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# The Impact of p.H63D and p.C282Y Polymorphisms Associated with Iron Status on Autism in Iraqi Children

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## Abstract

**Background:** Autism is a neurodegenerative disease associated with alterations in the metabolism of iron in the central nervous system. There is evidence that children with autism have distinct iron-related proteins in their serum, and the SNPs p.H63D and p.C282Y have been found to be significantly correlated with a number of neurological illnesses.

**Objectives:** To determine the impact of p.H63D and p.C282Y polymorphisms associated with iron status on autism in Iraqi children.

**Patients and Methods:** The study was conducted from June 2023 to January 2024, involving 30 individuals with autism and 30 controls, with ages ranging from 4 to14 years. After extracting the DNA, specific sequence amplification and restriction enzymes digestion were used to investigate the genotyping of p.H63D and p.C282Y as well as TIBC, iron, transferrin, and ferritin, which were measured using an autoanalyzer.

**Results:** Our findings showed the mean serum iron(70.68±20.21µg/dL),ferritin(32.11±9.15µg/dL) and transferrin (13.59±1.45(g/L))levels of autistic children were significantly lower than the mean of the control group(90.22±22.11,79.9±20.65,25.75± 3.69 respectively) p-value<0.05, and that an elevated risk of autism in the presence of homozygous H/H(83.3%)at p.H63D and C/C (100%) homozygote of p.C282Y, and the polymorphisms was substantially correlated with decreased serum transferrin levels (odd ratio =1.20 ,p-value=0.01(with H/H),1.18 ,p-value=0.02 with C/C).

**Conclusion:** The decreased serum transferrin levels were associated with a higher incidence of autism that is associated with the presence of p.H63D and p.C282Y polymorphisms. Low levels of iron, ferritin, and transferrin in autism patients can lead to cognitive and physical problems, which may increase the risk of developing autism symptoms.

**Keywords:** p.H63D, p.C282Y, Transferrin, Ferritin, Iron.

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## Introduction

Among the neurodevelopmental disorders of pediatrics, autism, also known as autistic spectrum disorder, is a complex behavioral phenotype with a multigenic etiology that is becoming increasingly significant. Prior to the age of three, its frequency increases (1), but the most current estimates of prevalence are between 6.5 and 6.6 per 1,000 people (2). Iraqi government records and epidemiological research have shown a rise in the prevalence of autism, which suggests the significance of potentially altering external or environmental causes (3). Difficulties with language, communication, social engagement, and imaginative play are signs of autism, according to the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders and the Tenth Revision of the International Classification of Diseases (4,5). One of the trace elements that has been studied the most for maintaining the reliability and optimal function of the central nervous system is iron. Trace elements have been linked in recent times to possible risk factors for autism (6). Iron has been identified as a key possible cause of increased generation of reactive oxygen species (ROS), which could result in glioneuronal injury in the central nervous system. Compared to their siblings without autism, children with autism have been found to have lower levels of two other antioxidant proteins, ceruloplasmin and transferrin (7). Ceruloplasmin's main function is to protect cell membranes from reactive oxygen radicals, which are produced in the brain (8). Serum and other bodily fluids contain transferrin, which is primarily responsible for moving iron to proliferating cells (9). Homeostatic iron regulator (HFE) is a class I-like gene for the major histocompatibility complex (MHC) (10). The HFE protein attaches to the transfer receptor (TfR) in competition with transferrin (Tf) and b2-microglobulin (ß2M). When it functions properly, it regulates iron endocytosis by acting as an inhibitor (11,12) In HFE, two frequent single nucleotide polymorphisms (p.C282Y and p.H63D) have been found in Caucasian groups at the greatest rate (13) More than 80% of individuals in North Europe, however, have a rare missense mutation at nucleotide 187 called a C/G transversion. It induces the transition of amino acid 63 (H63D) from histidine to aspartic acid. (14,15). The prevalence of the H63D polymorphism's D allele was found to be approximately 11% in a prior study (16) The most common mutation in Caucasians, C282Y, is a G/A transition at nucleotide 845 of the open reading frame, converting the cysteine amino acid to the amino acid tyrosine (14). Because of their established physiologic effects on iron metabolism, the p.H63D and C282Y polymorphisms were chosen as potential genetic risk indicators for autism in the present investigation. The aim of this study was to determine the impact of p.H63D and p.C282Y polymorphisms associated with iron status, such as ferritin, serum iron, transferrin, and TIBC level, on autism in Iraqi children.

