

# Autism and X-linked hypophosphatemia: A possible association?

Vermeersch Joël, Hellemans Hans, Deboutte Dirk

University Centre Child and Adolescent Psychiatry (UCKJA), ZNA Middelheim Antwerp, University of Antwerp, CAPRI, Belgium

We herein report the joint occurrence of an autistic disorder (AD) and X-linked hypophosphatemia. X-linked hypophosphatemia (XLH), an X-linked dominant disorder, is the most common of the inherited renal phosphate wasting disorders. Autism is a pervasive developmental disorder that occurs mainly due to genetic causes. In approximately 6–15% of cases, the autistic phenotype is a part of a broader genetic condition called syndromic autism.

Therefore, reports of cases with the joint occurrence of a known genetic syndrome and a diagnosis of ASD by a child psychiatrist are relevant. A joint occurrence does not, however, mean that there is always a causal link between the genetic syndrome and the autistic behavioural phenotype. In this case, there are a number of arguments countering a causal link.

**Keywords:** Autistic disorder, genetics, Syndromal autism spectrum disorders, X-linked hypophosphatemia.

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## Introduction

Autistic disorder (AD) is one of the autism spectrum disorders (ASD). It is a pervasive developmental disorder characterized by impaired language, impoverished social interaction and repetitive activities and behaviour. Overwhelming evidence exists to conclude that ASD are disorders with a high heritability. The identity and the number of genes involved remain unknown.<sup>[1]</sup> Recent insights show that a variety of genetic mechanisms may be involved, i.e. single gene disorders, copy number variations and polygenic mechanisms.<sup>[2]</sup>

It is important to distinguish between syndromic ASD and isolated, idiopathic ASD.<sup>[3]</sup> In syndromic ASD,

the autistic phenotype is a part of a broader genetic condition. This group with demonstrable genetic etiology represents approximately 6–15% of all persons with ASD, and the fraction is likely to be higher when micro-array comparative genome hybridization (CGH) is used.<sup>[2,4-7]</sup> Evidence suggests that idiopathic ASD is the result of interactions between multiple genes. Epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits.<sup>[1]</sup>

X-linked hypophosphatemia (XLH) is the most common of the inherited renal phosphate wasting disorders. It is an X-linked dominant disease with full penetrance. The syndrome is the result of a gene deficit on Xp22.1. 140,141. XLH patients frequently present with short stature, lower extremity deformities (valgus or varus), dental abscesses, and bone pain. The severity of disease varies significantly even among members of the same family.<sup>[8]</sup>

A search for reported association between ASD and XLH using Medline and OMIM proved to be fruitless.

## Case Report

XY2 is a boy of seven years of age with X-linked hypophosphatemia. He inherited this genetic disorder from his mother, who in turn inherited it from her father. Mutations in the PHEX gene to Xp22.1 are responsible for the clinical impression of X-linked hypophosphatemia.<sup>[9]</sup> A molecular analysis of the PHEX gene and sequence analysis showed a hemizygote 1735 G>A(G579R) missense mutation in exon 17 of the PHEX gene in all subjects.

**Address for correspondence:** Dr. J Vermeersch, (UCKJA) ZNA Middelheim, Lindendreef 1, B-2020 Antwerp, Belgium.  
E-mail: binujoel@hotmail.com

XY2 was reported by both his parents due to a suspicion of developmental problems. The parents noticed a major head start over his peers at school level. On a social level, however, there appears to be a lag. Owing to hypophosphatemia, there has been a lack of growth. XY2 is intellectually gifted (WISC-III Full Scale IQ: 135, Verbal IQ: 136, Performance IQ: 133)

Psychiatric examination demonstrated a DSM-IV-diagnosis of AD, confirmed by the ADI-R (autism diagnostic interview – revised) of the parents and the ADOS-G (autism diagnostic observation schedule).

XY2 is the middle of the three sons in a family. Both XY1 and XY2 have been diagnosed with X-linked hypophosphatemia. Using chorionic villus sampling, the disorder has been ruled out in the youngest son, XY3. After XY2 was diagnosed as suffering from AD, the parents requested to test XY1 also. They were also concerned about his development and desired further clarity.

An extensive psychiatric analysis was conducted and for XY1 an ADI-R was conducted with the parents and an ADOS-G for XY1. Both these tests gave values just below the autism threshold. His intelligence was determined using a WISC-III test. XY1 is of normal intelligence (total IQ: 107, verbal IQ: 106, performance IQ: 107).

In the familial anamnesis, no past history of ASD was reported. In addition, the parents, grandparents, and siblings of the parents were asked to complete a questionnaire for the calculation of autism quotient.<sup>[10]</sup> This questionnaire has been developed to measure the degree to which an adult with normal intelligence has autistic traits. Everyone took scores ranging from below average to high average; only the paternal grandfather took a high score, which often corresponds to the score of people with autism

## Discussion

We herein concerned discuss the joint occurrence of an autistic disorder (AD) and X-linked hypophosphatemia. Until recently, it was assumed that ASD belongs, in approximately 10% of the cases, to the behavioural phenotype of an underlying genetic disorder namely syndromal ASD. Recent research has demonstrated

that with more accurate screening of the genome using microarray CGH, this figure could be up to 15% of the cases with ASD.

Therefore, reports of cases with the joint occurrence of a known genetic syndrome and a child psychiatric diagnosis of ASD are relevant. A joint occurrence does not, however, mean that there is always a causal link between the genetic syndrome and the autistic behavioural phenotype. In this case, there are a number of arguments countering a causal link:

- In the case described, the genetic disorder is a result of a point mutation in the PHEX gene. This gene is known for its association with X-linked hypophosphatemia and to date no associations with autism have been reported.
- Single genes that are associated with autism are often also genes that express themselves in the brain or in brain-related processes.<sup>[2]</sup> The genetic deviation in this case only affects the bone metabolism.<sup>[8]</sup>
- The AQ questionnaires suggest that there is a familial affliction of ASD on the paternal side and provides little argument in favour of a familial affliction of autism on the maternal side. In the event of a possible association between autism and X-linked hypophosphatemia, the opposite is expected.

It is important that underlying genetic syndromes are sought out for people diagnosed with an autistic disorder (AD). But should such a syndrome be found, this does not mean that a causal link exists as a matter of course. With a prevalence of at least 6 out of 1,000, ASD is not rare and it can be expected that additional diagnoses will frequently be established.

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