Published in final edited form as:

Am J Med Genet B Neuropsychiatr Genet. 2011 January ; 0(1): 59–66. doi:10.1002/ajmg.b.31138.

Increased Symptoms of Attention Deficit Hyperactivity Disorder and Major Depressive Disorder Symptoms in Nail-Patella Syndrome: Potential Association with *LMX1B* Loss-of-Function

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Abstract

Nail-Patella syndrome (NPS) is an autosomal dominant disorder that is the result of heterozygous loss-of-function mutations in *LMX1B*, coding for a LIM homeobox (LIM-HD) transcription factor. Analyses of *lmx1b* mutant mice have revealed the role of Lmx1b in the development of mesencephalic dopaminergic neurons and the serotonergic system; these areas have been linked with symptoms of attention deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD). Fifty adults (38 females, 12 males) with NPS completed the *Conners' Adult ADHD Rating Scales—Self-report: Long Version (CAARS)* and *Beck Depression Inventory-II (BDI-II)*. The objective was to describe the neurobehavioral phenotype of these subjects and examine possible relationships between neurobehavioral symptoms and NPS. Elevated levels of DSM-IV-TR ADHD Inattentive symptoms were reported on the *CAARS* by 22% of the NPS sample. The *BDI-II Total* score was elevated for 40% of the NPS sample. There was a significant increase in the odds of an elevated *BDI-II Total* score when any of the three *CAARS* scales were elevated (odds ratios ranging from 11.455 to 15.615). The *CAARS* and *BDI-II* did not significantly differ with gender, age, or education level. There was no significant association between genetic mutation-predicted protein status and elevations on *CAARS* or *BDI-II*. Individuals with NPS reported co-occurring symptoms of ADHD and MDD, with higher levels of co-occurrence than reported in the literature for the general population. The co-occurrence of these symptoms may be related to mesencephalic dopaminergic neurologic pathway abnormalities that are a consequence of *LMX1B* loss of function.

Keywords

ADHD; MDD; behavior phenotype; neurobehavior

INTRODUCTION

Congenital absence of the patellae has been recognized as a familial condition since early in the 19th century when a newborn infant with genu recurvatum and absent patella presented to the Swiss surgeon A. C. Chatelain [Chatelain, 1822]. Several additional cases were reported throughout the 1800s [Editor, 1833; Hartigan, 1879; Little, 1897]. In 1933, Turner described two families with musculoskeletal abnormalities and nail dysplasia, becoming the first report of onycho-osteodysplasia or the nail-patella syndrome (NPS) [Turner, 1933]. NPS is an uncommon (1/50,000 live births) autosomal dominant genetic condition characterized by iliac horns, absent or dysplastic patellae and nails, and abnormal elbows. NPS has been regarded primarily as a connective tissue disorder; however, it is now recognized that nephropathy and several ocular problems, including glaucoma, are constituent parts of the syndrome [Sweeney et al., 2003; McIntosh et al., 2005]. Individuals with NPS have clinically appeared to have normal intelligence and no apparent learning disabilities. No studies of these features or other behavioral phenotypic features in individuals with NPS have been reported. The syndrome is the result of loss-of-function mutations in *LMX1B*, encoding a LIM-HD transcription factor [Dreyer et al., 1998; McIntosh et al., 1998].

A mouse model of NPS was created by deleting *lmx1b* [Chen et al., 1998]. *Lmx1b* has been shown to be expressed in mouse mesencephalic dopaminergic neurons including the substantia nigra, pars compacta, and ventral tegmental area [Smidt et al., 2000]. In the adult mouse brain, *lmx1b* is expressed (from rostral to caudal) in: subthalamic nucleus, posterior hypothalamus, premammillary nucleus, supramammillary nucleus, substantia nigra, ventral tegmental area, interpeduncular nucleus, pons (dorsal Raphe nucleus, medial Raphe nucleus), parabrachial nucleus, pontine reticular nucleus, trigeminal nucleus, and dorsal horn of the spinal cord. Analyses of mice with *lmx1b* deletion (null mutation; *lmx1b*^{-/-}) have demonstrated that midbrain expression is required for proper development of mesencephalic dopaminergic neurons under control of the isthmic organizer [Smidt et al., 2000] and that the expression observed in the developing hindbrain is required for the proper formation of the entire serotonergic system in the adult hindbrain [Cheng et al., 2003].