## Patients and Methods

**Study design:** Thirty autistic patients were taken as cases, all from the National Autism Center Children's Protection Teaching Hospital in Medical City in Baghdad, Iraq, from June 2023 to January 2024, and their ages ranged from 4 to 14 years old. A confirmed medical diagnosis was made using the standards for autistic disorder as stated in (4). Thirty samples of healthy kids in the identical age range were employed in the study as the control group.

**DNA extraction and PCR analysis:** In order to extract DNA, blood was taken in tubes containing EDTA. Using the Qiagen DNA extraction kit and normal protocols, genomic DNA was obtained. Primers and sequences were used for PCR, with annealing temperatures set at 55°C. Primers HFE F (5′-TGTGGAGCCTCAACATCCT-3′) and

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HFE R (5′-TGAAAAGCTCTGA CAACCTCA-3′) were used to amplify exon 2 carrying the p.H63D mutation, as well as primers HFE F(5′-TCCAGTCTTCCTGGCAA-3′) and HFE R (5′-TTCTAGCTCCT GGCTCTCA-3′) for the amplification of exon 4 carrying the p.C282Y mutation (10). The PCR reaction mixture contained the following components: ten microliters of the ReddyMix 2x (ABgene), 10 pmol forward and 10 pmol reverse primers, 50ng DNA, and twenty µl of nuclease-free water. The cyclic settings were as follows: Thirty cycles for 30 seconds at 95°C, thirty seconds at 57°C, and at 72°C for 45 seconds, ending in a last 10-minute period at 72°C. The HFE p.C282Y polymorphism underwent the identical cycle conditions but annealed at 55◦C, as previously mentioned. As previously mentioned, optimal restriction endonuclease combinations (New England Biolabs), MboI for p.H63D and RsaI for p.C282Y were used to identify the candidate SNP. Ethidium bromide staining was used to visualize the digestion products after, the 210 bp H63D and 320 bp p.C282Y PCR products had been electrophoresed on 2.5 % agarose gelb (11).

**Laboratory tests:** Blood containing five milliliters was drawn for analysis of the hemoglobin, iron, total iron binding capacity (TIBC), and serum ferritin levels. The auto-analyzer Cobas Integra 400 plus (Basel, Switzerland: Roche Diagnostics) was used to measure blood iron, transferrin, and TIBC. The Beckman Coulter Access 2 CLIA method was used to measure serum ferritin, and the Drabkins method was used to measure hemoglobin level (17). The World Health Organization (WHO) recommended a cut-off of <12 µg/L, which was followed due to variations in low-value cut points (18) so when ferritin in serum is less than 12 ng/dL and hemoglobin concentration is lower than 11–12 g/dL, anemia is considered to exist (12). The ferritin cutoff was less than 10–12 ng/ml (13).

## Statistical Analysis

Using the SPSS version 20 software package, all continuous variables were expressed using the mean and standard deviation (SD). To compare various means, the t-test was utilized. The $\chi 2$ test was used to compare categorical data, such as genotype frequency. We used the odds ratio (OR) and a 95% confidence interval (CI) to examine the impact of important risk factors. A p-value of below 0.05 is considered to indicate the presence of statistical significance.

