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# Genetic Insights: Examining CNTNAP2 rs7794745 Gene Polymorphism and Its Impact on ABLLS Assessment in Middle Euphrates Children in Iraq with Autism Spectrum Disorder

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**Abstract**

**Objective:** Examine the effect of CNTNAP2 gene polymorphism on behavioral therapy response in Iraqi children with autism spectrum disorder using ABLLS-r.

**Methods:** In this study, 150 samples for autism spectrum disorder were obtained from AL-SIBTEIN ACADEMY, however owing to many challenges, the final number of samples was 50 patients. Polymerase Chain Reaction-Restriction refers to a technique that combines the use of polymerase chain reaction (PCR) with restriction enzymes to amplify and analyze certain DNA sequences. Fragment Length Polymorphism (PCR-RFLP) was used to genotype the CNTNAP2 gene at rs7794745. All 25 ABLLS-R repertoires and all four primary components had their dependent parameters determined by aggregating and converting the ABLLS data to a percentage. This provided us with the proportion of finished assignments from each repertoire.

**Results:** After correlating the genotype data (AA/AT/TT) with the behavioral therapy response as indicated by ABLLS-R, we only discovered a statistically significant difference between the frequency of AA/TT genotypes in the rs7794745 variant in patients and the social interaction domain. Conversely, the remaining 24 subdomains exhibited no discernible correlation.

**Conclusion:** This research topic could provide significant information on targeting and categorizing which skill areas need to be developed based on genetic models' influence.

**Keywords:** Autism, developmental disorder, ABLLS-R, polymorphism, CNTNAP2 gene

## Introduction

Autism spectrum disorder (ASD) has evolved from a strictly defined, uncommon affliction that starts in childhood to a well-known, extensively studied, championed, and lifelong condition that is now acknowledged as quite common and very diverse. Since its initial delineation, the description of the basic features of ASD as social communication deficits and repetitive and unusual sensory-motor behaviors has not changed significantly.[1] However, autism has been defined as a spectrum that ranges from extremely mild to severe. Nonetheless, numerous Individuals with autism spectrum disorder (ASD) require some (but not all) lifelong support. Several intervention options are accessible, including the Picture Exchange Communication System, floor time, holding, medicine, diets and vitamins, applied behavior analysis (ABA), speech and music therapy, special education, and visual time.[2] Early Intensive Behavioral strategy (EIBI), a well-studied strategy for children with Autism Spectrum Disorder (ASD), is mostly based on studies conducted in the 1960s.[3] The approach is grounded in operant learning principles and centers on addressing language deficiencies, imitation, pre-academic skills, self-care abilities, and social interaction. The abilities are deconstructed into separate elements and taught individually, either in an educational institution or a domestic environment. The teaching approach commonly used is discrete trial teaching, which incorporates planned generalization, reinforcement, backward chaining, shaping, extinction, prompting, and prompt fading.[4] Numerous studies have demonstrated that genetic inheritance contributes to the development of this condition.[5] Copy number variants, point mutations, and rare variants in synaptic cell adhesion proteins have all been implicated in the pathogenesis of Autism Spectrum Disorder (ASD), according to genetic investigations.[6] Genetic studies indicates that the primary cause of ASD is the disturbance of synapse development and stability.[7] An extensive number of genes that are essential for the formation and function of synapses have been identified by scientists. Many genes, such as CNTNAP2, NLGN3, and NLGN4X, have been linked to the process of glial adhesion to neurons.[8] Brain regions associated with autism spectrum disorder (ASD) contain the CNTNAP2 gene, which has been linked to ASD.[9] CNTNAP2, a member of the neurexin superfamily, is composed of 24 exons that span 2.3 megabases on chromosome 7q. It is acknowledged to be among the most sizable genes found in mammals.[10] Significant levels of CNTNAP2 are expressed in the developing spinal cord and brain. Caspr2 is a protein situated within the cell membrane that functions as a scaffolding molecule in neurons and is accountable for encoding contactin-associated protein-like.[2] The aggregation of K+ channels occur in the juxta paranodal region of the nodes of Ranvier in myelinated axons, which is its function. Moreover, it is postulated to be involved in cellular migration and the subsequent establishment of laminar organization.[11,12] Its significance in the realm of speech and language is indicated by the upregulation of CNTNAP2 in Broca's area and other perisylvian brain regions.[13] It has been demonstrated that both prevalent and uncommon CNTNAP2 variants affect susceptibility to ASD and autism.[9] The non-coding variant Rs7794745 is situated within intron 2 of the CNTNAP2 gene. The results

