including two novel rare missense mutations (Arg306His in exon 9 and Asn714Ser in exon 17), each observed in one case, but absent in controls. The remaining rare variants were observed in other regions as shown in the table.

The experiment was designed to test the hypothesis of an excess of rare non-synonymous mutations in cases. Because only two such mutations were observed in cases, i.e., not enough for a significant excess to be observed, the test of the hypothesis was conclusively negative even without sequencing controls. However, we went on to sequence a limited number of exons in controls: those containing non-synonymous variants or common (MAF > 0.05) polymorphisms.

More common variants (frequency > 5%) are listed in Table 4, and results of case-control association tests are also shown. All were in Hardy-Weinberg equilibrium in both cases and controls. Allele frequencies of three of these SNPs differed in cases vs. controls at the $p < 0.05$ level without correcting for multiple tests. Two of these three SNPs were in almost complete LD with each other, and all were in modest, but significant LD with four of the five nominally

associated SNPs in the family-based LD mapping experiment (Supplementary Figure 1). Thus the association observed in the family-based analysis was also observed in the case-control analysis although the results would not be significant after correcting for multiple tests. All association results for *NTRK3* are depicted in Figure 1.

Discussion

An initial LD mapping study of the 15q25–26 MDD-RE linkage region produced nominally significant evidence for association of MDD-RE to common variants in nine genes, but none of these findings can be considered statistically significant given the multiple tests performed. It is possible that common variants in one or more of these genes play a role in susceptibility to MDD-RE. However, much larger studies and denser SNP maps will be required for full evaluation of this region.

We began our investigations of these genes by carrying out a resequencing study of *NTRK3*, with the primary goal of identifying any rare functional susceptibility variants. Although we identified 21 rare novel variants in *NTRK3*, we did not observe an excess of rare functional variants in cases. Further, the total number of variants identified did not exceed that expected by chance. Among the two novel missense mutations we did identify, Arg306His in exon 9 is located in the neurotrophin binding domain, within which mutations could significantly reduce the affinity of the *NTRK3* receptor for neurotrophin 3 (14).

Our case-control analysis revealed modest association of three common *NTRK3* variants (rs4887379, rs6496463, rs3825882). Interestingly, these SNPs are located quite close to and are in modest LD with the ones that showed family-based association. The finding that similar associations were seen both with family-based and case-control methods suggests that the signal is unlikely to be the result of genotyping or other artifact.

Several limitations of this study should be considered. We could have missed true case-control differences in the frequency of rare variants, as: a) rare variation was studied neither in the introns nor the flanking regions; and, b) there could be case-control differences in the frequency of very rare variants requiring a larger sample to detect. Further, our case-control findings could be false positives due to population stratification, though the similar self-reported ancestries of our cases and controls (Supplementary Table S3) make this less likely, as do our positive family-based association findings. We are currently conducting a genome-wide association study in a much larger group of cases and controls, which should help clarify the role of *NTRK3* and other chromosome 15q25–26 genes in MDD-RE susceptibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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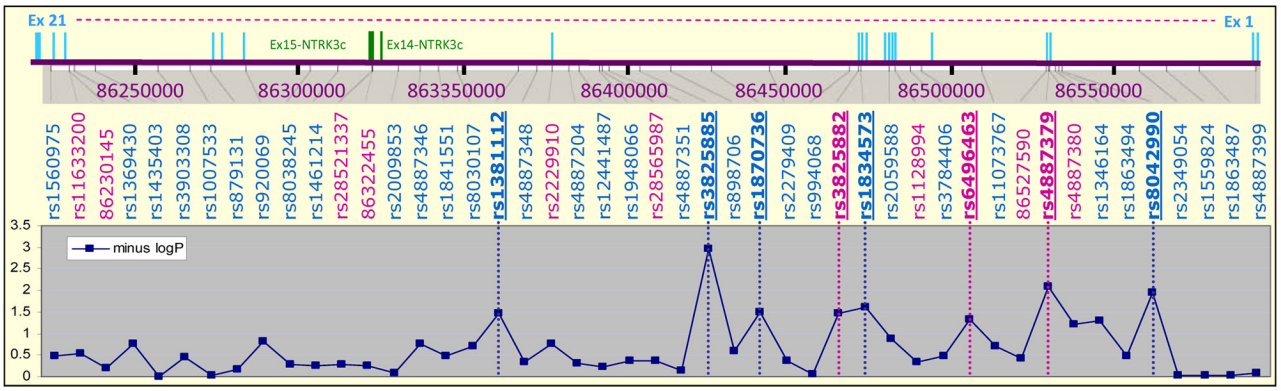

Figure. Genomic organization and allelic association results for the *NTRK3* gene

The upper panel shows the exonic structure of the *NTRK3* gene while the middle panel depicts the distribution of 47 common variants (MAF > 0.05) analyzed in the family-based (blue) and case-control (pink) association studies. The lower panel shows the allelic association –log *p*-values obtained through TRANSMIT and Fisher's exact test statistics. The associated SNPs ($p < 0.05$) are marked in bold and underlined.

