

Short report

Normal intelligence and social interactions in a male patient despite the deletion of *NLGN4X* and the *VCX* genes

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Abstract

Xp22.3 deletion in males can be associated with short stature (*SHOX*), chondrodysplasia punctata (*ARSE*), mental retardation (MRX49 locus), ichthyosis (*STS*), Kallmann syndrome (*KALI*) and ocular albinism (*OAI*), according to the size of the deletion. Studies of terminal and interstitial deletions in male patients with a partial nullisomy of the X chromosome have led to the identification of the *VCX-3A* gene at the MRX49 locus on Xp22.3. The *NLGN4X* gene has then been identified less than 350 kb away from *VCX-3A*. Nonsense mutations in *NLGN4X* have been associated with autism and/or moderate mental retardation in males. We report a 17-year old male patient presenting with severe ichthyosis and Kallmann syndrome related to a 3.7 Mb interstitial Xp22.3 deletion, encompassing *STS* and *KALI* genes, respectively. However, despite the deletion of *NLGN4X* and all *VCX* genes, including *VCX-3A*, our patient did not manifest any learning disabilities or behavioural problems. Therefore, our case argues against a major role of *NLGN4X* and the *VCX* genes alone in cognitive development and/or communication processes. © 2007 Elsevier Masson SAS. All rights reserved.

Keywords: Mental retardation; X-linked; Autistic disorder; *NLGN4X*; *VCX*

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1. Introduction

Genotype–phenotype correlations in male patients with various types of nullisomy for the Xp22.3 region have enabled the assignment of six genes or loci to Xp22.3: *SHOX* for short stature [1], *ARSE* for X-linked chondrodysplasia punctata [2], the MRX49 locus for X-linked mental retardation [3], *STS* for X-linked ichthyosis [4], *KALI* for hypogonadotrophic hypogonadism with anosmia [5], and *OAI* for ocular albinism type 1 [6]. From an approximate size of 3 Mb [7], the critical region for MRX49 has been narrowed to ~1.5 Mb [8], and correlated with a two-point linkage analysis [3]. Additional deletion mapping on Xp22.3 has narrowed down the MRX49 critical interval to ~15 kb [9,10], therefore, leading to the identification of the *VCX-3A* gene [10]. The implication in autism [11] and mental retardation [12] of another gene on Xp22.3, *NLGN4X*, has further complicated the interpretation of the neurobehavioural phenotype from patients with Xp22.3 deletions. Indeed, *NLGN4X*, encoding a postsynaptic cell-adhesion molecule, is only 200 kb distal from *VCX-3A*.

In this study, we report a 17-year old male patient with a 3.7 Mb interstitial Xp22.3 deletion, involving the genes *NLGN4X*, *VCX-3A*, *VCX-1*, *VCX-2*, *VCX-3B*, *STS* and *KALI*. We discuss the role of *NLGN4X* and the family of *VCX* genes in mental retardation and/or autism.

2. Material and methods

2.1. Case report

The patient is the only child of healthy and non-consanguineous parents. He was born at term, after an uneventful pregnancy. Birth weight was 3210 g, length was 50 cm, and head circumference was 35 cm. Since the age of 1 year old, a dermatologist has followed the patient due to severe ichthyosis. His psychomotor development was strictly normal and he has attended normal school. His parents reported no behavioural problems. Because of low self-esteem due to his skin problems, a neuropsychologist evaluated the patient at 15 years of age and found normal social skills. Specific cognitive testing also reported an overall IQ of 90 (WISC-III). The patient had normal growth rate and parameters until 11 years old. His growth velocity then slowed down progressively to –2 standard deviations (SD) at 14 years old and –3SD at 16 years old. At 14 years old, he was referred to an endocrinologist for short stature and hypogonadism. Hormonal testing revealed isolated hypogonadotrophic hypogonadism. The Kallmann syndrome diagnosed in our patient was associated with hyposmia (olfactory testing) but no renal abnormalities [13].

The mother of the patient was phenotypically normal, including her height (168 cm). Both parents are from middle socio-economic classes, employed as high school teachers.

2.2. Methods

R banding chromosome and high-resolution chromosomes analysis were obtained by standard techniques. Fluorescent in situ hybridization (FISH) was performed with LSI *STS* and LSI *KALI* probes (Vysis probes). Characterization of the deletion size was carried out using BAC and PAC clones obtained from Invitrogen including RP11-800K15 (*SHOX*), RP11-802I24 (*ARSE*), RP11-769N24 (*NLGN4X*), RP11-359O20 (*VCX-3A*), RP11-274G7 (*VCX-1*), RP11-351B15 (*VCX-3B*), RP11-126O22 (*TBLIX*) and RP11-98L4 (*OAI*). The relative order of the probes is shown in Fig. 1. We determined the size of

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