suggest that the A/T variant in rs7794745 substantially diminishes the cerebral response associated with the perception of human speech.[14] In the Chinese Han population, the A/T variant of rs7794745 has also been identified as a risk genotype for ASD.[15] Additionally, a correlation between autism and the rs7794745 CNTNAP2 gene polymorphism was demonstrated in an Iranian study.[16] Epidemiological studies reveal a rising trend in the annual prevalence of ASD. In addition to the actual rise in ASD prevalence, many additional factors have been proposed to explain this phenomenon, including a larger definition of ASD, modifications to diagnostic standards and screening instruments, changes in research methodologies, and greater public awareness of ASD.[17] ASD is now four to five times more common in boys than in girls (sex ratio is 4.2:1).[18] It has been estimated that the average prevalence of autism spectrum disorder in Asia, Europe, and North America is approximately 1%.[19] Limited research has been conducted on the prevalence of autism in the Middle East. According to the Institute of Health Metrics and Evaluation (IHME), the children's Autism rate in Iraq is 328.27 per 100k, in Saudi Arabia is 340.15 per 100k, in the United Arab Emirates is 335.45 per 100k, in Qatar is 340.74 per 100k. This statistic serves as evidence of the growing demand for efficient teaching strategies and educational services. Guldberg identified several factors that describe best practices, such as the ability to recognize significant differences between individuals with ASD in terms of their skills, intelligence, and behavior.[20] She also emphasized the significance of thoroughly analyzing each individual's skills and customizing subsequent interventions to match his or her specific requirements. The use of effective and developmentally appropriate teaching strategies, as well as long-term tracking of children's progress, can all be inferred as necessary components of best practices in achieving optimal learning and development. The Assessment of Basic Language and Learning Skills-Revised (ABLLS-R) is a popular criterion-referenced assessment tool that provides a comprehensive overview of several essential skills and could be useful for measuring skill development and informing educational programming.[21] This study aims to investigate the effect of CNTNAP2 rs7794745 gene polymorphism on ABLLS-R response in Middle Euphrates Iraqi children with autism.

## Materials and Methods

### *Patients*

Fifty autistic patients (males and females, mean age 4.5 ± 2 years) were recruited from Al-Sibtein Academic Center for Autism. ASD patients were diagnosed by well-trained psychiatrists using DSM-IV criteria and accessible historical information from interviews and clinical records. This study was made known to all participants and their families. The ethics committee of the University of Kufa has authorized this initiative.

### *ABLLS Assessment*

From June to August 2023, data from the ABLLS-R assessment sheets was gathered. Following the admission of children to the Al-Sibtein Academic Center for autism spectrum disorders, the assessors commenced data collection two to three weeks later. The dependent variables for each of the four main sections and all 25 ABLLS-R repertoires were determined by calculating the percentage of completed items out of the total number of items in each repertoire. This provided us with the proportion of jobs accomplished from each repertoire.

### *Genotyping*

PCR is a widely used method to analyze genomic variations, which are single nucleotide polymorphisms (SNPs) in DNA, which can serve as genomic character markers in diseases or drug responses, highlighting the growing recognition of genomic variations in disease etiology.[22] As a result of the challenges encountered in procuring blood samples from all ASD patients, buccal swaps were utilized to obtain their blood. These buccal swaps were then preserved in a tube containing normal saline. From the SNP database of the National Center for Biotechnology, one single nucleotide polymorphism (rs7794745) in the CNTNAP2 gene was chosen. Genomic DNA was extracted using the AddPrep Genomic DNA Extraction Kit. The manufacturer recommended using polymerase chain reaction (PCR-RFLP) to genotype the SNP. Utilizing the designated primer, a 315-bp fragment containing the targeted SNP was amplified via PCR. The variants of CNTNAP2 were initially genotyped using a conventional PCR-RFLP assay. Utilizing the subsequent primers, a 315-bp fragment containing the loci was amplified. 5′ AATACGGACCAAGATACCAAC 3′ is the F primer, and 5′ TTCAGACCAACAGTGCCTT 3′ is the R primer. A 50-l volume was added to each reaction, which contained the following components: 25 µl of PCR master mix, 4 µl of each primer, 13 µl deionized water, and 4 µl of DNA. The conditions for PCR were as follows: Thirty seconds of initial denaturation at 94°C, thirty seconds of annealing at 56°C, one minute of extension at 72°C, and five minutes of final extension at 72°C To figure out how big the PCR products were, the results were put on a 1% agarose gel, and 5 µl of Safe-Green 100 bp Opti-DNA marker was used to color them. This marker was introduced into the first-line pores of the gel. Following this, the gel was transferred to the UVP apparatus, where the PCR products were crystallized using a 320 nm UV light source. The restriction enzyme digestion of Mluc1 (New England Biolabs) was employed to cut the wild-type sequence by 315 base pairs. The CNTNAP2 gene harbors an A-to-T base pair mutation that confers a restriction site for Mluc1. Ten units of the necessary restriction enzyme were mixed with 1 to 3 µg of the PCR product in a 1X restriction buffer. Following a three-hour incubation at 37°C (or an enzyme-appropriate temperature), the digests underwent electrophoresis to observe the outcomes. After electrophoresis, the digestive products were seen on a 1% agarose gel that had been colored with a Safe-Green marker.

