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PERICENTRIC INVERSION inv(7)(p11q21.1): REPORT ON TWO CASES AND GENOTYPE-PHENOTYPE CORRELATIONS

We report on two unrelated cases of pericentric inversion 46,XY,inv(7)(p11q21.1) associated with distinct pattern of malformation including mental retardation, development delay, ectrodactyly, facial dismorphism, high arched palate. Additionally, one case was found to be characterized by mesodermal dysplasia. Cytogenetic analysis of the families indicated that one case was a paternally inherited inversion whereas another case was a maternally inherited one. Molecular cytogenetic studies have shown paternal inversion to have a breakpoint within centromeric heterochromatin being the cause of alphoid DNA loss. Maternal inversion was also associated with a breakpoint within centromeric heterochromatin as well as inverted euchromatic chromosome region flanked by two disrupted alphoid DNA blocks. Basing on molecular cytogenetic data we hypothesize the differences of clinical manifestations to be produced by a position effect due to localization of breakpoints within variable centromeric heterochromatin and, alternatively, due to differences in the location breakpoints, disrupteding different genes within region 7q21-q22. Our results reconfirm previous linkage analyses suggested 7q21-q22 as a locus of ectrodactily and propose inv (7)(p11q21.1) as a cause of recognizable pattern of malformations or a new chromosomal syndrome.

Introduction. Pericentric inversions of human chromosomes can be theoretically divided into two groups with respect to the pathogenic value. Thus, a number of recurrent pericentric inversions involving heterochromatic chromosome regions are apparently benign in contrast to the remainder which can be the cause of congenital malformation. Apart from benign ones the frequency of pericentric inversions in general population is ranged between 0.12 and 0.7 % [1]. When looking throughout the literature, it is hard to avoid the conclusion that pericentric inversions of chromosome 7 are rare chromosome abnormalities which phenotypic consequences are extremely variable. However, the extreme rarity of chromosome 7 pericentric inversions recurrence leads to poor understanding of its phenotypic manifestations.

Here, we report on two first familial cases of precentric inversion inv(7)(p11q21.1) characterized by recognizable patterns of congenital malformation. Additionally, we have used clinical and cytogenetic data obtained in order to develop genotype-phenotype correlations.

Materials and methods. The first case: proband is a 14-years-old boy with growth retardation, mental and ectrodactily, short neck, characteristic facial dysmorphisms (manifested as exophtalmus, long philtrum, thick low lip, bubble nose), transverse palmar crease, high arched palate, irregular placement of teeth.

Among the different clinical signs revealed in this case there were mesodermal dysplasia (red atrophic macules that may be slightly raised and have asymmetric distribution on thorax and limbs; lipomatous nodules projecting through localized areas of skin atrophy; hypoplasia of teeth; dystrophic nails) and pectus curinatum.

The second case: proband is a 10-years-old boy with growth and mental retardation, ectrodactily, short neck, characteristic facial dysmorphisms (manifested as exophtalmus, long philtrum, thick low lip, bubble nose), transverse palmar crease, high arched palate, irregular placement of teeth. Brahidactily was observed in the second case in contrast to the first one.

Conventional cytogenetic and C-banding analyses were performed on cultured blood lymphocytes of the members of both families (I — affected boy, his sibling (sister), father and mother; II — affected boy and his father and mother) according to the routine procedures [2, 3]. Molecular cytogenetic studies via fluorescent in situ hybridization

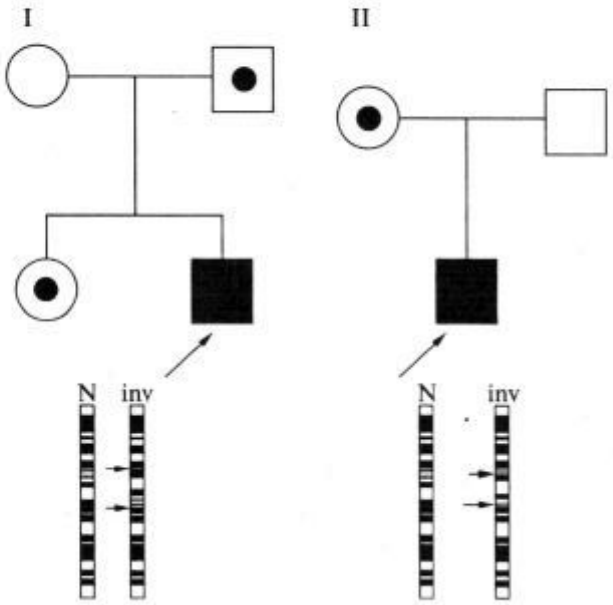

Fig. 1. Pedigrees and ideogram illustration of chromosome 7 inversions (Pedigree: point marks asymptomatic carriers, colored squares show probands. Ideogram: N — normal chromosome 7, inv — inverted chromosome 7).

