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Case Report

Recurrent 2q13 microduplication encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1* associated with autism spectrum disorder, intellectual disability, and liver disorder

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ABSTRACT

Objective: We present recurrent 2q13 microduplication in a family with autism spectrum disorder (ASD), intellectual disability, and liver disorder.

Case Report: A 45-year-old woman and her 52-year-old husband were referred for genetic counseling because of mental and liver disorders in their two sons and their planning for prenatal diagnosis of familial disorders in the future pregnancy. She and her husband were normal and healthy, but their 21-year-old elder son had suffered from ASD, severe intellectual disability, poor motor function, liver cirrhosis, and esophageal varices, and their 19-year-old younger son had suffered from ASD, mild intellectual disability, poor balance and coordination, hepatosplenomegaly, fatty liver, and mild liver cirrhosis. The karyotypes of the parents and sons were normal. Array comparative genomic hybridization of the family revealed a 686.5-kb 2q13 microduplication encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1* in the elder brother, a 658.9-kb 2q13 microduplication encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1* in the younger brother, and an 83.83-kb 2q13 microduplication encompassing *NPHP1* in the asymptomatic father.

Conclusion: Recurrent phenotypic abnormality in the family with normal karyotype should include a differential diagnosis of pathogenic copy-number variations.

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Introduction

NPHP1 (OMIM 607100) is located at 2q13 and encodes nephrocystin 1 which participates in a common signaling pathway. Homozygous or compound heterozygous deletions and loss-of-function mutations in *NPHP1* have been associated with autosomal recessive disorders of Joubert syndrome 4 (OMIM 609583), juvenile nephronophthisis 1 (OMIM 256100), and Senior-Løken syndrome (OMIM 266900). Duplication of the *NPHP1* gene has been identified in autism spectrum disorder (ASD) patients [1–4].

Recurrent deletion and duplication of chromosome 2q13 have been associated with developmental delay, dysmorphism, and variable outcomes [5,6]. Familial 2q13 duplications have also been associated with variable adult neuropsychiatric expression [7]. Here, we present a family with familial transmission of recurrent

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2q13 microduplication encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1* associated with ASD, intellectual disability, and liver disorder.

Case Report

A 45-year-old, gravida 2, para 2, woman and her 52-year-old husband were referred for genetic counseling because of mental and liver disorders in their two sons and their planning for prenatal diagnosis of familial disorders in the future pregnancy. The couple's karyotypes were normal.

Their 21-year-old elder son had a body weight of 48 kg, a body height of 165 cm, and a head circumference of 55.2 cm. He manifested ASD, severe mental retardation, poor motor function, poor balance and coordination, ataxia, poor cognitive function, self-talking with meaningless repeated words, liver cirrhosis, hepatosplenomegaly, and a history of rupture of esophageal varices. There were no seizures, congenital heart defects, dysmorphism, central nervous system malformations, copper metabolism disorder, or hepatitis. His karyotype was 46,XY.

Their 19-year-old younger son had a body weight of 60.3 kg, a body height of 166 cm, and a head circumference of 55.8 cm. He manifested ASD, mild mental retardation, clumsy hand movement, problems with balance and coordination, ataxia, hepatosplenomegaly, fatty liver, myopia, exotropia, and mild liver cirrhosis. There were no seizures, congenital heart defects, dysmorphism, central nervous system malformations, copper metabolism disorder, or hepatitis. His karyotype was 46,XY.

Array comparative genomic hybridization analysis on the DNA extracted from the peripheral bloods of the parents and the two sons using CytoChip ISCA (Illumina, San Diego, CA, USA) revealed a result of arr 2q13 (110,862,507-111,548,962) × 2.90 with a 686.5-kb genomic gain in 2q13 encompassing 15 genes including four OMIM genes of *MALL*, *NPHP1*, *RGPD6*, and *BUB1* in the elder son (Figure 1), a result of arr 2q13 (110,783,258-111,442,160) × 2.90 with a 658.9-kb genomic gain in 2q13 encompassing 16 genes including four OMIM genes of *MALL*, *NPHP1*, *RGPD6*, and *BUB1* in the younger son (Figure 2), and a result of arr 2q13 (110,880,881-110,964,708) × 2.70 with an 83.83-kb genomic gain in 2q13 encompassing two genes including one OMIM gene of *NPHP1* in the asymptomatic healthy father (Figure 3). The maternal array comparative genomic hybridization result showed no genomic imbalance.

