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

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 pericentric 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 ectroactily, short neck, characteristic facial dysmorphism (manifested as exophthalmus, 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 curvatum.

The second case: proband is a 10-years-old boy with growth and mental retardation, ectroactily, short neck, characteristic facial dysmorphism (manifested as exophthalmus, 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...
(FISH) were performed according to the previously detailed protocols [4—6] using centromeric alpheid 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 (alpheid DNA) of chromosome 7 and in 7q21.1 region. The
differences observed at cytogenetic level were referred to complete inversion and partial loss of aliphoid 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 aliphoid DNA blocks and partially dispersed aliphoid 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 ectodactyly have indicated 7q21-q22 as a possible one [7]. Therefore, our data concerning these two cases reconfirm previous molecular genetic investigations of ectodactyly. 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 appearances are caused by different patterns of aliphoid 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.

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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Paternal inversion</th>
<th>Maternal inversion</th>
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<tbody>
<tr>
<td>Growth retardation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Ectodactyly</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Brachidactyly</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Transverse palmarcrease</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Exophthalmus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Long philtrum</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Thick low lip</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Bubble nose</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Skin abnormalities</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Pectus curvatum</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Short neck</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Teeth abnormalities</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>High arched palate</td>
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**РЕЗЮМЕ** Описаны два неродственных случая перцентрической инверсии 46,XY;inv(7)(p11q21.1), связанной с умственной отсталостью, задержкой развития, эктродактилией, аномалиями лица, гипотическими небом. Помимо этого, в одном случае наблюдали иезодермальную 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 перестрочными блоками альфоидной ДНК. Наши данные подтверждают результаты анализа скреплений, 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 новий хромосомный синдром. На основе 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.

РЕЗУЛЬТАТЫ. Описано два нередких випадки перистроичной инверсии 46,XY,inv(7)(p11q21.1), повязанной с розумевою валидностью, затрудняющую редукцию, экстратилцию, аномалиями амнион, гипотрохием и патологией. Крм того, в одном випадку стоперегиали мезодирольную дисплазию. Цитогенетический анализ симей показал, что в этом випадку инверсия мала батьковская походження, в другому — материнская. За допомогою молекулярно-цитогенетичних досліджень було виявлено, що точка розриву інверсії батьківського походження локалізована в центральному гетерохроматині та пов'язана з арахноїдною ДНК. При аналізі інверсії материнського походження було показано, що точка розриву також локалізована в центральному гетерохроматині та еухроматині ділянки 7q21-q22, а також інвертуваний еухроматиновий ділянка знаходиться між двома перебудованими блоками альфоїдної ДНК. Націй дані підтверджують результати аналізу чеплень, який ідентифікував локус 7q21-q22 як ділянку гена, мутації в якому пов'язані з андростаденольною, а також розглядати inv(7)(p11q21.1) як причиною ініціальних фенотипових порушення або новий хромосомний синдром. Пропонується гіпотеза про те, що фенотипівідмінності у описаніх випадках можна пояснити ефектом положения генів, пов'язаним з розщепленням переведованих білка варіабельної ділянці гетерохроматину чи з відмінностями в точках розриву різних генів на ділянці 7q21-q22.

REFERENCES


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