A Case Report of a Child with a Marker Chromosome Presenting as Isodicentric Yp and Literature Review

Chi Hyun Cho1, Baik-Lin Eun2, Seon Hee Kwon1, Myung Hyun Nam1, Chae Seung Lim1, Chang Kyu Lee1, Yunjung Cho1, Young Kee Kim1, and Soo Young Yoon1

1Department of Laboratory Medicine, College of Medicine, Korea University and 2Department of Pediatrics, College of Medicine, Korea University, Seoul, Korea

Introduction

Abnormal Y chromosome includes Yq− of various extents (excluding normal Yq variation), Yp−, r(Y), and isochromosomes or isodicentric chromosomes, written variously as i(Yp), idic(Yp), i(Yq), and idic(Yq) [1]. The least rare of these rare conditions is the Y isochromosome, or isodicentric chromosome, usually seen as 46,X,i(Y)(p10) or 46,X,i(Y)(q11), in which the essential imbalance is a double dose of Yp material, and absence (or nearly so) of Yq [1]. There have only been a few definite reports of nonmosaic isodicentric Yp [2-4]. We describe a case with non-mosaic isochromosome of the short arm of Y in which the phenotype includes mild developmental delay, heart defects, normal genitalia, and normal stature. In addition, we review the literature associated with non-mosaic isochromosome of the short arm of Y.

Case Report

The proband is a 5-year-old boy who is the second child to non-consanguineous Korean parents. The cousin of the proband had a history of developmental delay; he started talking at the age of 6 years. He was born at term following caesarean section due to no progress in induced labor, with birth weight of 3.3 kg. At birth, he had an atrial septal defect (ASD) and a ventricular septal defect (VSD). He was regularly checked up for heart defects in the pediatric department, and he had the ASD and VSD closed at the age of one and four years, respectively. In addition, he had a protruding umbilicus with discharge, for which he was checked up in the department of colorectal surgery. Additionally, concerns about his language development arose from the age of 2 years. At 4 years, he had receptive and expressive language skills equivalent to those of a normal 2.5 and 2 year old, respectively. His gross and fine motor development has been normal. Examination demonstrated head circumference 52.5 cm (75th-90th centile). He had a non-dysmorphic facial appearance and his eyes and ears were normally set. His external genitalia were normally developed.

Chromosome analysis with peripheral blood was performed as part of the investigation of his speech delay. The karyotype was interpreted as 46,X,+mar (Figure 1). Marker chromosome was identified as an isochromosome of the Y chromosome short arm by three kinds of fluorescence in situ hybridization (FISH) studies using the following probes: (1) Probes for the X centromere (CEP X, alpha satellite, and DXZ1) and the SRY gene on Yp11.3 (2) Probes for the X centromere (CEP X, alpha satellite, and DXZ1) and the Y heterochromatin on Yq12 (CEPY, satellite III, and DYZ1) (3) Probes for the X centromere (CEP X, alpha satellite, and DXZ1) and the Y centromere (CEPY, alpha satellite, and DYZ3). The marker chromosome shown to be dicentric, included the Y chromosome short arms and proximal Y long arm material between the two centromeres with the break at Yq11.2. The patient’s karyotype was interpreted as 46,X,i(Y)(p10).ish idic(Y)(q11.2)(DXZ1+, SRY++, DYZ3++, DYZ1-) (Figure 2). G-banding and FISH studies on 50 cells showed no evidence of mosaicism. Parental chromosomes have been normal.

Discussion

Y isochromosome may be seen in both non-mosaic and (typically more) mosaic form [1]. However, almost all cases to date have been mosaic cases, with the second cell line typically being 45, X [1,2]. To our knowledge, there were five cytogenetic studies worldwide in which non-mosaic isochromosome of the short arm of Y was identified definitely [2-5]. The phenotype in those cases has ranged from developmentally delayed but otherwise normal male to actual genital ambiguity (Table 1). While the case no. 2, 3, and 5 had developmental delay as a
main clinical feature, case no. 4 and our case had dyspraxia and heart defects as an additional clinical feature, respectively. The existence of a low level of mosaicism for an unidentified second cell line could have resulted in the variegated phenotypes of the reported cases shown in table 1 [2,6].