(FISH) were performed according to the previously detailed protocols [4—6] using centromeric alphoid DNA probe for chromosome 7 as well as site-specific probes mapped to pericentromeric region of 7p and 7q21.1 [5, 6].

Results and discussion. Cytogenetic investigations revealed karyotype 47,XY,inv(7)(p11q21.1) in both boys with congenital malformations. Additionally, these techniques allowed determination of the same chromosome abnormality in father and sibling of the first case and in mother of the second case. Therefore, the first case represented paternally inherited inversion whereas the second case was the maternally inherited one. Clinical examination has indicated members of families who carried the inversion to lack congenital malformation observed in affected boys. Molecular cytogenetic studies provided us for information concerning inversion breakpoints. Thus, in both cases breakpoints were localized within the centromeric heterochromatin (alphoid DNA) of chromosome 7 and in 7q21.1 region. The

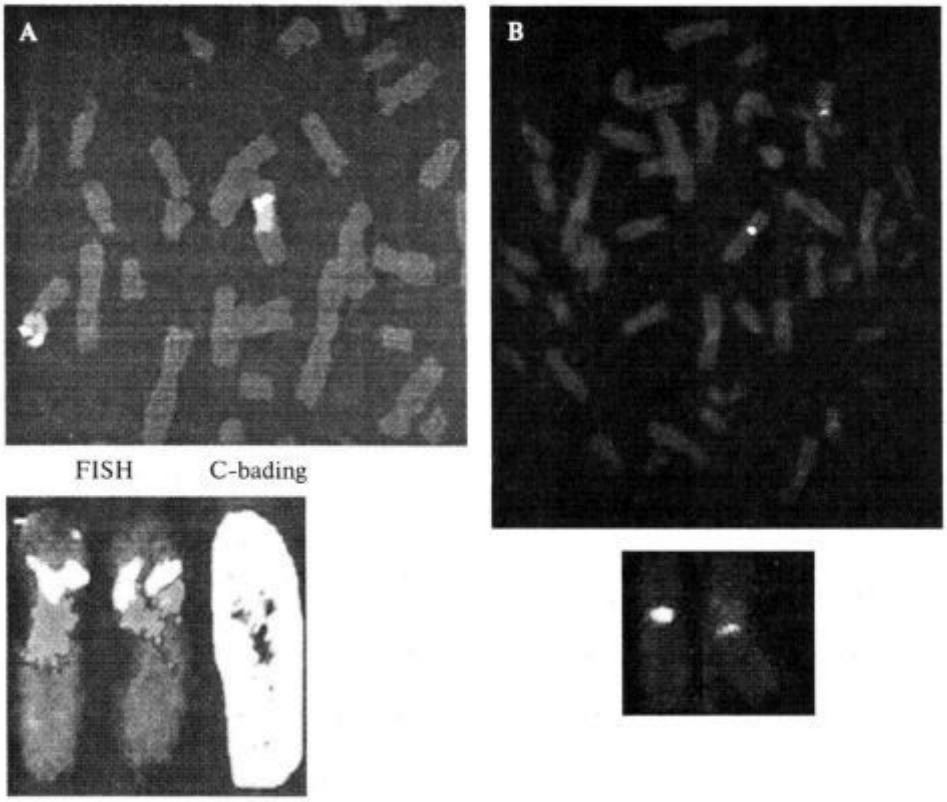

Fig. 2. A. FISH with alphoid DNA probe for chromosome 7 and probe mapped to pericentromeric region 7p and C-banding performed on cultured blood lymphocytes of boy with paternally inherited inversion (*A*) and FISH with alphoid DNA probe for chromosome 7 performed on cultured blood lymphocytes of the boy with maternally inherited inversion (*B*)

differences observed at cytogenetic level were referred to complete inversion and partial loss of alphoid DNA block in the first case in contrast to the second case detected to be associated with flanking of inverted euchromatic regions by two disrupted alphoid DNA blocks and partially dispersed alphoid DNA within the euchromatic region (Fig. 1, 2).

In order to define whether inv(7)(p11q21.1) is associated with clinically distinct phenotypic manifestations genotype-phenotype correlations were attempted to be developed. Table shows the comparison of clinical signs in these two cases. It allows concluding that the majority of phenotypic features in these two cases are shared. Therefore, chromosome abnormality inv(7)(p11q21.1) cause distinct patterns of congenital malformation permitting to name arbitrarily inversion of chromosome 7 with breakpoints located within 7p11 and 7q21.1 as a new chromosome syndrome.