Based upon the brain regions involved in the mouse with *lmx1b* deletion, we hypothesized that individuals affected with NPS would report more symptoms of attention deficit hyperactivity disorder (ADHD) and major depressive disorder (MDD) than typically reported by the general population. ADHD is a complex behavioral condition with an estimated population prevalence of 4.4% in adults in the U.S.A. [Kessler et al., 2006]. Studies of adult ADHD have shown a higher incidence of ADHD in males, with a male to female odds ratio of 1.6 [Kessler et al., 2006]. ADHD combined type includes symptoms of inattention, hyperactivity, and impulsivity. Multiple linkage and meta-analysis studies have provided evidence for involvement of dopaminergic neurons in the etiology of ADHD; association scans are starting to appear but have not yet had sufficient power to produce conclusive results [Coghill and Banaschewski, 2009].

MDD has reported a 30-day prevalence of 4.9% (based on community surveys in the U.S.A.) [Blazer et al., 1994] and a 12-month prevalence of 6.6% [Kessler et al., 2003]. It has a lifetime prevalence of 16.2% in adults in the U.S.A., and affects slightly more females than males (female odds ratio = 1.7) [Kessler et al., 2003]. Symptoms of MDD are expressed

both emotionally (e.g., excessive crying, sadness) and physically (e.g., change in sleep and appetite). It has been established at the neuroanatomical level that there is a close relationship between 5-hydroxytryptophan (5HT) and dopamine (DA) containing neurons in all three major dopaminergic pathways [Azmitia and Segal, 1978; Herve et al., 1987] and both serotonergic and dopaminergic receptors have been associated with the pathophysiology of MDD [Barnes and Sharp, 1999; Berton and Nestler, 2006; Alex and Pehek, 2007]. Thus, we designed a study to test the hypothesis that heterozygous loss-of-function mutations in *LMX1B* and subsequent abnormalities in the mesencephalic dopaminergic pathway and serotonergic system predispose individuals with NPS to have symptoms of ADHD and MDD at a higher incidence than the general population.

MATERIALS AND METHODS

This study was approved by the Johns Hopkins Medicine Institutional Review Board and written informed consent was obtained from all subjects in the study.

Subjects

The inclusion criteria for entry into the study were (1) diagnosis of NPS based on clinical assessment, (2) informed consent, and (3) at least 18 years old. Participants were recruited from an ongoing NPS Genotype–Phenotype study, via an advertisement on the NPS website and flyers/announcements at an NPS meeting.

Mutation Screening

Identification of mutations was sought in subjects' genomic DNA as described previously [McIntosh et al., 1998; Dunston et al., 2004]. Genotype information was available for 33 of 50 subjects; in addition phenotyping was done to confirm a clinical diagnosis if molecular analysis was not done or inconclusive (Table I). Subjects were grouped based upon their predicted protein status. Three categories were assigned: non-functional protein predicted (n = 16), no protein product predicted (n = 17), and unknown (n = 17). Mutations italicized in Table I are predicted to result in synthesis of a non-functional protein product; all other listed mutations are predicted to result in no protein product.

Procedures

The following behavioral measures/checklists were completed by adults with NPS. These checklists have good reliability and validity and are used to assess for symptoms of ADHD and MDD. Note that a high score (indicating abnormality) on a symptom checklist is not sufficient for diagnosis of a disorder; additional data are required for determining when a clinical diagnosis is appropriate. Each of the measures used were scored and then rescored independently by two individuals; resulting data were placed into electronic databases using a double-entry method.

Conners' Adult ADHD Rating Scales—Self-Report: Long Version (CAARS)

The *CAARS* addresses symptoms of ADHD as defined in the Diagnostic and Statistical Manual, 4th edition, Text Revision (DSM-IV-TR) [American Psychiatric Association, 2000] and associated features of ADHD that may present in the domains of home, work, and interpersonal functioning. This measure contains seven scales relating to inattention, memory, hyperactivity, restlessness, impulsivity, emotional lability, and problems with self-concept. Sound psychometric properties have been established, as well as normative data for 2,000 adults [Conners et al., 1999]. The *CAARS* is appropriate for evaluating individuals aged 18 years and older. Each item is rated on a Likert scale of 0 ("Not at all, never") to 3 ("Very much, very frequently") based on recent symptoms.

