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European Journal of Medical Genetics 50 (2007) 1–10
EUROPEAN JOURNAL OF MEDICAL GENETICS
http://www.elsevier.com/locate/ejmg

Original article

Tall stature and duplication of the insulin-like growth factor I receptor gene

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Received 20 October 2005; accepted 19 March 2006
Available online 14 September 2006

Abstract

Trisomy of 15q26-qter is frequently associated with tall stature and mental retardation. Here we describe a patient with such trisomy, without a partial monosomy of another chromosome. The tall stature in this patient is most probably caused by duplication of the *IGF1R* gene. A duplication of the *IGF1R* gene is not a frequent finding in patients with tall stature. In 38 patients with features of Sotos syndrome without *NSD1* alterations, a duplication was found only once. This patient was already known to have an unbalanced 2;15 translocation. Looking for a duplication of the 15qter region is still worth consideration in patients with tall stature and features of Sotos syndrome without an *NSD1* alteration, especially when there is craniosynostosis or marked speech delay.

Keywords: Insulin-like growth factor I receptor gene; Tall stature; Overgrowth; Trisomy 15q26.1-qter

1. Introduction

Zollino et al. [27] hypothesized that distal 15q trisomy causes a syndrome characterized by mental retardation of variable severity and postnatal growth retardation. In about half of the

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doi:10.1016/j.ejmg.2006.03.005

cases microcephaly is reported. In contrast, tall stature and macrocephaly are found in most of the patients in whom the 15q duplication is very distal, from 15q25-26 to 15qter. Nagai et al. [14] and Faivre et al. [7] both reported patients with a duplication 15q26.1-15qter and tall stature, and suggested that the tall stature in these patients was caused by a dosage effect of the insulin-like growth factor 1 receptor (*IGF1R*) gene located on 15q26.3.

In most patients with a duplication of 15qter the duplication is caused by an unbalanced translocation, which usually also leads to partial monosomy of another chromosome. Five patients have been reported with pure trisomy 15qter. In one of the reported patients the trisomy contained only the distal part of 15q (15q25.2-qter). This patient did have postnatal overgrowth and was autistic with a marked delay in speech development. In three of the patients the breakpoint was located in 15q24, and they did not have tall stature [21]. The fifth patient was a foetus with overgrowth and a mosaic trisomy 15q25-15qter [8].

Here we describe a patient with tall stature and mild developmental delay, who has a duplication of 15q26.1-qter due to an unbalanced translocation between 15q and the short arm of chromosome 21, resulting in a pure trisomy 15qter. Subsequently, 38 patients with features of Sotos syndrome, in whom no *NSD1* gene (nuclear receptor-binding SET domain protein 1) alteration could be found, were tested for duplication of the *IGF1R* gene, and one patient was found to be positive for this finding.

2. Methods

2.1. Patients

This study was conducted with the prior consent of the Medical Ethical Committee of the Leiden University Mecical Center. Written consent for publication of photographs from the parents of patients A and B was obtained. Patient A is a girl who was referred to the clinical geneticist because of tall stature and features suspicious of Sotos syndrome (Fig. 1a and b). She is the second child of healthy, non-consanguineous parents. Pregnancy was complicated by premature rupture of membranes. The patient was born at a gestational age of 34 + 6 weeks, confirmed by early ultrasound, with a birth weight of 3045 g (+1.8 SDS), a birth length of 52 cm (+2.1 SDS) and a head circumference of 35 cm (+1.7 SDS) [15]. Although she had slightly

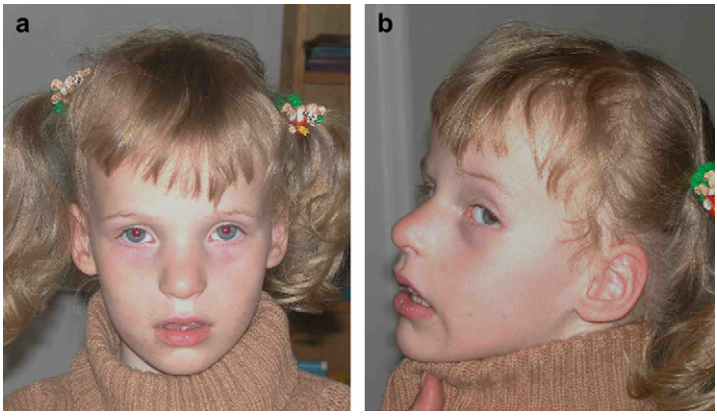

Fig. 1. Patient A at the age of 3 years. Note the elongated face and the wide nasal bridge.