## Result

An examination was conducted on a group of fifty children diagnosed with autism. The MlucI enzyme results indicate that patients with the CNTNAP2 genotype AA, who do not have the A→T mutation, produce a PCR fragment of size 315 bp. On the other hand, individuals with the heterozygous genotype AT exhibit three bands in their PCR product, measuring 220, 95, and 315 bp. In addition, individuals with homozygous genotypes (TT) that carry a mutation (A→T) exhibit two pieces, measuring 220 and 95 base pairs (bp) respectively. As seen in Figure 1.

A combination of observation and direct tests are used to complete the ABBLS. ABLLS consists of 25 domains, each

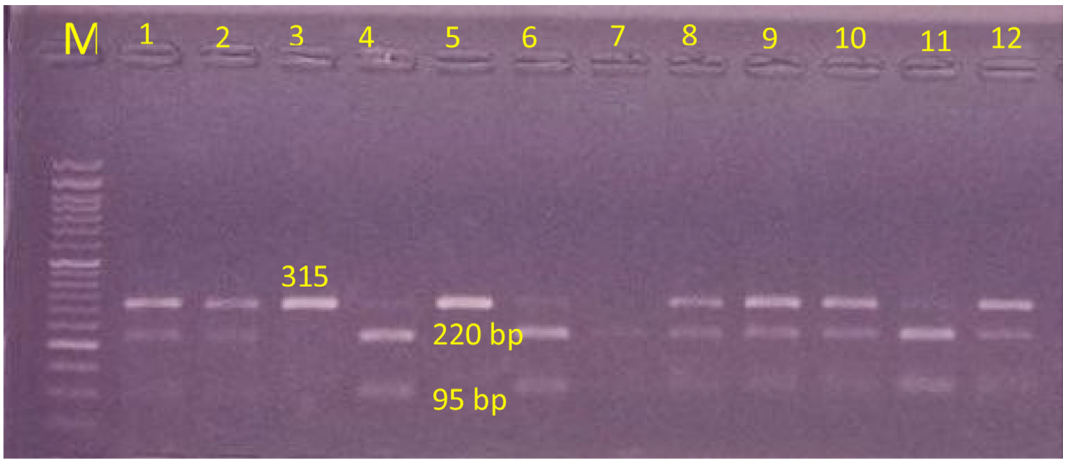


Fig. 1 **Agarose gel electrophoresis stained by Redsafe after PCR-RFLP. M is the ladder, Lanes 3 and 5 show the AA genotype, lanes 4, 6, and 11 show the AT genotype, and Lanes 1, 2, 8, 9, 10, and 12 show the TT genotype.**

Table 1. **Illustrates HWE for patients, consistent with HWE**

| Genotype | Observed | Expected | $X^2$ | P value |
|---|---|---|---|---|
| AA | 12 | 11.52 | 0. 074 | 0.786 |
| AT | 24 | 24.96 | | |
| TT | 14 | 13.52 | | |
| A | 48% | | | |
| T | 52% | | | |

domain contains 6 to 52 tasks that are rated on a 0–4 scale to determine whether each skill is an absent, emerged, or mastered part of their repertoire. The six meta domains represented learning skills, language, social/play, academic, self-help, and finally motor skills. Scores were obtained for each 25 ABLLS domains and converted to percentage scores. Statistical analysis was performed using the SPSS version 26. IBM to analyze the association between genotype models (AA/AT/TT) and HWE based on the ANOVA and chi square tests (Table 1). Results of this analysis are presented in Table 2 illustrating the mean scores and *P*-values generated from the test.

According to our statistical results, there is a significant association between AA and TT genotypes and social interaction meta domain only (*P* value 0.01), in contrast to other domains, there no significant association with CNTNAP2 gene polymorphism rs7794745 (*P* value ranging from 0.2 to 0.9).