Although the entire *CAARS* was completed by each subject, only three scales were selected for analysis on the basis of content. The *CAARS DSM-IV-TR ADHD Inattentive Symptoms scale (INATT)* and *DSM-IV-TR ADHD Hyperactive-Impulsive Symptoms scale (HI)* are based on ratings of the 18 DSM-IV-TR symptomatic criteria for ADHD. These two *CAARS* DSM-IV-TR-based scales describe frequency/severity of these symptoms. The *CAARS ADHD Index (ADHD Index)* is a statistically derived scale representing the best items to differentiate people with ADHD from people in the general population; an elevated *ADHD Index* indicates that the respondent is more similar to the normative ADHD sample than the general population sample on these items. Raw scores on these three *CAARS* scales were converted to age- and gender-adjusted T-scores for each of the 50 subjects. For purposes of the analyses, *CAARS* scores were categorized as “elevated” if they were at least one standard deviation above the mean ($T \geq 60$).

The *CAARS* also includes an *Inconsistency Index (IncX)*; elevations on the *IncX* suggest concerns about the validity of report due to excessive inconsistency in the responses. Subjects with a *CAARS IncX* greater than 7 were not included in analyses for this manuscript (this eliminated 10 subjects from analyses). Subject data were also excluded from analysis if missing data prevented scoring of the scales described above (i.e., *INATT*, *HI*, *ADHD Index*, or *IncX*; this eliminated an additional five subjects from analyses). These eliminations for inconsistent or missing data resulted in the final sample of 50 subjects described in this article.

Beck Depression Inventory-II (*BDI-II*)

The *BDI-II* is a self-report questionnaire that corresponds to the criteria for MDD [Beck et al., 1996] as defined in the DSM-IV-TR. The form includes 21 multiple-choice questions regarding mood, self-concept, sleep and other somatic symptoms of MDD that have occurred over the past 2 weeks. Sound psychometric properties have been established through a large spectrum of clinical and non-clinical populations; validity and reliability are both high [Beck et al., 1996]. The *BDI-II* normative samples included a general population sample ($n \approx 900$) and a clinical MDD sample ($n = 500$); this scale is suitable for use with subjects 13 years of age and older. The total raw score (*BDI-Total*) is categorized with a four-tier scale of minimal (0–13), mild (14–19), moderate (20–28), and severe (29–63) levels of depressive symptoms. For purposes of the analyses, per the recommendations of the *BDI-II* manual, *BDI-Total* raw scores of 14 and higher were categorized as “elevated.”

Data Analysis

The statistical software Statview, version 5.0.1 and PASW (formerly SPSS), version 18, were used for analyses. Descriptive statistics including means, standard deviations, and correlations for the measures determined distributions of values and their interrelations (e.g., correlations with age). Analyses of variance and *t*-tests were conducted to establish the presence of sex differences and education differences. Logistic regression analyses were performed to predict MDD as a function of ADHD status. Tests of between-group differences in composite scores were performed on all three mutation groups via Kruskal–Wallis Test. The significance level for all tests was set at $P < 0.05$.

RESULTS

Demographics

All 50 subjects, mean age $46.3 (\pm 13.9)$ years (38 females [45.6 ± 12.8], 12 males [48.3 ± 17.6]), completed the *CAARS* and *BDI-II*. There was an overrepresentation of females with

NPS (76%) in this study compared to the general population (51%) [U.S. Census Bureau, 2010].

Levels of education data were available for 43 of the 50 subjects (31 females, 12 males). These data were collapsed into three categories: (1) did not complete high school: 4/50 subjects (8%; 3 females, 1 male); (2) completed high school: 10/50 subjects (20%; 6 females, 4 males); and (3) higher education (e.g., some college, college degree, post-graduate education): 29/50 subjects (58%; 22 females, 7 males). Overall, the sample has a higher educational level than typical for adults in the U.S.A., where 8.7% of students do not complete high school, 74% complete high school, and 29.4% complete a bachelor's degree or higher [The National Center for Education Statistics (NCES), 2008].