## Results

**The genotype of p.H63D:** In autistic patients, the frequency of the H/H homozygote is 25 (83.3 %), and for the H/D heterozygote, it is 3(10%), while the prevalence of the D/D homozygote is 2(6.7%). In contrast to the control group, which has zero homozygote D/D, a pair (10%) of H/D heterozygotes, and 28 (90%) H/H wild type homozygotes. The allele D and autism do not significantly correlate, based on the chi-square analysis (p = 0.17) as shown in Table 1.

**Table 1.** Genotyping frequency for p.H63D in the two study groups.

| Genotype | Case NO. (%) (95% CI) | Control NO. (%) (95% CI) |
|---|---|---|
| H/H | 25 (83.3 %) (1.59–3.55) | 28(90) (1.01-2.56) |
| H/D | 3(10%) (0.01–0.79) | 2(10%) (0.01–0.79) |
| D/D | 2(6.7%) (0.09–0.29) | 0(0%) |

**The genotype of p.C282Y:** The 320 bp p.C282Y PCR products were employed through the use of 2.5% agarose gel. In our cases, 19 are wild type C/C (95%), while one control sample (5%) has C/Y genotyping. There are no heterozygotes C/Y found in autistic patients; only the wild-type C/C is observed. There were no homozygotes Y/Y in either the control or autistic subjects (Table2). Logistic regression analysis revealed that neither age nor sex had a significant impact on the

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existence of autistic traits in the cases under study (p-value = 0.07). Neither the C nor the Y allele was found to have a significant influence. In two sample groups, p.H63D is more prevalent than C282Y and there is no linking of our sample's HFE polymorphisms to autism.

**Table 2.** Genotyping frequency for p.C282Y in the samples under study.

| Genotype | Case NO. (%) (95% CI) | Control NO. (%) (95% CI) |
|---|---|---|
| C/C | 30 (100 %) (1.78–3.95) | 29(95%) (1.60-3.58) |
| C/Y | 0(0%) | 1(5%) (0.01–0.53) |
| Y/Y | 0(0%) | 0(0%) |

**Chemical biomarkers:** According to foundation chemical biomarkers, the mean serum ferritin value of autistic children was 32.11±9.15 µg/L, considerably less than the mean of the non-autistic group, 79.9±20.65 µg/L ($p<0.05$). The study found that the mean hemoglobin concentration was dropped in the autistic group, but the variance between them was not substantial (p-value=0.421). The autistic group's iron level was significantly lower than the non-autistic group's, 70.68±20.21 against 90.22±22.11.71 µg/dL ($p<0.001$). The autistic group's mean TIBC is significantly higher than the normal groups. All autistic children had significantly lower transferrin saturation levels (13.59 ± 1.45%) than normal children (25.75 ± 3.69%) at the same age, as shown in Table 3.

**Correlation:** Table 4 demonstrated that there was actually not a correlation among blood ferritin, iron, transferrin saturation, and homozygous H/H at p.H63D polymorphism in the two sample groups, since the odd ratio was shown to be 0.79, 0.86, and 0.74, respectively, in autism cases, while in controls, it was 0.64, 0.74, and 0.74, respectively, and there was no significant difference (p-value > 0.05), while the presence of homozygous H/H at p.H63D polymorphism in autism cases was significantly associated with serum transferrin levels in autism cases (odd ratio = 1.20, p-value < 0.05), while there was no correlation with control groups (p-value > 0.05). Table 5 indicated that there was actually not a correlation among blood ferritin, iron, transferrin saturation, and homozygous C/C at p.C282Y polymorphism in the two sample groups, since there was shown the odd ratio was in autism cases = 0.86, 0.74, and 0.74, respectively, while in controls = 0.79, 0.71, and 0.71, respectively, and there was no significance (p-value > 0.05), while the presence of homozygous C/C at p.C282Y polymorphism in autism cases was significantly associated with serum transferrin levels in autism cases (the odd ratio = 1.18, p-value < 0.05), while there was no correlation with control groups (p-value > 0.05).

