OMCR

Oxford Medical Case Reports, 2017;9, 178–181

doi: 10.1093/omcr/omx032
Case Report

CASE REPORT

A unique association of Noonan syndrome and 47,XYY syndrome in a male presenting with failure to thrive

Edward J. Bellfield[1,†] and Zohra Shad[2,†*]

[1]Division of Pediatric Endocrinology, University of Illinois College of Medicine, Chicago, IL, USA, and
[2]Department of Genetics, University of Illinois College of Medicine, Chicago, IL, USA

*Correspondence address. Department of Genetics, University of Illinois College of Medicine, MC-856, 840 South Wood Street, Chicago, IL 60612, USA. Tel: +1-312-355-0732; Fax: +1-312-355-0739; E-mail: zshad@uic.edu

Abstract

We describe a 24-month-old male patient who presented to our Genetics-Endocrinology Clinic with a history of failure to thrive, short stature and cryptorchidism. Soon after birth he was diagnosed with 47,XYY syndrome, but due unusual facial features had further diagnostic workup which revealed Noonan syndrome (NS) as well. This report illustrates significant phenotypic–cytogenetic variability within the clinical presentation of NS and 47,XYY syndrome, as well as the need to investigate patients for other genetic defects when phenotype does not correlate with genotype. Furthermore, in this case, the cellular pathways attenuating growth via *PTPN11* mutation appear to supersede the *SHOX* overdosage—an observation that can lead to further research in genetic mechanisms of growth physiology.

INTRODUCTION

Noonan syndrome (NS) is a well-described autosomal dominant disorder characterized by short stature, facial dysmorphism and a wide spectrum of congenital heart defects [1]. The distinctive facial features consist of a broad forehead, hypertelorism, down-slanting palpebral fissures, a high-arched palate and low-set, posteriorly rotated ears. Cardiac involvement is present in up to 90% of patients—pulmonic stenosis and hypertrophic cardiomyopathy are the most common forms of cardiac disease, but a variety of other lesions are also observed [1]. Additional relatively frequent features include multiple skeletal defects (chest and spine deformities), webbed neck, mental retardation, cryptorchidism and bleeding diathesis.

47,XYY syndrome occurs in about 1 in 1000 newborn males and is usually diagnosed late, if ever [2]. The XYY phenotype commonly includes tall stature, macrocephaly, macroorchidism, hypotonia, hypertelorism and tremor, in addition to cognitive and motor delays [2]. Most males with 47,XYY syndrome have normal sexual development and are able to father children.

CASE REPORT

The patient was a 24-month-old Hispanic male who presented to our Endocrinology-Genetics Clinic for a follow-up evaluation due to his history of failure to thrive and short stature (Figs 1, 2). He was the third child born to his parents and was delivered at 38 weeks of gestation to a 32-year-old mother via spontaneous vaginal delivery. The pregnancy was complicated by diet-controlled gestational diabetes. His birth weight was 3.3 kg (25%ile) and birth length 47 cm (7%ile), both appropriate for gestational age. He was identified with undescended testes after birth. The only postnatal issue was jaundice that required 2 days of phototherapy. Family history was significant for one older male sibling with poor weight gain beginning at age 2 years until age 5, which subsequently resolved without medical intervention. Genetic testing

[†]Both authors contributed equally to this article.
Received: September 28, 2016. **Revised:** March 13, 2017. **Accepted:** April 27, 2017

Figure 1: patient presenting with Noonan syndrome phenotype of short stature, hypertelorism, downturned palpebral fissures, upturned nose, low set posteriorly rotated ears and short neck. ((A) Anterior view, (B) lateral view).

was not indicated on the sibling after evaluation by the genetics team. No other family history of syndromic conditions, recurrent pregnancy losses, abnormal short stature, or learning disabilities. His father's height was 152 cm and his mother's height 144 cm, resulting in a mid-parental height of 154.5 cm (0.1%ile). Despite recommendations for parental genetic testing, neither parent has the financial means nor health coverage to do so.