Discussion

The present case adds to the list of duplication of the *NPHP1* gene in patients with ASD, intellectual disability, and phenotypic variability. To date, at least nine cases with duplication of the *NPHP1* gene and cognitive and behavioral disorders have been reported [1–4]. Baris et al [1] first identified duplication of *NPHP1* in two patients with attention deficit hyperactivity disorder (ADHD). In their report, one patient was a 12-year-old boy with ADHD, obsessive-compulsive disorder, language-based learning disability, speech delay, and facial dysmorphism, and the other patient was a 10½-year-old girl with developmental delay, speech delay, behavioral problems, ADHD, and facial dysmorphism. Both cases had a duplication of 2q13 covering *MALL* and *NPHP1*. Pinto et al [2] identified a maternal transmission of 362.7-kb duplication in 2q13 encompassing *MALL* and *NPHP1* in a male with ASD, below-average verbal IQ, and average nonverbal IQ, but no dysmorphism and no epilepsy. Kaminsky et al [3] identified four patients with ASD, intellectual disability, and developmental delay associated with 2q13 microduplication. In their report, one patient had a 506.4-kb duplication in 2q13 encompassing *MALL*, *NPHP1*, and *RGPD6*, one patient had a 266.3-kb duplication in 2q13 encompassing *MALL* and *NPHP1*, and two patients had a 96.6-kb duplication in 2q13 encompassing *MALL* and *NPHP1*. Yasuda et al [4] identified two patients with ASD, no intellectual disability, and *de novo* duplication of *NPHP1*. In their report, one patient was a 24-year-old male with ASD, no intellectual disability, no dysmorphism, no epilepsy, and a 892-kb duplication in 2q13 encompassing *MALL*,

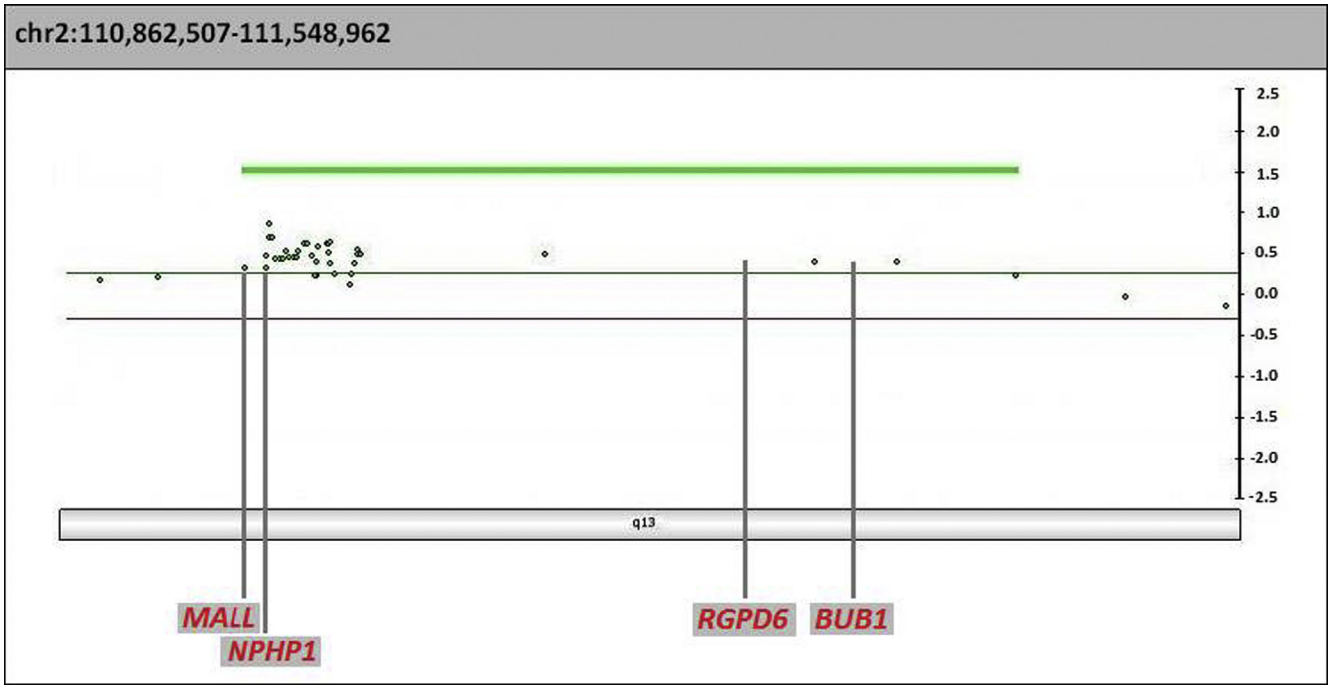

Figure 1. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from the peripheral blood of the affected elder son shows a 686.5-kb genomic gain in 2q13 encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1*.

