Review Article

Molecular Bases and Phenotypic Determinants of Aromatase Excess Syndrome

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Received 9 July 2011; Revised 22 September 2011; Accepted 2 October 2011

Aromatase excess syndrome (AEXS) is a rare autosomal dominant disorder characterized by gynecomastia. This condition is caused by overexpression of \( \text{CYP19A1} \) encoding aromatase, and three types of cryptic genomic rearrangement around \( \text{CYP19A1} \), that is, duplications, deletions, and inversions, have been identified in AEXS. Duplications appear to have caused \( \text{CYP19A1} \) overexpression because of an increased number of physiological promoters, whereas deletions and inversions would have induced wide \( \text{CYP19A1} \) expression due to the formation of chimeric genes consisting of a noncoding exon(s) of a neighboring gene and \( \text{CYP19A1} \) coding exons. Genotype-phenotype analysis implies that phenotypic severity of AEXS is primarily determined by the expression pattern of \( \text{CYP19A1} \) and the chimeric genes and by the structural property of the fused exons with a promoter function (i.e., the presence or the absence of a natural translation start codon). These results provide novel information about molecular mechanisms of human genetic disorders and biological function of estrogens.

1. Introduction

Aromatase encoded by \( \text{CYP19A1} \) is a cytochrome P450 enzyme that plays a key role in estrogen biosynthesis [1]. It catalyzes the conversion of \( \Delta^4 \)-androstenione into estrone (E1) and that of testosterone (T) into estradiol (E2) in the placenta and ovary as well as in other tissues such as the fat, skin, bone, and brain [1].

Overexpression of \( \text{CYP19A1} \) causes a rare autosomal dominant disorder referred to as aromatase excess syndrome (AEXS, OMIM no. 139300) [2–8]. AEXS is characterized by pre- or peripubertal onset gynecomastia, gonadal dysfunction, advanced bone age from childhood to pubertal period, and short adult height in affected males [2–8]. In particular, gynecomastia is a salient feature in AEXS, and, therefore, this condition is also known as hereditary gynecomastia or familial gynecomastia [5]. Affected females may also show several clinical features such as macromastia, precocious puberty, irregular menses, and short adult height [5, 6, 8].

Recently, three types of cryptic genomic rearrangements around \( \text{CYP19A1} \) have been identified in 23 male patients with AEXS [2–4]. The results provide useful implications not only for the clarification of underlying mechanisms but also for the identification of phenotypic determinants. Here, we review the current knowledge about AEXS.

2. The Aromatase Gene (\( \text{CYP19A1} \))

\( \text{CYP19A1} \) encoding aromatase is located on 15q21.2 adjacent to \( \text{DMXL2} \) and \( \text{GLDN} \) (Figure 1) [3, 9]. It spans \( \sim 123 \) kb and consists of at least 11 noncoding exons 1 and nine coding exons 2–10 [9–12]. Each exon 1 is accompanied by a tissue-specific promoter and is spliced alternatively onto a common splice acceptor site at exon 2, although some transcripts are known to contain two of the exons 1 probably due to a splice error [9–11]. Transcription of \( \text{CYP19A1} \) appears to be tightly regulated by alternative usage of the multiple
promoters [9–13]. Actually, CYP19A1 is strongly expressed in the placenta and moderately expressed in the ovary, whereas it is only weakly expressed in a rather limited number of tissues including skin, fat, and hypothalamus [4, 13]. Of the 11 noncoding exons 1, exon I.4 seems to play a critical role in the regulation of estrogen biosynthesis in males, because this exon contains the major promoter for extragonadal tissues [9, 10].

3. Molecular Bases of AEXS

A family with dominantly transmitted gynecomastia of prepubertal onset was first described in 1962 by Wallach and Garcia [14]. After this initial report, several cases have been described [5–8, 15]. Laboratory examinations of the affected males revealed markedly elevated serum estrogen values and estrogen/androgen ratios and significantly increased aromatase activity in fibroblasts and lymphocytes [5–8, 15]. Linkage analyses in two families indicated a close association between CYP19A1-flanking polymorphic markers and the disease phenotype [5, 6]. Thus, the condition was assumed to be caused by gain-of-function mutations of CYP19A1, and, therefore, the name of AEXS was coined for this condition [7, 8]. However, since direct sequencing and Southern blotting analysis failed to detect mutations or copy number abnormalities in the coding region of CYP19A1 [5, 6], the molecular basis of this entity remained elusive until recently.