Notably, five cases among six cases had a developmental delay (Table 1). Each sex chromosome has two pseudoautosomal regions (PAR1 and PAR2). The genes identified in PAR2 have no known role

<table>
<thead>
<tr>
<th>Author et al. (1995)</th>
<th>No.</th>
<th>Age and sex</th>
<th>Karyotype in PB</th>
<th>FISH</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genuardi et al. (1995)</td>
<td>1</td>
<td>16 year old/female</td>
<td>46,X,idic(Y)(q11.2)</td>
<td>Nil</td>
<td>Primary amenorrhoea, hypotrophic female external genitalia, 2 cm blind-ended vagina, inguinally situated testes but no female internal genitalia, normal stature, no developmental delay</td>
</tr>
</tbody>
</table>

| Neas et al. (2005) | 2   | 4 year old/male | 46,X,idic(Y)(p10) | Ish idic(Y)(q11.2) | Mild developmental delay, normal genitalia, and normal stature |

| Bruyere et al. (2006) | 3   | Prenataly diagnosed case/male | 46,X,idic(Y)(q11.2) | Ish idic(Y) | Normal male genitalia at birth and at 8 months, Height at 95th centile |

| DesGroseilliers et al. (2006) | 4   | 4 year old/male | 46,X,idic(Y)(q11.2) | Ish idic(Y)(q11.2) | Dysmorphic features, (SRY++, DYZ3++, high growth parameters, global developmental delay, dyspraxia |

| DesGroseilliers et al. (2006) | 5   | 2 year old/male | 46,X,idic(Y)(q11.2) | Ish idic(Y)(q11.2) (9H4.5++, DYZ3++, DYZ1-) | Mild language delay |

| This case | 6   | 5 year old/male | 46,X,idic(Y)(p10) | Ish idic(Y)(q11.2) (DXZ1+, SRY++, DYZ3++, DYZ1-) | Mild developmental delay, heart defects, normal genitalia, and normal stature |

Abbreviations: FU, follow up; Nil, no study or no information; No., number; PB, peripheral blood.

Figure 1. G-banded Karyotype demonstrating an isodicentric Yp.
in neurodevelopment [7]. Whereas, PAR1 at the tip of the short arm (Xp-Yp PAR) is thought to play a role in the neuropsychiatric features. Neas et al. reported a case of non-mosaic isodicentric Yp with mild developmental delay, normal genitalia, and normal stature [7,8]. They suggested that the patient was trisomic for PAR1, and had mild developmental delay not unlike that seen in some girls with 47,XXX [2]. Similarly, three PAR1 in our case could have caused developmental delay, although further genetic tests were not performed due to non-approval by the parents.

Given that absence of SRY present in Yp leads to female development [1], in all cases except case No. 1, the probands were males with normal genitalia (Table 1). However, case No. 1 was a 16-year-old female with primary amenorrhoea and normal stature in spite of the presence of Yp. She had hypotrophic female external genitalia, a 2 cm blind-ended vagina, and inguinally situated testes but no female internal genitalia [5]. In that case, there might be a mutation in SRY or other genes controlling a later event in the testicular developmental pathway [9]. Those genes include WT1, SF1, WNT4, RSPO1, SOX9, FGF9, MAP3K1, CBX2, DHH, DAX1, DMRT1, SOX3, and TSPYL1 [9].

The genes controlling spermatogenesis are located in Yq11.2 [10]. It has been postulated that Yq11 encompasses three nonoverlapping regions, AZFa, AZFb, and AZFc, which could be responsible for

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**Figure 2.** Interphase (A) and metaphase (B) fluorescence in situ hybridization (FISH) results, showing the probe DXZ1 (green) and duplication of the probe SRY (red). Interphase (C) and metaphase (D) FISH results, showing the probe DXZ1 (red) and absence of the probe DYZ1 for Y heterochromatin (green). Interphase (E) and metaphase (F) FISH results, showing the probe DXZ1 (green) and duplication of the probe DYZ3 (red).
disruption of spermatogenesis [10]. Accordingly, intactness of Yp with loss of Yq loci, and in particular the azoospermia factor regions (AZF) spermatogenesis loci, is associated with male infertility [1]. Therefore, the four cases in Table 1 (No. 2,3,4,5) and our case could have had infertility but were not tested for infertility.

In conclusion, we have presented the cytogenetic analysis of a case with non-mosaic isodicentric Yp, reviewing the previously reported five cases. Nevertheless, further cases need to be reported to elucidate clearly the correlation between the phenotype and the karyotype.

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