**Table 3.** Iron Deficiency (ID) parameters in the two study groups.

| Parameters | Patients | Healthy | P- value |
|---|---|---|---|
| Serum ferritin (µg/L) | 32.11±9.15 | 79.9±20.65 | 0.02 (Sig.) |
| Serum iron (µg/dL) | 70.68±20.21 | 90.22±22.11 | 0.04 (Sig.) |
| Serum TIBC (µg/dL) | 450.11±80.21 | 350.72±40.21 | 0.04 (Sig.) |
| Transferrin (g/l) | 13.59 ±1.45 | 25.75± 3.69 | (0.01) (Sig.) |
| Hemoglobin (g/dL) | 11.21±0.99 | 13.11±1.01 | 0.41 (N.S) |

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**Table 4.** The relationship between iron status and H63D.

| Iron statute on samples combined estimated with H/H homozygote of p .H63D | Samples | SNP (N) | Odd Ratio | 95% CI | P- value |
|---|---|---|---|---|---|
| ferritin (µg/L) | Cases | 5 | 0.79 | 0.65–1.59 | 0.58 |
| | Control | 6 | 0.64 | 0.51–1.32 | 0.41 |
| Serum iron (µg/dL) | Cases | 5 | 0.86 | 0.88–1.41 | 0.87 |
| | Control | 6 | 0.74 | 1.06–1.11 | 0.62 |
| Transferrin (g/l) | Cases | 10 | 1.20 | 1.69–1.75 | 0.01* |
| | Control | 10 | 0.89 | 0.79–1.48 | 0.11 |
| Transferrin saturation (%) | Cases | 5 | 0.74 | 1.06–1.11 | 0.32 |
| | Control | 6 | 0.72 | 0.98–1.01 | 0.25 |
| (*) Significant, SNP: Single nucleotide polymorphism | | | | | |

**Table 5.** The relationship between iron status and C282Y.

| Iron statute on autism combined estimated with C/C homozygote of p.C282Y | Samples | SNP (N) | Odd Ratio | 95% CI | P- value |
|---|---|---|---|---|---|
| ferritin (µg/L) | cases | 5 | 0.86 | 0.88–1.41 | 0.87 |
| | control | 5 | 0.79 | 0.65–1.59 | 0.54 |
| Serum iron (µg/dL) | Cases | 8 | 0.74 | 1.06–1.11 | 0.87 |
| | Control | 8 | 0.71 | 1.01–1.02 | 0.75 |
| Transferrin (g/l) | Cases | 9 | 1.18 | 1.02–1.40 | 0.02* |
| | Control | 9 | 0.71 | 1.01–1.02 | 0.31 |
| Transferrin saturation (%) | Cases | 8 | 0.74 | 1.06–1.11 | 0.32 |
| | Control | 7 | 0.68 | 0.88–1.06 | 0.25 |
| (*) Significant, SNP: Single nucleotide polymorphism | | | | | |

## Discussion

Despite several research studies having been conducted to explore the relationship between iron status and autism (14,15,) this investigation is conducted to analyze the inherently causal connection between iron status and autism risk. Our findings showed that genetically indicated serum transferrin was linked to an increased risk of autism, suggesting that transferrin could be an indicator for autism development.

The iron-regulating gene HFE's most prevalent functional polymorphism (p.H63D and C282Y), it has been connected to several neurological conditions (19,20). There is no evidence in this study linking our sample's HFE polymorphisms to autism. The lack of correlation between p.H63D (the prevalence of the D/D homozygote is 2(6.7%) and autism may be due to the age-related effect of the D/D homozygote and distinct CNS biological pathways that are disrupted in the