In 2003, Shozu et al. reported a father-son pair and a sporadic case with AEXS in whom they identified heterozygous chromosomal inversions of the chromosome 15 [2]. Subsequently, Demura et al. performed detailed molecular studies for these cases and additional two cases and characterized four types of inversions affecting the 5′ region of CYP19A1 [3]. Each inversion has resulted in the formation of a chimeric gene consisting of CYP19A1 coding exons and exon 1 of the widely expressed neighboring genes, that is, CGN1L, TMOD3, MAPK6, and TLN2. These data imply that overexpression of CYP19A1 in the inversion-positive cases is caused by cryptic usage of constitutively active promoters. Consistent with this, in silico analysis revealed the presence of promoter-compatible sequences around exon 1 of CGN1, TMOD3, and MAPK6 in multiple cell types, although such sequences remain to be identified for noncoding exons of TLN2 [4].

We recently studied 18 males from six families with AEXS (families A–F) and identified three types of heterozygous cryptic genomic rearrangements in the upstream region of the CYP19A1 coding exons (Figure 2) [4]. In families A and B, we identified the same 79,156 bp tandem duplication encompassing seven of the 11 noncoding exons 1 of CYP19A1. Notably, this duplication includes exon I.4 that functions as a major promoter for extragonadal tissues such as fat and skin; therefore, CYP19A1 overexpression in these families would be explained by increasing the number of this promoter. Indeed, RT-PCR analysis detected a splice variant consisting of exon I.4 at the 5′ side and exon I.8 at the 3′ side in lymphoblastoid cell lines and skin fibroblasts of the patients, indicating that the duplicated exon I.4 at the distal nonphysiological position actually functions as transcription start sites. In family C, we identified a 211,631 bp deletion affecting exons 2–43 of DMXL2 and exons 5–10 of GLDN. This deletion appears to have caused CYP19A1 overexpression because of cryptic usage of DMXL2 exon 1 as an extra transcription start site for CYP19A1. Indeed, RT-PCR revealed the presence of chimeric mRNA clones consisting of DMXL2 exon 1 and CYP19A1 exon 2, supporting the notion that aberrant splicing has occurred between these two exons. Such DMXL2/CYP19A1 chimeric mRNA accounted for 2–5% of CYP19A1-containing transcripts from skin fibroblasts. In families D–F, we identified
Figure 2: Schematic representation of duplications and deletions identified in patients with AEXS. (a) the tandem duplication of families A and B [4]. Genome: the duplication (yellow boxes) includes seven of the 11 noncoding exons 1 of CYP19A1. mRNA: the sequence of a rare transcript is shown. The 3′-end of exon I.4 is connected with the 5′-end of exon I.8. (b) The deletion of family C [4]. Genome: the deletion (a gray area) includes exons 2–43 of DMXL2 and exons 5–10 of GLDN. mRNA: The sequence of a rare chimeric gene transcript is shown. DMXL2 exon 1 consisting of a noncoding region and a coding region is spliced onto the common acceptor site of CYP19A1 exon 2. (c) The deletion of families D–F [4]. Genome: the deletion (a gray area) includes exons 2–43 of DMXL2. mRNA: the sequence of a rare chimeric gene transcript is delineated. The mRNA structure is the same as that detected in family C.

Collectively, three types of genomic rearrangements on 15q21 have been identified in AEXS to date, namely, inversion type (four subtypes), duplication type, and deletion type (two subtypes) (Figure 3(a)) [2–4]. In this regard, sequence analyses for the breakpoints have indicated that (1) inversion types are formed by a repeat sequence-mediated nonallelic intrachromosomal or interchromosomal recombination or by a replication-based mechanism of fork stalling and template switching (FoSTeS) that occurs in the absence of repeat sequences and is often associated with microhomology [16], (2) duplication type is generated by FoSTeS, and (3) deletions are produced by nonhomologous end joining that takes place between nonhomologous sequences and is frequently accompanied by an insertion of a short segment at the fusion point or by a nonallelic recombination [16].
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Wild-type