Conners' Adult ADHD Rating Scales—Self-Report: Long Version (CAARS)

The *INATT scale* was elevated for 11/50 subjects (22%; 9/38 females [24%] and 2/12 males [17%]), the *HI scale* was elevated for 7/50 subjects (14%; 7/38 [18%] females and no males), and the *ADHD Index* was elevated for 8/50 subjects (16%; 6/38 females [16%] and 2/12 males [17%]) (Tables II and III). The range of T-scores for the *INATT scale*, *HI scale*, and *ADHD Index* are present in Figure 1; these T-scores reference age- and gender-based normative samples. Simple correlations of the T-scores on the *INATT scale*, *HI scale*, and *ADHD Index* indicated that elevations on the *INATT scale* tended to co-occur with elevations on the *HI scale* ($r[48] = 0.78$, $P < 0.001$) and *ADHD Index* ($r[48] = 0.86$, $P < 0.001$). The *HI scale* and *ADHD Index* were also highly related ($r[48] = 0.86$, $P < 0.001$).

Analyses of Age, Sex, and Educational Level Differences on the CAARS

The use of T-scores from the *CAARS* adjusts for age and sex differences in the raw data. Accordingly, there were no differences among the three education groups for any of the *CAARS* scales (all $F_s[2,40] \leq 1.64$, $P_s \geq 0.21$). Likewise, men and women did not differ significantly (all $F_s[1,48] < 0.86$, $P_s > 0.36$).

Beck Depression Inventory II (BDI-II)

The *BDI-Total score* was elevated for 20/50 subjects (40%; 15/38 [39%] females and 5/12 [42%] males) (Tables II and III), with 10 subjects reporting “mild,” 9 “moderate,” and 1 “severe” levels of MDD symptoms. The one “severe” case (raw *BDI-Total score* = 41) was included in the “elevated” group for purposes of logistic regressions, but was excluded from nominal regressions using the minimal, mild, and moderate categories. *BDI-Total* scores were mathematically converted to T-scores for ease of comparison; these T-scores do not reference a normative sample. The range of T-scores for the *BDI-Total* is present in Figure 1.

Analyses of Age, Sex, and Educational Level on BDI-Total Score

Correlation analyses showed no significant correlation between subject age and the *BDI-Total score* ($r[48] = 0.15$, $P = 0.30$). Analysis of variance indicated no mean *BDI-Total* differences among the three education groups, $F(2, 40) = 1.78$, $P = 0.18$. Men and women also did not differ significantly in their *BDI-Total score* ($t[48] = 0.50$, $P = 0.62$).

CAARS Versus BDI-II (n = 50)

Odds ratios indicated a significant increase in the odds of elevated *BDI-Total* when any of the three *CAARS* scores are elevated (Table IV). Elevations on the three *CAARS* scores were not always significantly associated with increased odds of a more severe *BDI-Total* classification (i.e., minimal, mild, or moderate); however, there were significant increases in

the odds of a moderate *BDI-Total* score (in comparison with a minimal *BDI-Total* score) when one of the three *CAARS* scores was elevated.

Mutation Screening

Kruskal–Wallis tests indicated there were no significant associations between predicted protein status (based on genetic mutation) and elevations on the *CAARS* or *BDI-II* (all $\chi^2[2, n=50] < 3.61, p > .165$).

DISCUSSION

Based upon the neuroanatomical abnormalities seen in *lmx1b*^{-/-} mice, and the notion that ADHD is a set of related but not identical dysexecutive disorders which are the result of dysfunctional frontal–striatal–cerebellar regions and circuits, it was hypothesized that humans with NPS would have similar abnormalities and would report more features of ADHD than reported by the general population. *Lmx1b* is required for proper formation of the entire 5-HT system in the hindbrain, as indicated by the loss of expression of genes necessary for serotonin synthesis and transport in *lmx1b* null mice [Cheng et al., 2003]. Possible symptoms of MDD were also evaluated given these pathways. Sixteen percent of the subjects with NPS reported high levels of general ADHD symptoms on the *CAARS*. This is consistent with statistically based expectations for using a cut-off of one standard deviation to identify “elevated” versus “not elevated” *CAARS* scores. More subjects with NPS reported symptoms of inattention on the *CAARS* than expected based on normative data (11/50, or 22%). Forty percent of the individuals with NPS reported elevated levels of MDD symptoms as measured by the *BDI-II*. Although the NPS sample may not be unique in terms of elevated *CAARS* scores, it is interesting that within the NPS sample those who had elevated *CAARS* scores had a significant increase in the odds of also reporting high levels of MDD symptoms. These comparisons ranged from a 10- to 15-fold increase. This is higher than described in other studies of MDD in adults with ADHD [McGough et al., 2005; Kessler et al., 2006].