Table 1

Power of the LD mapping sample to detect association using TRANSMIT under a multiplicative model

RR[a]	Freq[b]	Power for *p*-values of:	
		0.05	**0.001**
1.3	0.1	0.64	0.17
1.3	0.25	0.75	0.25
1.3	0.5	0.73	0.22
1.5	0.1	0.97	0.68
1.5	0.25	0.98	0.77
1.5	0.5	0.97	0.73

[a] RR refers to allelic relative risk.

[b] Freq refers to risk allele frequencies.

Table 2

LD mapping results: SNPs with nominally significant *p*-values

rs ID	Loc (Build 36.2)	MAF	Gene	Region	Chi-sq	*p*-value
rs1381112	86 366 855	0.125	*NTRK3*	Intron	4.44	0.0351
rs3825885	86 403 845	0.328	*NTRK3*	Intron	10.70	0.0011
rs1870736	86 425 625	0.425	*NTRK3*	Intron	4.56	0.0327
rs1834573	86 471 117	0.298	*NTRK3*	Intron	5.11	0.0239
rs8042990	86 532 457	0.318	*NTRK3*	Intron	6.46	0.0110
rs1530309	86 640 008	0.043			5.37	0.0204
rs1561806	86 657 188	0.495			5.79	0.0161
rs2028389	86 967 765	0.143	*FLJ12484*	Intron	5.33	0.0209
rs2072693	87 815 949	0.481	*RHCG*	Exon synon	4.45	0.0349
rs1256840	88 329 016	0.122			5.71	0.0169
rs1256841	88 349 309	0.121	*DKFZp547K1113*	Intron	4.77	0.0290
rs1867225	89 364 833	0.401	*VPS33B*	Intron	4.61	0.0317
rs1005060	89 389 551	0.425			4.53	0.0334
rs2597909	89 462 723	0.082	*SV2B*	Intron	4.75	0.0293
rs4525467	89 840 777	0.398			8.02	0.0046
rs4300626	89 896 689	0.198			5.65	0.0175
rs4632107	89 941 183	0.334			7.22	0.0072
rs7165398	90 195 099	0.255	*SLCO3A1*	Promoter	6.86	0.0088
rs1568209	90 382 294	0.467	*SLCO3A1*	Intron	6.21	0.0127
rs2892291	90 430 815	0.337	*SLCO3A1*	Intron	10.71	0.0011
rs871167	90 435 137	0.335	*SLCO3A1*	Intron	11.13	0.0008
rs2286355	90 439 197	0.374	*SLCO3A1*	Exon synon	4.79	0.0287
rs207974	90 439 656	0.256	*SLCO3A1*	Intron	8.62	0.0033
rs2048945	90 443 405	0.381	*SLCO3A1*	Intron	4.90	0.0269
rs1517620	90 451 267	0.292	*SLCO3A1*	Intron	9.63	0.0019
rs207964	90 453 177	0.149	*SLCO3A1*	Intron	6.33	0.0119
rs2238360	90 457 120	0.442	*SLCO3A1*	Intron	4.03	0.0447
rs732546	90 491 552	0.358	*SLCO3A1*	Intron	4.96	0.0259
rs2132616	91 039 384	0.407			4.36	0.0368
rs1534780	91 426 217	0.422	*RGMA*	Intron	7.06	0.0079
rs7180175	92 080 839	0.485			6.49	0.0109
rs1351306	92 388 421	0.434			5.33	0.0210
rs11853883	92 520 920	0.288			4.72	0.0298
rs2117215	92 680 688	0.461	*MCTP2*	Intron	5.67	0.0172
rs2388779	93 058 282	0.288			3.84	0.0499
rs2388881	93 084 371	0.344			6.48	0.0109
rs2388883	93 122 138	0.193			6.64	0.0100
rs1026453	93 377 084	0.241			4.48	0.0343
rs4984553	93 444 400	0.275			5.57	0.0182
rs1471169	93 463 523	0.306			6.56	0.0104
rs1834212	93 876 557	0.403			4.27	0.0388
rs2397813	93 929 511	0.393			5.75	0.0165
rs766716	94 489 374	0.208			4.52	0.0336

Table 3

Frequencies of 22 uncommon variants identified through resequencing of *NTRK3* in 176 MDD cases