Genome

Families A and B (duplication)

Family C (deletion type 1)

Families D–F (deletion type 2)

||
---|---

Family 1 (inversion type 1)

Sporadic case 1 (inversion type 3)

Family 2 (inversion type 2)

Sporadic case 2 (inversion type 4)

GLDN

DMXL2

CYP19A1

| NMD | CYP19A1 |
---|---|---|

Figure 3: Structural and functional properties of the fused exons. (a) Schematic representation of the rearranged genome and mRNA structures. The white and the black boxes of CYP19A1 exon 2 show untranslated region and coding region, respectively. For genome, the striped and the painted arrows indicate noncoding and coding exons, respectively (5′ → 3′). The inverted genomic regions are delineated in blue lines. For mRNA, colored striped boxes represent noncoding regions of each gene. The DMXL2-CYP19A1 chimeric mRNA has two translation initiation codons and therefore is destined to produce not only CYP19A1 protein but also a 47 amino acid protein which is predicted to undergo nonsense-mediated mRNA decay (NMD). The deletion and the inversion types are associated with heterozygous impairment of neighboring genes (deletion or disconnection between noncoding exon(s) and the following coding exons). The inversion subtype 1 is accompanied by inversion of eight of the 11 CYP19A1 exons 1, and the inversion subtype 2 is associated with inversion of the placenta-specific CYP19A1 exon I.1. (b) Expression patterns of CYP19A1 and the five neighboring genes involved in the chimeric gene formation [4]. Relative mRNA levels against TBP in normal human tissues are shown.

Thus, it appears that genomic sequence around CYP19A1 harbors particular motifs that are vulnerable to replication- and recombination-mediated errors. The results provide novel mechanisms of gain-of-function mutations leading to human diseases.

4. Clinical Features of AEXS

To date, a total of 23 male cases from 10 families have been reported to have molecularly confirmed AEXS (Table 1, Figure 3(a)) [2–4]. They exhibited pre- or peripubertal onset
Table 1: Summary of clinical studies in male patients with aromatase excess syndrome (modified from [4]).

<table>
<thead>
<tr>
<th>Family</th>
<th>Family A</th>
<th>Family B</th>
<th>Family C</th>
<th>Family D</th>
<th>Family E</th>
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<tr>
<td>Mutation types</td>
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<td>Duplication</td>
<td>Deletion</td>
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<td>Deletion</td>
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<td>The promoter involved in</td>
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<td>CYP19A1</td>
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<th>Case 5</th>
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<td>20</td>
<td>15</td>
<td>15</td>
<td>13</td>
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<tr>
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<td>2</td>
<td>2</td>
<td>3</td>
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<td>4</td>
<td>4</td>
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<td>13</td>
<td>10</td>
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<td>11</td>
<td>11</td>
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<td>10</td>
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<tr>
<td>Mastectomy (year)</td>
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<td>Yes (15)</td>
<td>No</td>
<td>Yes (15)</td>
<td>Yes (15)</td>
<td>Yes (13)</td>
<td>No</td>
<td>No</td>
<td>Yes (12)</td>
<td>Yes (13)</td>
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<tr>
<td>Testis (ml)</td>
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<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>N.E.</td>
<td>3</td>
<td>12</td>
<td>20</td>
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<tr>
<td>Pubic hair (tanner stage)</td>
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<td>4</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>N.E.</td>
<td>1</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Facial hair</td>
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<td>Scarcely</td>
<td>Scarcely</td>
<td>Normal</td>
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<td>Absent</td>
<td>N.E.</td>
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<tr>
<td>Height (SDS)*</td>
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<td>−0.3</td>
<td>+0.4</td>
<td>+0.8</td>
<td>−2.0</td>
<td>−1.0</td>
<td>−1.6</td>
<td>+2.7</td>
<td>±0</td>
<td>+1.8</td>
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<tr>
<td>Bone age (year)**</td>
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<td>N.E.</td>
<td>N.E.</td>
<td>16.0</td>
<td>16.0</td>
<td>13.5</td>
<td>N.E.</td>
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</tbody>
</table>