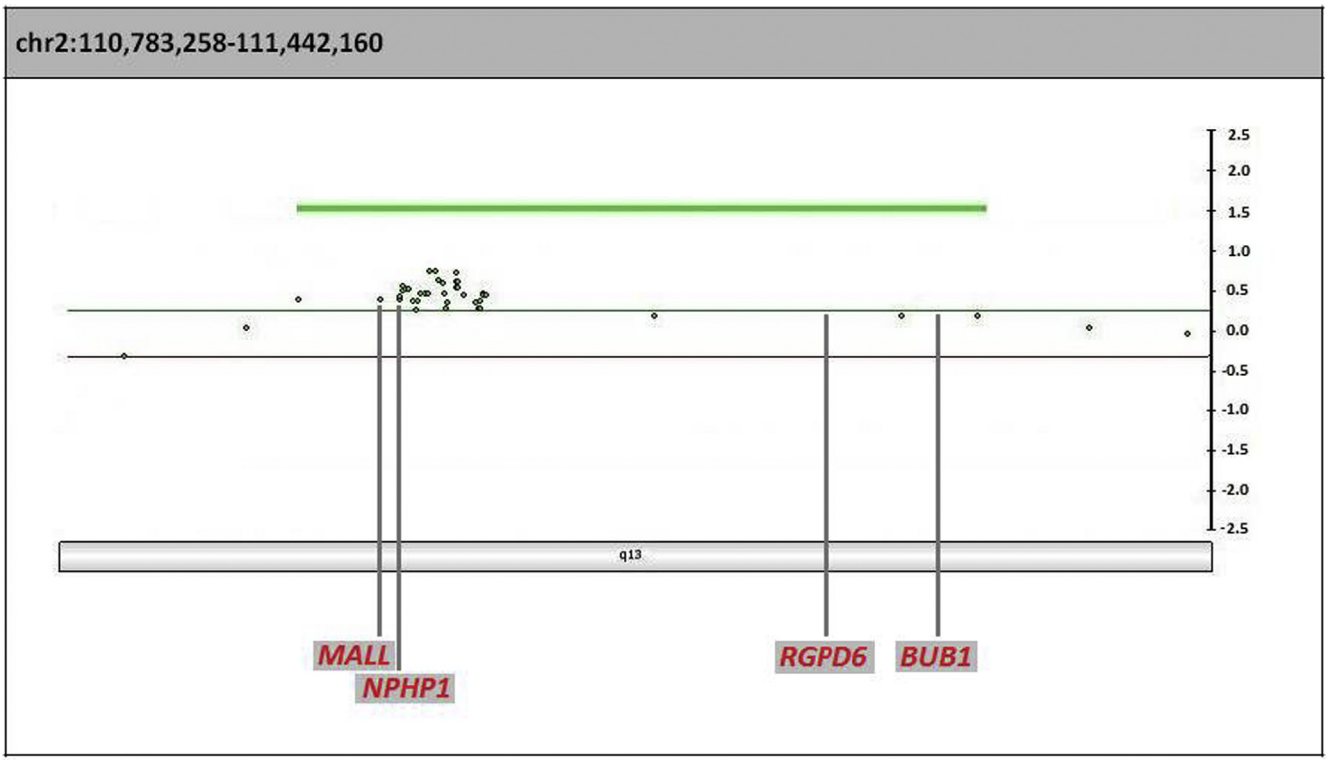

Figure 2. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from the peripheral blood of the affected younger son shows a 658.9-kb genomic gain in 2q13 encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1*.