At 4 months of age, the patient began to display poor weight gain in absence of vomiting or diarrhea. No febrile illnesses or difficulty swallowing. He was breastfed until 8 months of age, then transitioned to regular formula without difficulty. He was also started on pureed table foods without problem. At 10 months of age he was referred to pediatric gastroenterology due to lack of appropriate weight gain. He was started on fortified milk and foods. Sweat test, CBC and electrolytes were reassuring. At 12 months of age he was

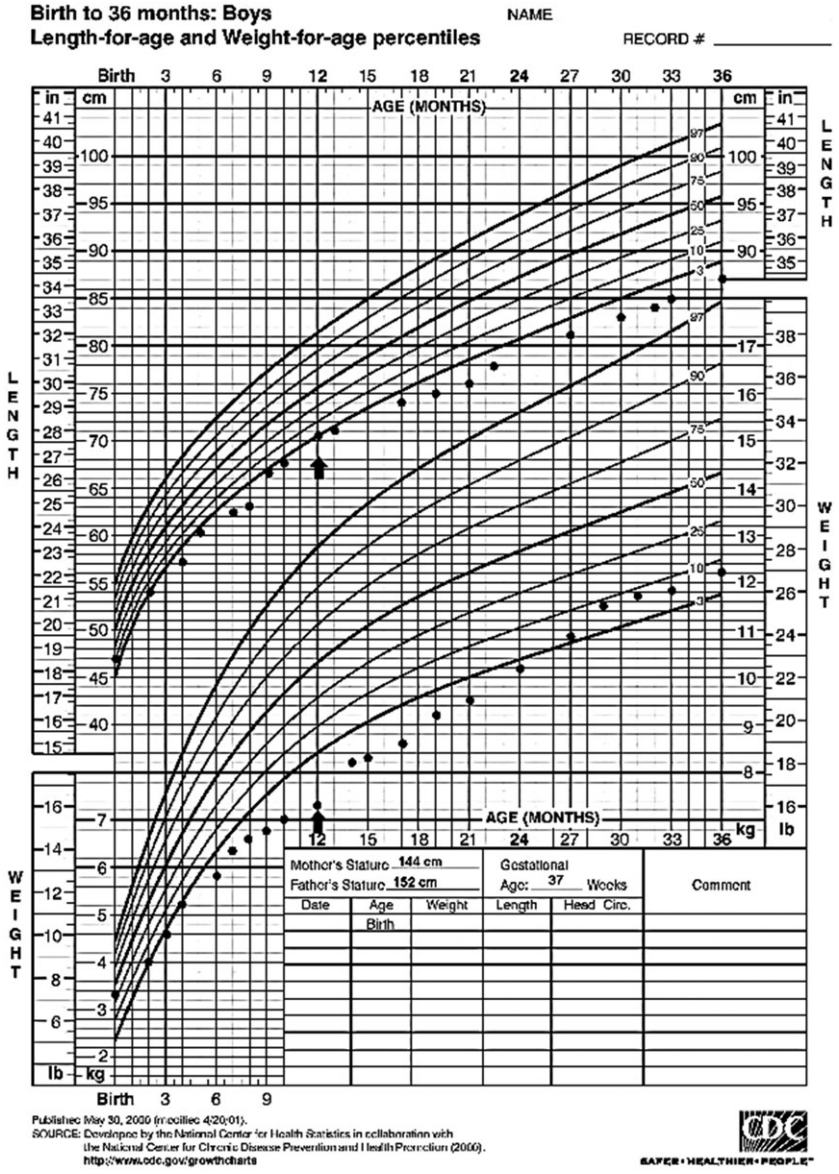

Figure 2: patient's growth chart. The arrow denotes the start of medical intervention.

followed weekly for weight checks. At 16 months of age he was admitted when noticed dropping his weight from 7.2 to 7.0 kg from the previous week, and had intensive workup for failure to thrive.

Due to suspicion of abnormal facial features, the genetics service was consulted. On examination he appeared small for his age, but was interactive. He had hypertelorism with inner-canthal distance 3.5 cm (above +2SD), down-slanting palpebral fissures, flat midface and philtrum, low set ears, upturned nose and overlapping toes. He also had a 2/6 systolic murmur. The rest of the exam was unremarkable. Transthoracic echocardiogram, plasma amino acids, urine organic acids, ammonia, lactate, thyroid stimulating hormone, free thyroxine and celiac screen were negative for abnormalities. Chromosomal microarray and karyotype was ordered, which demonstrated 47,XYY (Figs 3, 4). The karyotype finding was incidental, as it would not explain his facial features and growth difficulties. At the follow-up clinic visit at age 18 months, his presentation was more suspicious for NS, so a NS genetic panel was ordered. The gene test was conducted via Sanger sequencing of the tyrosine phosphatase non-receptor type 11 gene (*PTPN11*) gene, which detected one pathogenic mutation: c.922A > G; p.Asn308Asp. The p.Asn308Asp has been reported in many patients with NS and is estimated to account for about 30% of cases [3]. He had