<p>| LH (mIU/mL) | GnRHc | 3.8 | 2.3 | 14.3 | 2.1 | 17.0 | 2.4 | 29.4 | 1.9 | 49.6 | 1.8 | 69.2 | 1.1 | 11.5 | 0.6 | 39.5 | 6.7 | 14.8 |
| LH (mIU/mL) | GnRH (after priming)f | 1.8 | 9.5 | 1.3 | 10.7 | |
| FSH (mIU/mL) | GnRHc | 1.7 | 3.1 | 5.3 | &lt;0.5 | 1.2 | 0.9 | 2.4 | 1.4 | 4.2 | 2.0 | 7.8 | 3.2 | 6.6 | 0.6 | 2.9 | 0.7 | 1.0 |
| FSH (mIU/mL) | GnRH (after priming)f | 2.6 | 3.2 | &lt;0.5 | 0.9 | |
| Prolactin (ng/ml) | | 4.3 | 5.3 | 8.2 | 9.1 | 11.3 | 18.8 | |
| Δ4A (ng/mL) | | 0.5 | 1.1 | 1.2 | 0.6 | 0.7 | 2.4 | 2.9 | |
| T (ng/mL) | hCGg | 2.9 | 1.6 | 2.2 | 4.0 | 2.6 | 7.2 | 1.4 | 7.9 | 0.6 | 3.6 | 2.4 | 3.2 | 9.7 | |
| DHT (ng/mL) | | 0.4 | 0.2 | |
| Inhibin B (pg/mL) | 61.6 | 74.6 | 83.5 | 75.2 | |
| E1 (pg/mL) | 157 | 120 | 124 | 57 | 63 | 53 | |
| E2 (pg/mL) | 29 | 15 | 22 | 59 | 56 | 38 | 24 | 19 | 25 | 58 | |
| E2/T ratio (×103) | 10.0 | 9.4 | 10.0 | 14.8 | 21.5 | 27.1 | 31.7 | 10.4 | 18.1 | |</p>
<table>
<thead>
<tr>
<th>Family</th>
<th>Mutation types</th>
<th>The promoter involved in</th>
<th>CYP19A1 overexpression</th>
<th>Age at examination (year)</th>
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</tbody>
</table>

Phenotypic findings

| Gynecomastia (tanner breast stage) | Yes | Yes | Yes | Yes | 2   | 3   | 3   | 3   | Yes | 3   | 5   | N.E. | Yes |
|-----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Mastectomy (year)                 | ?   | ?   | ?   | ?   | 8   | 8   | 11  | 10  | 5    | 5   | 8   | 7   | ?   | ?   |
| Testis (ml)                       | N.E. | N.E. | N.E. | N.E. | 2   | 1.5 | 2   | 2   | N.E. | N.E. | N.E. | N.E. | N.E. | N.E. |
| Pubic hair (tanner stage)         | N.E. | N.E. | N.E. | N.E. | 1   | 2   | 1   | 2   | N.E. | Normal | 1 | 2-3 (at 21.0) | N.E. | N.E. |
| Facial hair                       | N.E. | N.E. | N.E. | N.E. | Absent | Absent | Absent | Absent | Absent | Absent | Absent | Absent | N.E. | N.E. |
| Height (SDS)                      | N.E. | ~−1.5 | ~−1.5 | ~−1.5 | +1.4 | N.E. | +2.0 | +2.4 | Short | +2.5 | −1.6 (at 21.0) | Short | N.E. |
| Bone age (year)b                  | N.E. | N.E. | N.E. | N.E. | 12.5 | 13.0 | 15.0 | 14.5 | 14.5 (at 12.5) | N.E. | 13.0 | 17.0 | N.E. | N.E. |

Fertility (spermatogenesis)