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disease group, even though the D/D homozygote has been implicated in neurodegenerative diseases such as Parkinson's and Alzheimer's diseases and aging white matter lesions (21,22). Many studies suggest that proteins involved for intracellular iron pooling for the brain, such as the HFE protein, associated with immunological function and glutamate transport, also have linked the D/D homozygote to reduced glutamate uptake in neuroblastoma lineages (20,21). The second polymorphism in this investigation, C282Y, is infrequent in the samples we examined and has been seen in other populations where Y has a negligible significance as a risk allele for autism. This was in line with earlier research on this polymorphism in neurological diseases (10, 15). These results were agreed upon by the author, who showed there was not provide proof that their sample's HFE polymorphisms are linked to autism (15). In the current investigation, compared to the control group, the mean serum ferritin level was substantially reduced in the autism patients. Previous research from South Wells, Turkey, and Canada found that autistic children had a greater rate of ferritin insufficiency than the general population, and according to another study, autism-related children have significantly lower levels of ferritin, iron, and hemoglobin (14) which agrees with our finding (12,23). While another study discovered that 52% of children with autism had iron deficiency (ID) and a high ferritin level (24). At the same time, serum transferrin levels in autistic children were considerably lower than those in non-autistic siblings (25). These findings suggested that transferrin levels, rather than iron levels, may be a more sensitive and effective predictor for autism development (7,14). Transferrin saturation may also be a helpful diagnostic criterion for iron insufficiency (9). Furthermore, transferrin has been shown to have an anti-oxidative activity, which may lessen the incidence of autism (19,26). The current investigation also revealed a low mean value for serum iron, which was consistent with some earlier findings that discovered that the mean serum iron levels of autistic children were noticeably lower than those of the control group (27). Low mean iron levels were also discovered in children with autism, according to other studies (12,28). It has been observed that children with autism have little dietary preferences, finicky eating habits, and extreme resistance to eating. This corroborates the group's lower mean iron level (6). Given the critical role iron plays in the development of cognitive, motor, sensory, social, and emotional abilities. Because iron is needed for the protein and enzyme involved in the formation of the central nervous system, it plays a crucial role in that process. Additionally, serotonergic and dopaminergic pathways as well as neuronal myelination depend on iron (25). Furthermore, it has been suggested that there is a genetic propensity to ID in ASD (8). Thus, ID raises the chance of developing psychiatric conditions such as attention deficit hyperkinetic disorder, mood disorders, and ASD (28). Although ID is present in autism patients, it was found that the level of transferrin is low in the blood may be associated with increased oxidative stress in autism; a prior study found a substantial correlation between these changes and the regression of acquired language abilities (9). Low serum ferritin levels and ID prevalence in autistic disorders point to a potential iron deficiency as a cause of autism. In this investigation, it was shown that serum transferrin was linked to an elevated risk of autism($p$-value$<0.05$) and that the increased risk of autism in the presence homozygous H/H at p.H63D and homozygous C/C at p.C282Y polymorphisms was significantly associated with serum transferrin levels. According to this research, iron, ferritin, and transferrin levels in autistic patients should be checked as a baseline inquiry. They can also be utilized to assist individuals with severe symptoms by acting as a screening signal. Despite the fact that oxidative

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stress has been linked to autistic spectrum disorder. Ferritin may be a good indicator of the central nervous system's iron status and, consequently, of oxidative stress in these cells. Our results advise doctors to pay closer consideration and to be more concerned about iron status in children with autistic families. It is critical for directing autism prevention and treatment.

## Conclusion

There appears to be no linking of our sample's HFE polymorphisms to autism, while there is a correlation between the lower levels of iron, ferritin, and transferrin in individuals with autism, and it is showed that the increased risk of autism in the presence of homozygous H/H at p.H63D and homozygous C/C at p.C282Y polymorphisms was significantly associated with decreased serum transferrin levels. Thus, serum transferrin levels may be associated with a higher incidence of autism. Our study recommends further comprehensive investigations, including iron genes and protein expression in autism-affected children.