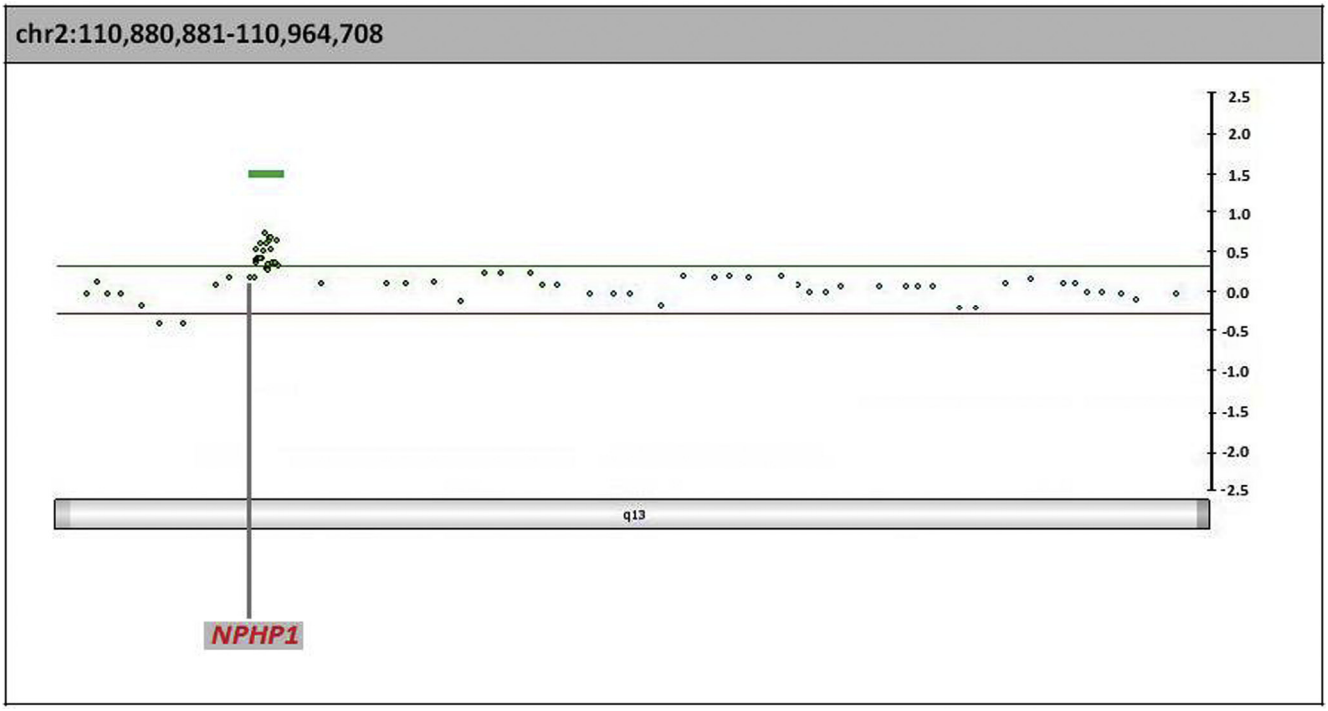

Figure 3. Array comparative genomic hybridization (aCGH) analysis of the DNA extracted from the peripheral blood of the asymptomatic father shows an 83.83-kb genomic gain in 2q13 encompassing only *NPHP1*.

NPHP1, and *RGPD6*, and the other patient was a 33-year-old male with ASD, no intellectual disability, no dysmorphism, no epilepsy and a 475-kb duplication in 2q13 encompassing *MALL* and *NPHP1*.

The present report provides evidence for a duplication of 2q13 encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1* associated with recurrent ASD, intellectual disability, and liver disorder. The peculiar aspect of the present case is the association of *BUB1*

duplication with liver cirrhosis and ASD. *BUB1* (OMIM 602452) is a mitotic checkpoint gene associated with chromosome instability. *BUB1* overexpression induces aneuploidy and tumor formation through aurora B kinase hyperactivation [8,9]. Tavassoli et al [10] previously reported a missense mutation in *TEL1*, a splice site mutation in *SCN2A*, and two synonymous mutations in *BUB1* in a boy with ASD.

In summary, we present recurrent 2q13 microduplication encompassing *MALL*, *NPHP1*, *RGPD6*, and *BUB1* associated with ASD, intellectual disability, and liver disorder. We suggest that recurrent phenotypic abnormality in the family with normal karyotype should include a differential diagnosis of pathogenic copy-number variations.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

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