Endocrine findings

<table>
<thead>
<tr>
<th>LH (mIU/mL)</th>
<th>GnRH+&lt;sup&gt;h&lt;/sup&gt;</th>
<th>0.2</th>
<th>3.5</th>
<th>1.7</th>
<th>3.0</th>
<th>0.2</th>
<th>&lt;0.1</th>
<th>2.6</th>
<th>6.3</th>
<th>1.5</th>
<th>1.7</th>
<th>0.1</th>
<th>2.6</th>
<th>10.0</th>
<th>4.3</th>
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</thead>
<tbody>
<tr>
<td>LH (mIU/mL)</td>
<td>GnRH (after priming)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.4</td>
<td>2.3</td>
<td>0.8</td>
<td>0.8</td>
<td>1.4</td>
<td>0.5</td>
<td>0.8</td>
<td>1.2</td>
<td>1.2</td>
<td>1.5</td>
<td>0.3</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>2.7</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>GnRH+&lt;sup&gt;h&lt;/sup&gt;</td>
<td>1.4</td>
<td>0.4</td>
<td>1.7</td>
<td>0.5</td>
<td>0.3</td>
<td>&lt;0.3</td>
<td>0.9</td>
<td>1.5</td>
<td>1.3</td>
<td>0.8</td>
<td>0.3</td>
<td>2.4</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Prolactin (ng/mL)</td>
<td>hCG&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2.6</td>
<td>2.5</td>
<td>2.1</td>
<td>2.5</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>2.7</td>
<td>9.2</td>
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<td>1.2</td>
<td>3.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Δ4A (ng/L)</td>
<td>DHT (ng/mL)</td>
<td>3.8</td>
<td>2.6</td>
<td>11.4</td>
<td>12.4</td>
<td>9.3</td>
<td>14.8</td>
<td>69.6</td>
<td>148.3</td>
<td>170.4</td>
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<tr>
<td>T (ng/mL)</td>
<td>Inhibin B (pg/mL)</td>
<td>32</td>
<td>34</td>
<td>59</td>
<td>34</td>
<td>26</td>
<td>41</td>
<td>77</td>
<td>86</td>
<td>903</td>
<td>119</td>
<td>544</td>
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<tr>
<td>Inhibin B (pg/mL)</td>
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<td>19</td>
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<td>225</td>
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<td>178</td>
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<tr>
<td>E&lt;sub&gt;2&lt;/sub&gt;/T ratio (&lt;xsup&gt;×&lt;/xsup&gt;10&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>E&lt;sub&gt;2&lt;/sub&gt; (pg/mL)</td>
<td>3.8</td>
<td>2.6</td>
<td>11.4</td>
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<td>170.4</td>
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</table>

SDS: standard deviation score; Dx: diagnosis; Tx: therapy; LH: luteinizing hormone; FSH: follicle stimulating hormone; Δ4A: androstenedione; T: testosterone; DHT: dihydrotestosterone; E1: estrone; E2: estradiol; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; N.E.: not examined; B: basal; and S: stimulated.

Abnormal clinical findings are boldfaced.

Abnormally low hormone values are boldfaced, and abnormally high hormone values are underlined.

<sup>a</sup>Evaluates by age- and ethnicity-matched growth references; heights ≥+2.0 SD or below ≤−2.0 SD were regarded as abnormal.

<sup>b</sup>Assessed by the Tanner-Whitehouse 2 method standardized for Japanese or by the Greulich-Pyle method for Caucasians; bone age was assessed as advanced when it was accelerated a year or more.

<sup>c</sup>Evaluates by age-matched male reference data, except for inhibin B and E<sub>1</sub> that have been compared with data from 19 adult males.

<sup>d</sup>Treated with aromatase inhibitors (anastrozole).

<sup>e</sup>GnRH 100 μg i.m. (max. 100 μg) bolus i.v.; blood sampling at 0, 30, 60, 90, and 120 minutes.

<sup>f</sup>GnRH test after priming with GnRH 100 μg i.m. for 5 consecutive days.

<sup>g</sup>hCG 3000 IU/m2 (max 5000 IU) i.m. for 3 consecutive days; blood sampling on days 1 and 4.

<sup>h</sup>Although Case 3 has not yet fathered a child, he has normal spermatogenesis with semen volume of 2.5 ml (reference value: >2 ml), sperm count of 105 × 10<sup>6</sup>/ml (>20 × 10<sup>6</sup>/ml), total sperm count of 262.5 × 10<sup>6</sup> (>40 × 10<sup>6</sup>), motile cells of 70% (>50%), and normal morphological sperms 77% (>30%).

<sup>i</sup>These four patients allegedly had gynecomastia that required mastectomy (age unknown).

<sup>j</sup>The sister has macromastia, large uterus, and irregular menses; the parental phenotype has not been described.