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**Ethical clearance:** The Ethics Committee approved all blood donations and the research protocol that was certified by the study's ethical committee of the Middle Technical University /AL-Suwaira Technical Institute/ Medical Technical Laboratory Department/Wasit, Ethics Committee, Reference Number: (MEC 19 in 11/10/2024), Iraq. From the patient's samples, a consent form that complied with the Declaration of Helsinki was acquired.

**Conflict of interest:** None.

**Use of Artificial Intelligence (AI):** The authors state they did not use any generative AI tools for creating or editing the manuscript's language.

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# تأثير تعدد أشكال p.H63D و p.C282Y المرتبط بحالة الحديد على التوحد لدى الأطفال العراقيين

[1] اقبال حنش ضفير

## الملخص

**الخلفية:** التوحد مرض تنكسي عصبي يرتبط بتغيرات في استقلاب الحديد في الجهاز العصبي المركزي. تشير الدلائل إلى أن الأطفال المصابين بالتوحد لديهم بروتينات مميزة مرتبطة بالحديد في مصل دمهم، وقد وُجد أن تعدد أشكال النوكليوتيدات المفردة p.H63D وp.C282Y يرتبط ارتباطًا وثيقًا بعدد من الأمراض العصبية.

**الأهداف:** تحديد تأثير تعدد أشكال p.H63D وp.C282Y المرتبط بحالة الحديد على التوحد لدى الأطفال العراقيين.

**المرضى والطرق:** أُجريت الدراسة من حزيران ٢٠٢٣ إلى كانون الثاني ٢٠٢٤، وشملت ٣٠ فردًا مصابًا بالتوحد و٣٠ فردًا من مجموعة الضبط الاصحاء، تراوحت أعمارهم بين ٤ و١٤ عامًا. بعد استخراج الحمض النووي، تم استخدام تضخيم التسلسل المحدد ولانزيمات الهاضمة للتحقيق في تحديد النمط الجيني لـ p.H63D و p.C282Y . وكذلك تم قياس كل من السعة الكلية الرابطة للحديد، الحديد ،الترانسفيرين والفيريتين، والتي تم قياسها باستخدام جهاز التحليل التلقائي.

**النتائج:** أظهرت نتائجنا أن متوسط مستويات الحديد في المصل (٧٠,٦٨ ± ٢٠,٢١ ميكروجرام / ديسيلتر) والفيريتين (٣٢,١١ ± ٩,١٥ ميكروجرام / ديسيلتر) والترانسفيرين (١٣,٥٩ ± ١,٤٥ (جم / لتر)) لدى الأطفال المصابين بالتوحد كانت أقل بشكل ملحوظ من متوسط المجموعة الضابطة (٩٠,٢٢ ± ٢٢,١١، ٧٩,٩ ± ٢٠,٦٥، ٢٥,٧٥ ± ٣,٦٩ على التوالي) قيمة p <0.05، وأن هناك خطرًا مرتفعًا للإصابة بالتوحد في وجود متماثل الزيجوت H / H (٨٣,٣٪) في p.H63D و C / C (١٠٠٪) متماثل الزيجوت من p.C282Y، وكانت تعدد الأشكال مرتبطة بشكل كبير بانخفاض مستويات الترانسفيرين في المصل (نسبة فردية = ١,٢٠، قيمة p = 0.01 (مع H / H)، ١,١٨ القيمة الاحتمالية = ٠,٠٢ مع C/C).

**الاستنتاج:** ارتبط انخفاض مستويات الترانسفيرين في المصل بارتفاع معدل الإصابة بالتوحد، والذي يرتبط بوجود تعدد أشكال p.H63D وp.C282Y. كما ويمكن أن يؤدي انخفاض مستويات الحديد والفيريتين والترانسفيرين لدى مرضى التوحد إلى مشاكل معرفية وجسدية، مما قد يزيد من خطر ظهور أعراض التوحد.

**الكلمات المفتاحية:** p.H63D، p.C282Y، الترانسفيرين، الفيريتين، الحديد.

**المؤلف المراسل: اقبال حنش ضفير**

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