## Discussion

The goal of this cross-sectional study was to delineate CNTNAP2 rs7794745 gene polymorphism impact on the response of the behavioral therapy treatment, as measured by the ABLLS-R, so that parents and educators can make decision according to these data when determining educational programs for individuals diagnosed with ASD. It is well known that the CNTNAP2 gene, which belongs to the extended Neurexin gene superfamily, plays a significant role in the development of autism spectrum disorder (ASD) as well as several linked disorders like dyslexia, language

Table 2. **The association of genotypes and the percentage of skills from each ABBLS-R repertoire and their *P*-value**

| Parameter/ genotype | | *N* | Mean | SD | *P*-value |
|---|---|---|---|---|---|
| A | AA | 12 | 37.8289 | 30.89432 | 0.643 |
| | AT | 24 | 29.0570 | 25.33919 | |
| | TT | 14 | 33.0774 | 24.53563 | |
| | Total | 50 | 32.2880 | 26.23303 | |
| B | AA | 12 | 14.1204 | 18.72829 | 0.61 |
| | AT | 24 | 9.5293 | 13.03316 | |
| | TT | 14 | 13.3639 | 14.01526 | |
| | Total | 50 | 11.7049 | 14.66691 | |
| C | AA | 12 | 16.4663 | 21.61579 | 0.48 |
| | AT | 24 | 10.7171 | 11.72549 | |
| | TT | 14 | 11.1678 | 7.47147 | |
| | Total | 50 | 12.2231 | 13.78675 | |
| D | AA | 12 | 15.4321 | 29.29188 | 0.85 |
| | AT | 24 | 10.6096 | 24.33890 | |
| | TT | 14 | 12.4328 | 20.20709 | |
| | Total | 50 | 12.2775 | 24.14147 | |
| E | AA | 12 | 16.3542 | 35.72885 | 0.55 |
| | AT | 24 | 7.4479 | 17.47078 | |
| | TT | 14 | 9.6536 | 16.97587 | |
| | Total | 50 | 10.2030 | 22.78967 | |
| F | AA | 12 | 7.3994 | 7.94753 | 0.42 |
| | AT | 24 | 4.9210 | 9.20255 | |
| | TT | 14 | 3.2710 | 4.55781 | |
| | Total | 50 | 5.0538 | 7.85532 | |
| G | AA | 12 | 4.1667 | 8.84508 | 0.86 |
| | AT | 24 | 3.3910 | 9.58578 | |
| | TT | 14 | 2.3511 | 4.93724 | |
| | Total | 50 | 3.2860 | 8.22229 | |

(Continued)

Table 2. **The association of genotypes and the percentage of skills from each ABBLS-R repertoire and their *P*-value—Continued**