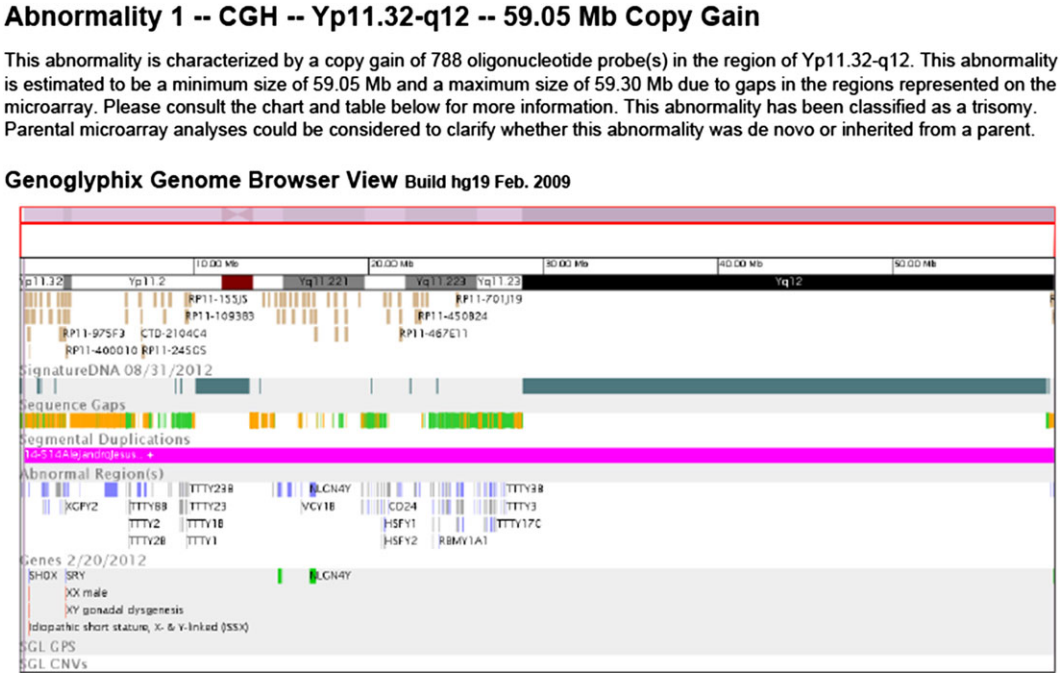

Figure 3: comparative genomic hybridization demonstrating duplication of Y chromosome material, confirming the diagnosis of 47,XYY syndrome.

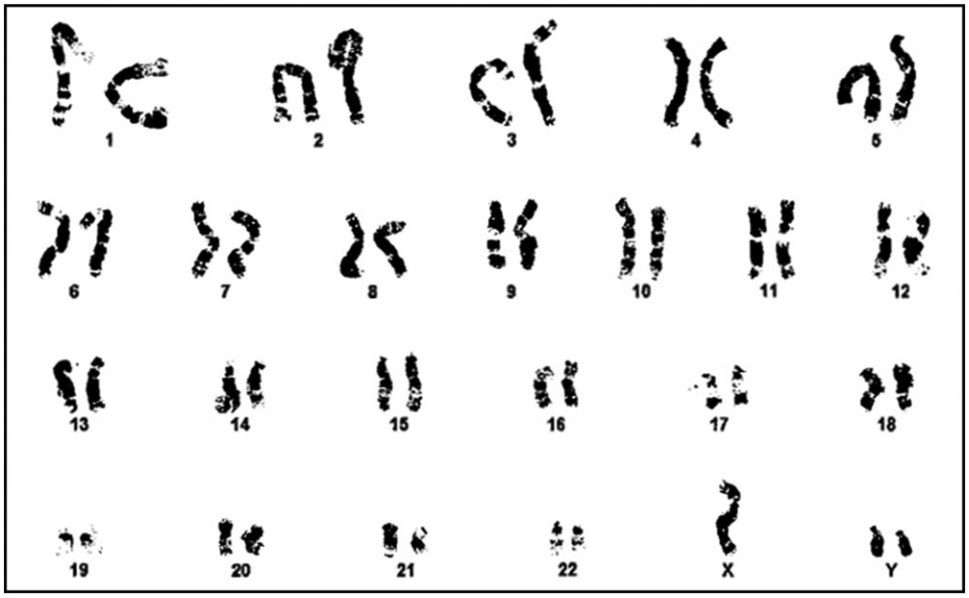

Figure 4: the patient's karyotype consistent with 47,XYY.

subsequent evaluation for related renal, cardiac, ophthalmologic and audiological abnormalities, which were reassuring.

With a confirmed diagnosis of NS and in the presence of poor growth, he was evaluated by pediatric endocrinology at age 24 months. Insulin-like growth factor-1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) were 61 ng/mL (30–122) and 1810 ng/mL (972–4123), respectively. He was demonstrating low normal growth velocity at 8 cm/year. The option of starting growth hormone (GH) treatment was discussed, though deferred due to parent's preference and questionable benefit to starting it at this age for growth failure. The clinical team recommended continued observation while on a high caloric diet.