The difference in odds ratios may be accounted for by the differences in evaluating data from symptom checklists, as opposed to clinical diagnoses. It is also possible that adults with NPS who have symptoms of ADHD are at increased risk for MDD symptoms, or that adults with NPS are more likely to report psychiatric symptoms in general. Without additional clinical data to guide differential diagnosis, it is difficult to determine if MDD symptoms could be presenting with features of inattention (although the report of elevated hyperactivity–impulsivity symptoms argues against this interpretation). It is possible that a common pathophysiologic process or pathway abnormality underlies these co-occurring symptoms. Regardless, it is important that clinicians evaluate for the presence of MDD, ADHD, and other psychiatric symptoms and disorders when working with adults who have NPS.

In the typical population, one would expect to see a higher rate of ADHD in males (odds ratio of 1.6) and a slightly higher rate of MDD in females (odds ratio of 1.7). Although in this group there were more females than males who volunteered to participate, the percentage of males and females did not differ in their rates of reported symptoms of ADHD and MDD. Although there may be more of a referral bias rather than actual gender bias in ADHD [Rucklidge, 2010] this should be further examined in control populations and larger NPS populations since there may be a neuroanatomical or functional effect of the *LMX1B* mutation on these pathways in NPS that could result in females and males being equally affected with symptoms of ADHD and MDD.

Previous articles have reported no significant correlation between mutations related to protein status and physical phenotypic features of NPS [McIntosh et al., 1998; Sweeney et al., 2003; Dunston et al., 2004]. This study adds to the existing literature by finding no significant correlation between mutations related to protein status and reported symptoms of ADHD or MDD as measured by the *CAARS* and *BDI-II*.

This study was limited in several ways. The size of the NPS population limited the available sample. The use of checklists rather than clinical evaluation (including interview, record review, and observation data) limits the extent to which conclusions can be reached about differential diagnosis. The reliance on using normative data (rather than a general population control group or clinical comparison group) limits interpretation as well. We did not obtain comprehensive data about other issues that could present as symptoms of MDD or ADHD, such as anxiety and chronic pain [Brown et al., 2002; Dick et al., 2008]; these issues might also be seen given the brain pathways that may be disrupted in NPS, and the joint, muscle, and tendon abnormalities that are present in NPS. Finally, the possibility of over-reporting or other validity-of-report concerns cannot be ruled out without inclusion of validity measures or measures intended to assess psychiatric symptoms that would not be expected to co-occur with NPS.

This is the first publication about psychiatric symptoms experienced by people with NPS. These data suggest further study is needed. Future studies in individuals with NPS should evaluate relationships among symptoms and disorders of attention, mood states, anxiety and pain by including additional measures. In addition to clinical interview and observations, evaluation with specific measures of intelligence, academic achievement, and attention would contribute to hypotheses regarding whether attention issues were primary deficits such as seen with ADHD or secondary to issues like anxiety, depression, and pain. Collecting data from a clinical control group with chronic pain (e.g., chronic back pain) might provide an interesting comparison, as well as collecting data from a general population sample.

Lmx1b expression in mice has been demonstrated within areas of the brainstem that possess direct neural connections to the regions implicated in the pathophysiology of ADHD. Furthermore, *lmx1b* is required for the development of neuronal systems to which drugs used in the treatment of ADHD are targeted [Dresel et al., 2000; Krause et al., 2000]. Together with evidence that ADHD and MDD symptoms can be co-elevated in individuals with NPS, these observations suggest that further investigation should be designed to comprehensively assess cognitive and psychiatric symptoms in order to confirm the elevated ADHD and MDD symptoms found with these screening tests within this population. Furthermore, due to nigrostriatal pathway neurons affected in NPS mice, motor symptoms should be assessed in the future. These data suggest that a deficit in *LMX1B* function may indeed induce symptoms related to dopaminergic neurologic pathway abnormalities, producing increased symptoms of ADHD (particularly inattention) and MDD.

Further research is required to determine if human subjects with NPS who have a *LMX1B* deficit are at higher risk of ADHD and MDD than the general population since *lmx1b* in the mouse is required for proper mesencephalic development. If so, a mental health screening should become part of routine care for patients with NPS in order to establish prevention and intervention strategies [Biederman et al., 2006; Fichter et al., 2009].