| Parameter/ genotype | | *N* | Mean | SD | *P*-value |
|---|---|---|---|---|---|
| H | AA | 12 | 1.0204 | 2.27131 | 0.5 |
| | AT | 24 | .5740 | 1.65710 | |
| | TT | 14 | .2529 | .58898 | |
| | Total | 50 | .5912 | 1.61772 | |
| I | AA | 12 | 4.0570 | 8.10055 | 0.74 |
| | AT | 24 | 5.1535 | 8.99065 | |
| | TT | 14 | 3.1015 | 5.62063 | |
| | Total | 50 | 4.3158 | 7.86353 | |
| J | AA | 12 | 1.2500 | 4.33013 | 0.43 |
| | AT | 24 | .1042 | .51031 | |
| | TT | 14 | .7143 | 2.67261 | |
| | Total | 50 | .5500 | 2.53999 | |
| K | AA | 12 | 20.9722 | 12.17421 | 0.72 |
| | AT | 24 | 18.9028 | 23.20367 | |
| | TT | 14 | 15.1264 | 13.71243 | |
| | Total | 50 | 18.3421 | 18.45761 | |
| L | AA | 12 | 13.0515 | 11.16945 | |
| | AT | 24 | 6.8137 | 11.66080 | 0.08 AA & AT |
| | TT | 14 | 2.6089 | 2.87362 | **0.01** AA & TT |
| | Total | 50 | 7.1334 | 10.41624 | 0.21 AT & TT |
| M | AA | 12 | 19.4444 | 31.68676 | 0.21 |
| | AT | 24 | 12.2743 | 18.02900 | |
| | TT | 14 | 5.0595 | 9.37818 | |
| | Total | 50 | 11.9750 | 20.70450 | |
| N | AA | 12 | 20.6250 | 26.26623 | 0.87 |
| | AT | 24 | 16.3542 | 23.61350 | |
| | TT | 14 | 16.2500 | 26.21564 | |
| | Total | 50 | 17.3500 | 24.54385 | |
| O | AA | 12 | 6.2500 | 17.08749 | 0.34 |
| | AT | 24 | 1.0417 | 3.73689 | |
| | TT | 14 | 4.7619 | 12.10455 | |
| | Total | 50 | 3.3333 | 10.78022 | |
| P | AA | 12 | 3.6765 | 10.12077 | 0.41 |
| | AT | 24 | .7353 | 2.63781 | |
| | TT | 14 | 1.6807 | 6.28850 | |
| | Total | 50 | 1.7059 | 6.17776 | |
| Q | AA | 12 | 1.7241 | 4.98620 | 0.82 |
| | AT | 24 | .9698 | 2.48181 | |
| | TT | 14 | 1.2931 | 3.11283 | |
| | Total | 50 | 1.2414 | 3.33723 | |
| R | AA | 12 | 5.6250 | 11.68356 | 0.33 |
| | AT | 24 | 9.5833 | 16.01064 | |
| | TT | 14 | 3.2143 | 6.68153 | |
| | Total | 50 | 6.8500 | 13.06196 | |
| S | AA | 12 | .0000 | .00000 | 0.9 |
| | AT | 24 | .0000 | .00000 | |
| | TT | 14 | .0000 | .00000 | |
| | Total | 50 | .0000 | .00000 | |
| T | AA | 12 | 12.5000 | 18.54901 | 0.45 |
| | AT | 24 | 16.1458 | 32.70034 | |
| | TT | 14 | 13.3033 | 19.70568 | |
| | Total | 50 | 14.4749 | 26.17056 | |
| U | AA | 12 | 41.6667 | 20.59715 | 0.46 |
| | AT | 24 | 46.4583 | 57.71894 | |
| | TT | 14 | 28.3329 | 21.54256 | |
| | Total | 50 | 40.2332 | 42.91925 | |
| V | AA | 12 | 19.6429 | 29.39164 | 0.75 |
| | AT | 24 | 14.5833 | 20.58152 | |
| | TT | 14 | 13.1965 | 18.76112 | |
| | Total | 50 | 15.4093 | 22.18708 | |
| W | AA | 12 | 11.0417 | 20.09801 | 0.91 |
| | AT | 24 | 14.2708 | 28.07675 | |
| | TT | 14 | 15.3929 | 25.79966 | |
| | Total | 50 | 13.8100 | 25.29800 | |
| X | AA | 12 | 21.1111 | 20.51525 | 0.47 |
| | AT | 24 | 12.8236 | 21.63473 | |
| | TT | 14 | 18.1895 | 16.96778 | |
| | Total | 50 | 16.3151 | 20.07923 | |
| Y | AA | 12 | 22.9167 | 20.90587 | 0.88 |
| | AT | 24 | 21.7679 | 23.62386 | |
| | TT | 14 | 18.5153 | 26.68879 | |
| | Total | 50 | 21.1329 | 23.49432 | |

impairment, epilepsy, and schizophrenia.[23] CNTNAP2 gene variants have shown both positive and negative associations with autism in different populations.[16,24] The current work is a pioneering study into the molecular genetics of autism and the relationship of polymorphisms in the CNTNAP2 gene rs7794745 to the behavioral therapy as assessed by ABLLS-R Among Middle Euphrates Iraqi population as a significant step toward a more comprehensive knowledge of the molecular mechanism of the CNTNAP2 gene's function in the disease and tailoring a specific learning program. This assessment tool is widely used because it provides a comprehensive overview of many important skills, allows for the measurement of skill development, and can be used to customize educational programming. These statistics can help with the process of establishing developmentally appropriate teaching objectives by illuminating which ABLLS-R skills to teach a student based on their present age and existing competencies. It has also been recognized as a valuable resource

for professionals and parents in helping children with autism spectrum disorder (ASD) acquire essential language and learning skills. This popular test includes 544 skills from 25 distinct repertoires, with a focus on language, social skills, academics, self-help, and motor skills. there're no previous studies about this association. According to the results, there is a significant association between (AA / TT) CNTNAP2 genotypes and subdomain L (social interaction), while there's no association with the three different genotypes with other 24 subdomains. There are several limitations to the current study indicating the need for more discussion. Initially, we selected a less-than-ideal group of participants, which was determined by the various challenges we encountered when gathering data from their families. Increasing the number of participant samples might improve the validity of our findings and, depending on the sample size, lead to the formation of normative data that records the child's skills who is typically developing at a specific age. Due to this restriction, we see our findings as preliminary evidence of the influence of genotype models on the development of typical skills; more study is needed to verify the correctness of our findings.

## Conclusion

As a conclusion, this research area could provide a valuable information about targeting and categorizing which skills area that needed to be developed according to their influence by genotypes models.

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## Conflict of Interest

None.

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