Loc (Build 36.2)	Region,[bc]	Variant	# of Heterozygotes (MAF)
86 600 697	5′ of gene	G/T	2 (0.006)
86 600 687	5′ of gene	C/A	1 (0.003)
86 600 681	5′ of gene	G/C	1 (0.003)
86 600 601	Exon 1 (5′UTR)	CGG repeat[d]	2 (0.006)
86 600 250	Exon 2	CGG→AGG (synonymous Arg)	4 (0.011)
86 577 488	Intron 2 (cons 1)	A/G	1 (0.003)
86 528 357	Intron 3	C/T	1 (0.003)
86 489 484	Intron 5 (cons 4)	G/A	9 (0.026)
86 489 409	Intron 5 (cons 4)	T/C	1 (0.003)
86 480 234	Exon 8	ACG→ACA (synonymous Thr)	1 (0.003)
86 479 623	Exon 9	CGT→CAT (Arg→His)[e]	1 (0.003)
86 323 519	Intron 13 (Exon 15 of *NTRK3*c-3′UTR)	T/C	1 (0.003)
86 323 054	Intron 13 (Exon 15 of *NTRK3*c-3′UTR)	G/A	1 (0.003)
86 322 802	Intron 13 (Exon 15 of *NTRK3*c-3′UTR)	C/A	2 (0.006)
86 314 079	Intron 13 (cons 7)	C/T	1 (0.003)
86 313 972	Intron 13 (cons 7)	C/T	2 (0.006)
86 313 902	Intron 13 (cons 7)	C/T	3 (0.009)
86 284 909	Exon 14	GCC→GCT (synonymous Ala)	1 (0.003)
86 277 456	Intron 14	G/A	8 (0.023)
86 277 203	Intron 15	C/T	2 (0.006)
86 277 170[a]	Intron 15	T/G	16 (0.045)
86 229 963	Exon 17	AAT→AGT (Asn→Ser)[e]	1 (0.003)

[a] dbSNP ID rs1006046 (Genotype data from Hap Map project available at www.hapmap.org). All other variants are novel.

[b] Regions are in reference to the *NTRK3a* transcript except where the *NTRK3c* transcript is specified.

[c] "cons" refers to highly conserved regions that are numbered in accordance with their location beginning from the 5′ end of *NTRK3*.

[d] Two cases were heterozygous for 'CGG' repeat alleles of length 4 and 8; all other subjects were homozygous for the 8-repeat allele.

[e] These two nsSNP were also sequenced in controls, and no carriers were observed.

Table 4

Frequency distribution and case-control association analysis of common variants in the *NTRK3* gene

Loc (Build 36.2)	Region,[ab]	Variant	rs ID	Group	Genotype Counts			Allele Counts (Frequencies)		*p*-value[d]
					Maj/ Maj	Het	Min/ Min	Major	Minor	
86 528 755	Intron 2	T/A	rs4887380	Cases	107	62	7	276 (0.784)	76 (0.216)	0.063
				Controls	120	53	3	293 (0.832)	59 (0.168)	
86 528 340	Intron3	G/C	rs4887379	Cases	100	66	10	266 (0.756)	86 (0.244)	**0.008**
				Controls	120	53	3	293 (0.832)	59 (0.168)	
86 527 590	Intron 4	C/T	Novel	Cases	111	59	6	281 (0.798)	71 (0.202)	0.386
				Controls	108	61	2	277 (0.810)	65 (0.190)	
86 489 658	Intron 5	A/G	rs6496463	Cases	36	92	45	164 (0.474)	182 (0.526)	**0.048**
				Controls	55	79	41	189 (0.540)	161 (0.460)	
86 481 688	Exon6	AAC→AAT (synonymous Asn)	rs1128994	Cases	94	70	12	258 (0.733)	94 (0.267)	0.466
				Controls	92	76	8	260 (0.739)	92 (0.261)	
86 470 386	Intron 12	C/G	rs3825882[c]	Cases	38	93	44	169 (0.483)	181 (0.517)	**0.034**
				Controls	60	73	41	193 (0.555)	155 (0.445)	
86 392 534	Intron 12 (cons 6)	G/T	rs28565987	Cases	138	34	2	310 (0.891)	38 (0.109)	0.431
				Controls	141	34	1	316 (0.898)	36 (0.102)	
86 377 189	Exon13	CGC→CGG (synonymous Arg)	rs2229910	Cases	67	85	24	219 (0.622)	133 (0.378)	0.173
				Controls	79	74	23	232 (0.659)	120 (0.341)	
86 322 455	Intron 13 (Exon 15 of *NTRK3*c-3′ UTR)	G/A	Novel	Cases	156	17	2	329 (0.940)	21 (0.060)	0.556
				Controls	156	19	1	331 (0.940)	21 (0.060)	
86 322 284	Intron 13 (Exon 15 of *NTRK3*c-3′ UTR)	G/C	rs28521337	Cases	37	92	47	166 (0.472)	186 (0.528)	0.530
				Controls	41	84	51	166 (0.472)	186 (0.528)	
86 230 145	Intron 16	T/C	Novel	Cases	152	24	0	328 (0.932)	24 (0.068)	0.616
				Controls	153	21	2	327 (0.929)	25 (0.071)	
86 230 080	Intron 16	T/C	rs11633200	Cases	17	86	73	120 (0.341)	232 (0.659)	0.290
				Controls	26	76	74	128 (0.364)	224 (0.636)	
86 224 467	Intron 18	G/A	rs1560975[c]	Cases	23	88	65	134 (0.381)	218 (0.619)	0.630
				Controls	23	81	67	127 (0.371)	215 (0.629)	

[a] Regions are in reference to the *NTRK3a* transcript except where the *NTRK1c* transcript is specified.

[b] "cons" refers to highly conserved regions that are numbered in accordance with their location beginning from the 5′ end of *NTRK3*.

[c] Genotype data from Hap Map project available at www.hapmap.org.

[d] Uncorrected *p*-values < 0.05 are marked in bold.