Acknowledgments

We are indebted to the individuals with NPS who participated in this study. We are also grateful to Laura Marsh, M.D., and Walter Kaufmann, M.D. for their assistance. This research was supported by NIAMS (AR44702 (IM)), the Alan and Kathryn Greenberg Center for Skeletal Dysplasias in the McKusick-Nathans Institute of Genetic

Medicine (JHF), the Kennedy Krieger Institute (ET), grant number UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

Grant sponsor: NIAMS; Grant Number: AR44702; Grant sponsor: Alan and Kathryn Greenberg Center for Skeletal Dysplasias in the McKusick-Nathans Institute of Genetic Medicine; Grant sponsor: Kennedy Krieger Institute Center for Disorders of Cognition and Behavior; Grant sponsor: National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) and NIH Roadmap for Medical; Grant Number: UL1 RR 025005.

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FIG. 1.

The range of T-scores from the *CAARS* and *BDI-II*. (The *BDI-Total* T-scores are based on a conversion, not relative to a normative population.)

TABLE I

Results of *Conners' Adult ADHD Rating Scale Self-Report: Long Version* and *Beck Depression Inventory II* for Individual Subjects Listing Sex, Age, Mutation Type, and Whether Scores on Measures Were Elevated Scores

Subject ID	Sex	Age	Mutation	CAARS-INATT	CAARS-HI	CAARS-ADHD Index	BDI-Total
007-07	f	52	p.R246X	N/E	N/E	N/E	N/E
018-01	f	41	p.L90fs	ELEVATED	ELEVATED	ELEVATED	ELEVATED
026-07	f	36	p.R223Q	N/E	N/E	N/E	N/E
027-03	f	54	p.W76X	N/E	N/E	N/E	N/E
029-06	m	75	p.C146Y	N/E	N/E	N/E	N/E
037-12	m	36	p.Q87X	N/E	N/E	N/E	N/E
047-03	f	35	p.R223Q	ELEVATED	N/E	N/E	N/E
057-02	f	72	p.C165W	N/E	N/E	N/E	N/E
057-05	f	42	p.C165W	N/E	N/E	N/E	N/E
057-07	m	19	p.C165W	N/E	N/E	N/E	ELEVATED
074-01	m	69	p.C143S	N/E	N/E	N/E	ELEVATED
074-08	f	55	p.C143S	ELEVATED	ELEVATED	ELEVATED	ELEVATED
075-01	f	35	p.R223Q	T-E N/E	N/E	N/E	ELEVATED
098-01	f	26	p.C140Y	N/E	N/E	N/E	ELEVATED
114-01	m	55	p.A236P	ELEVATED	N/E	ELEVATED	ELEVATED
116-01	f	49	p.L90_Q109dup	N/E	N/E	N/E	N/E
118-01	m	43	p.C83R	N/E	N/E	N/E	N/E
119-01	f	51	p.Q108X	N/E	N/E	N/E	ELEVATED
119-04	m	19	p.Q108X	N/E	N/E	N/E	N/E
133-01	f	47	p.K214fs	N/E	N/E	N/E	N/E
146-03	f	51	p.Q109X	N/E	N/E	N/E	ELEVATED
167-13	f	56	p.Q60X	N/E	N/E	N/E	ELEVATED
178-01	f	35	Unknown	N/E	N/E	N/E	ELEVATED
194-01	f	29	p.R249G	N/E	N/E	N/E	N/E
196-01	f	56	p.R261C	ELEVATED	ELEVATED	ELEVATED	ELEVATED
196-08	f	40	p.R261C	N/E	N/E	N/E	N/E
197-01	f	37	Unknown	N/E	N/E	N/E	N/E
205-01	m	54	p.S74X	N/E	N/E	N/E	N/E