The summary of phenotypic features of these two cases has shown that there is a number of similar clinical signs that are certainly caused by the breakpoint in 7q21.1 and, probably, by disruption within non-transcribed DNA sequences of centromeric heterochromatin of chromosome 7. Interestingly, previous linkage analyses targeted to define the loci of ectrodactily have indicated 7q21-q22 as a possible one [7]. Therefore, our data concerning these two cases reconfirm previous molecular genetic investigations of ectrodactily. However, certain phenotypic differences were observed. The latter was suggested to be produced by position effect known to be a feature of a number of human diseases [8]. We have hypothesized that differences between phenotypic appearences are caused by different patterns of alphoid DNA rearrangements in these two cases. Therefore, the carriers of the inversion are «protected» due to the lack of the inactivation of disease-causing disrupted genes. In addition, the affected boys probably demonstrate inactivation of non-disrupted genes located near the breakpoints and, therefore, lack of these genes expression may contribute to the phenotypic appearance. Finally, it should be noted that additional cases of inv(7)(p11q21.1) are required in order to come to definite conclusion about the role position effect plays in the phenotypic manifestation of this inversion.

Genotype-phenotype correlation developed evidences that this inversion is associated with a number of distinct clinical signs. Therefore, it is reasonable to propose this inv(7)(p11q21.1) as a new chromosomal syndrome.

Comparison of clinical signs present in the boys with pericentric inversion of chromosome 7

Symptom	Paternal inversion	Maternal inversion
Growth retardation	+	+
Mental retardation	+	+
Ectrodactily	+	+
Brachidactily	–	+
Transverse palmar crease	+	+
Exophtalmus	+	+
Long philtrum	+	+
Thick low lip	+	+
Bubble nose	+	+
Skin abnormalities	+	–
Pectus curinatum	+	–
Short neck	+	+
Teeth abnormalities	+	+
High arched palate	+	+

The assistance of Dr. Victoria V. Voinova-Ulas is acknowledged. The authors are supported by INTAS03-51-4060.

РЕЗЮМЕ. Описаны два неродственных случая перицентрической инверсии 46,XY,inv(7)(p11q21.1), связанной с умственной отсталостью, задержкой развития, эктродактилией, аномалиями лица, готическим небом. Помимо этого, в одном случае наблюдали мезодермальную дисплазию. Цитогенетический анализ семей показал, что в одном случае инверсия имела отцовское происхождение, в другом — материнское. С помощью молекулярно-цитогенетических исследований было определено, что точка разрыва инверсии отцовского происхождения локализована в центромерном гетерохроматине и связана с потерей альфоидной ДНК. При анализе инверсии материнского происхождения было показано, что точки разрыва также локализованы в центромерном гетерохроматине и эухроматине участка 7q21-q22, а также инвертированный эухроматиновый участок расположен между двумя перестроенными блоками альфоидной ДНК. Наши данные подтверждают результаты анализа сцепления, который идентифицировал локус 7q21-q22 как участок гена, мутации в котором связаны с эктродактилией, а также позволяют рассматривать inv(7)(p11q21.1) как причину характерных фенотипических нарушений или новый хромосомный синдром. На базе полученных данных предлагается гипотеза о том, что фе-

нотипические различия в описанных случаях можно объяснить эффектом положения генов, связанным с расположением перестройки вблизи вариабельного участка гетерохроматина или с различиями в точках разрыва разных генов в участке 7q21-q22.

РЕЗЮМЕ. Описано два неродинних випадки перицентричної інверсії 46,XY,inv(7)(p11q21.1), пов'язаної з розумовою відсталістю, затримкою розвитку, ектродактилією, аномаліями обличчя, готичним піднебінням. Крім цього, в одному випадку спостерігали мезодермальну дисплазію. Цитогенетичний аналіз сімей показав, що в одному випадку інверсія мала батьківське походження, в другому — материнське. За допомогою молекулярно-цитогенетичних досліджень було визначено, що точка розриву інверсії батьківського походження локалізована в центральному гетерохроматині та пов'язана з втратою альфоїдної ДНК. При аналізі інверсії материнського походження було показано, що точки розриву також локалізовані в центральному гетерохроматині та еухроматині ділянки 7q21-q22, а також інвертована еухроматинова ділянка знаходиться між двома перебудованими блоками альфоїдної ДНК. Наші дані підтверджують результати аналізу зчеплення, який ідентифікував локус 7q21-q22 як ділянку гена, мутації в якому пов'язані з ектродактилією, а також розглядати inv(7)(p11q21.1) як причину характерних фенотипових порушень або новий хромосомний синдром. Пропонується гіпотеза про те, що фенотипові відмінності в описаних випадках можна пояснити ефектом положення генів, пов'язаним з розташуванням перебудови біля варіабельної ділянки гетерохроматину чи з відмінностями в точках розриву різних генів на ділянці 7q21-q22.

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Received 29.11.05