DISCUSSION

We present a male patient with a unique association of NS and 47,XYY syndrome. To date there have been no individuals described in literature who possess these two syndromes. NS is an autosomal dominant condition characterized by short stature, characteristic facial features, chest deformities and congenital heart disease [4]. It is a relatively common disorder with an estimated prevalence of 1 in 1000–2500 live births [4]. Genetic mutations are identifiable in 70–80% of NS patients, with missense mutations on the *PTPN11* gene being the most frequently identified in around 40–50% of cases [4]. Affected individuals have normal chromosome studies.

47,XYY syndrome is also a relatively common genetic condition, occurring in males in ~1 per 1000 live births [5]. Many are diagnosed in adolescence or adulthood, as many who have this condition present only with tall stature. In fact, it is believed that 85% or more of males with XYY are never diagnosed [2]. Tall stature in 47,XYY syndrome is thought to be due to triplicate expression of the short stature homeobox-containing gene (*SHOX*) located on the distal ends of Xp and Yp [5]. Other characteristics include autistic traits and neurocognitive changes, such as speech and language problems, and reduced motor skills and educational achievement [5]. There is also increased risk of impulsivity, poor adaptation to social situations and behavioral problems related to externalizing behaviors [6].

At this time this patient presents with a predominantly NS phenotype, although quite mild. As mentioned above, the genetic etiology of this patient's failure to thrive and short stature is likely secondary to NS. Although it is presumed that the patient has a *de novo* mutation, it cannot be definitely determined without parental genetic testing. It is possible that over time, the patient will develop the acquired behavioral and cognitive issues and it will be difficult to determine which of the two syndromes is contributing. In terms of growth, it appears that the attenuation mediated by *PTPN11* mutation is superseding the *SHOX* overdosage. GH replacement has been considered for the management of his short stature, although the pathophysiology is yet unclear how NS modulates GH secretion or action. Studies in *PTPN11* mutated mice have demonstrated reduced sensitivity to GH, while studies in children with short statured NS have demonstrated low nocturnal levels of GH and unusual pulsatility of GH [7]. Treatment is effective in increasing growth velocity in a wide range of NS phenotypes and genotypes, however, because this child has the combined syndromes, it is unknown just how effective GH treatment may be. Given our patient's young age combined with his presumed familial short stature, it is reasonable to continue observing his growth pattern and maximizing daily caloric intake. He also needs close monitoring for developmental delays, behavioral disturbances, as these are demonstrated in both syndromes. In conclusion we feel it is important to consider testing both the molecular studies as well as chromosome microarray studies in individuals with failure to thrive and short stature to identify an association. This case also demonstrates that a patient can have more than one genetic syndrome—if the genotype does not match the expected phenotype, further testing is completely appropriate.

ACKNOWLEDGMENT

We thank the patient and family in allowing us to share his story, and to Cytogenetic Lab at the University of Illinois for conducting the laboratory studies. We also thank the Research Open Access Publishing (ROAAP) Fund of the University of Illinois at Chicago for financial support towards the open access publishing fee for this article.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

Not applicable.

CONSENT

Written consent was obtained from the patient's guardian.

GUARANTOR

Zohra Shad.

REFERENCES

1. Allandson JE, Roberts AE. Noonan syndrome. *GeneReviews* [Internet]. http://www.ncbi.nlm.nih.gov/books/NBK1124/. Published November 15, 2001. (30 August 2016, date last accessed).
2. Bardsley MZ, Kowal K, Levy C, Gosek A, Ayari N, Tartaglia N, *et al*. 47,XYY syndrome: clinical phenotype and timing of ascertainment. *J Pediatr* 2013;**163**:1085–94.
3. Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, *et al*. Mutations in *PTPN11*, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nature Genet* 2001;**29**:465–8.
4. Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, *et al*. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics* 2010;**126**: 746–51.
5. Stochholm K, Juul S, Gravholt CH. Socio-economic factors affect mortality in 47,XYY syndrome—a comparison with the background population and Klinefelter syndrome. *Am J Med Genet A* 2012;**158A**:2421–9.
6. Ross JL, Roeltgen DP, Kushner H, Zinn AR, Reiss A, Bardsley MZ, *et al*. Behavioral and social phenotypes in boys with 47, XYY syndrome or 47,XXY Klinefelter syndrome. *Pediatrics* 2012;**129**:769–78.
7. Noonan JA, Kappelgaard A. The efficacy and safety of growth hormone therapy in children with Noonan syndrome: a review of the evidence. *Horm Res Paediatr* 2015;**83**:157–66.