Subject ID	Sex	Age	Mutation	CAARS-INATT	CAARS-HI	CAARS-ADHD Index	BDI-Total
210-01	f	27	p.S259fs	ELEVATED	ELEVATED	ELEVATED	ELEVATED
213-01	m	49	p.L101fs	N/E	N/E	N/E	ELEVATED
216-01	f	60	<i>p.A236P</i>	N/E	N/E	N/E	N/E
221-01	f	21	Unknown	N/E	N/E	N/E	N/E
221-02	f	42	Unknown	N/E	N/E	N/E	N/E
222-01	f	39	Unknown	N/E	N/E	N/E	ELEVATED
229-01	f	56	p.L101fs	N/E	N/E	N/E	N/E
230-01	f	24	Unknown	N/E	N/E	N/E	N/E
234-01	f	63	p.R221X	N/E	N/E	N/E	N/E
234-03	m	64	p.R221X	N/E	N/E	N/E	N/E
236-01	f	57	Unknown	N/E	N/E	N/E	N/E
237-01	f	55	Unknown	ELEVATED	ELEVATED	ELEVATED	N/E
246-01	m	53	p.L101fs	ELEVATED	N/E	ELEVATED	ELEVATED
246-04	f	42	Unknown	ELEVATED	ELEVATED	ELEVATED	ELEVATED
248-01	f	44	Unknown	N/E	N/E	N/E	N/E
262-03	m	43	Unknown	N/E	N/E	N/E	N/E
263-01	f	44	Unknown	N/E	N/E	N/E	N/E
264-01	f	48	Unknown	ELEVATED	N/E	N/E	ELEVATED
267-05	f	41	Unknown	ELEVATED	ELEVATED	N/E	ELEVATED
272-01	f	77	Unknown	N/E	N/E	N/E	N/E
273-01	f	59	Unknown	N/E	N/E	N/E	N/E
424-01	f	35	Unknown	N/E	N/E	N/E	ELEVATED

N/E: Scores were not elevated; mutations are described using the nomenclature established by Dunston et al. [2004]. Mutations shown in italic font are predicted to result in synthesis of a non-functional protein product; all other mutations are predicted to result in no protein product. Genotype information was available in 33 of the 50 subjects; all had a clinical diagnosis of NPS.

TABLE II

Descriptive Statistics

Measure	Mean $\pm$ SD	Count
CAARS—S:L (T-scores)		
DSM-IV Inattentive Symptoms (INATT)	50.08 $\pm$ 15.63	50
DSM-IV Hyperactive Impulsive (HI)	47.08 $\pm$ 13.68	50
ADHD Index (ADHD Index)	49.24 $\pm$ 12.63	50
BDI-II Total (raw score)	11.30 $\pm$ 9.03	50

TABLE III

Summary of Results for all 50 Female (F) and Male (M) Subjects

	Elevated ADHD Index (T 60)	Elevated INATT (T 60)	Elevated HI (T 60)	Elevated BDI-Total score (raw 14)
F	6 of 38 (16%)	9 of 38 (24%)	7 of 38 (18%)	15 of 38 (38%)
M	2 of 12 (17%)	2 of 12 (17%)	0 of 12	5 of 12 (33%)
50 Subjects	8 (16%) of all subjects	11 (22%) of all subjects	7 (14%) of all subjects	20 (40%) of all subjects

TABLE IV

Odds Ratios for *BDI-II* × *CAARS* Data From NPS Sample

Dependent variable (DV)	Independent variable (IV)	Odds ratio (OR) ^a	Significance
Elevated BDI-Total score (raw < 14)	Elevated CAARS-INATT	11,455	0.005
	Elevated CAARS-HI	12,429	0.025
	Elevated CAARS-ADHD Index	15,615	0.014
	Elevated CAARS-INATT	9,346	0.022
Mild BDI-Total score (raw 14–19), as compared to Minimal BDI-Total score (raw <14)	Elevated CAARS-HI	7,246	0.124
	Elevated CAARS-ADHD Index	12,500	0.040
	Elevated CAARS-INATT	1,200	0.845
Moderate BDI-Total score (raw 20–28), as compared to Mild BDI-Total score (raw 14–19)	Elevated CAARS-HI	2,000	0.513
	Elevated CAARS-ADHD Index	1,167	0.876
	Elevated CAARS-INATT	11,200	0.015
Moderate BDI-Total score (raw 20–28), as compared to Minimal BDI-Total score (raw <14)	Elevated CAARS-HI	14,500	0.031
	Elevated CAARS-ADHD Index	14,500	0.031

^aData in this table can be read as “There is an [OR]-fold increase in the odds of a [DV] when [IV]” (e.g., the first row would read, “there is an 11-fold increase in the odds of an elevated *BDI-Total score* when *CAARS-INATT* is elevated”).