The conversion factor to the SI unit: LH 1.0 (IU/L), FSH 1.0 (IU/L), E<sub>1</sub> 3.699 (pmol/L), E<sub>2</sub> 3.671 (pmol/L), Δ4A 3.492 (nmol/L), and T 3.467 (nmol/L).
gynecomastia, small testes with fairly preserved masculin-
ization, obvious or relative tall stature in childhood and
grossly normal or apparent short stature in adulthood,
and age-appropriate or variably advanced bone ages. Blood
endocrine studies revealed markedly elevated E₁ values and
E₂/T ratios in all cases examined and normal or variably
elevated E₂ values. In addition, Δ₄-androstenedione, T, and
dihydrotestosterone values were low or normal, and
human chorionic gonadotropin (hCG) test indicated normal
T responses. Notably, LH values were grossly normal at
the baseline and variably responded to GnRH stimulation,
whereas FSH values were low at the baseline and poorly
responded to GnRH stimulation even after preceding GnRH
priming, in all cases examined.

The severity of such clinical phenotypes is primarily de-
pendent on the underlying mechanisms (Table 1). They are
obviously mild in the duplication type, moderate in the
deletion type, and severe in the inversion type, except for
serum FSH values that remain suppressed irrespective of
the underlying mechanisms. Likewise, gynecomastia has been
reported to be ameliorated with 1 mg/day of aromatase
inhibitor (anastrozole) in the duplication and the deletion
types and with 2–4 mg/day of anastrozole in the inversion
type [4].

5. Expression Pattern of CYP19A1 and
the Chimeric Genes as
One Phenotypic Determinant

Phenotypic severity is much milder in the duplication type
than in the deletion and the inversion types. This would
be explained by the tissue expression pattern of CYP19A1
and the chimeric genes. Indeed, RT-PCR analysis using
normal human tissue samples revealed that CYP19A1 is
expressed only in a limited number of tissues such as
placenta, ovary, skin, and fat, while the five genes involved
in the formation of chimeric genes are widely expressed with
some degree of variation (Figure 3(b)). Therefore, it is likely
that the duplication types would simply increase CYP19A1
transcription in native CYP19A1-expressing tissues, whereas
the deletion and the inversion types lead to CYP19A1
overexpression in a range of tissues, because expression
patterns of chimeric genes are predicted to follow those of
the original genes. Furthermore, it is also likely that the
native CYP19A1 promoter is subject to negative feedback
by elevated estrogens [17], whereas such negative feedback
effect by estrogen is weak or even absent for the chimeric
genesis in the deletion and the inversion types.

6. Structural Property of the Fused Exons as
Another Phenotypic Determinant

Phenotypic severity is also milder in the deletion type than
in the inversion types, despite a similar wide expression
pattern of genes involved in the chimeric gene formation
(Table 1, Figure 3(b)). In this context, it is noteworthy that
a translation start codon and a following coding region
are present on exon 1 of DMXL2 of the deletion type but
not on exons 1 of the chimeric genes of the inversion
types (Figure 3(a)). Thus, it is likely that DMXL2/CYP19A1
chimeric mRNAs transcribed by the DMXL2 promoter
preferentially recognize the natural start codon on DMXL2
exon 1 and undergo nonsense-mediated mRNA decay and
that rather exceptional chimeric mRNAs, which recognize
the start codon on CYP19A1 exon 2, are transcribed into
CYP19A1 protein. By contrast, such a phenomenon would
not be postulated for the inversion-mediated chimeric
mRNAs. Consistent with this, it has been shown that the
DMXL2/CYP19A1 chimeric mRNA is present only in 2–
5% of CYP19A1-containing transcripts from skin fibroblasts,
whereas the CGNL1/CYP19A1 chimeric mRNA and the
TMOD3/CYP19A1 chimeric mRNA account for 89–100%
and 80% of transcripts from skin fibroblasts, respectively
[2, 4].

In addition, the genomic structure caused by the rear-
rangements would affect efficiency of splicing between non-
coding exon(s) of neighboring genes and CYP19A1 exon 2.
For example, in the inversion subtype 1, the physical distance
between CGNL1 exon 1 and CYP19A1 exon 2 is short, and,
while a splice competition may be possible between exon 1 of
neighboring genes and original CYP19A1 exons 1, eight of 11
CYP19A1 exons 1 including exon I.4 have been disconnected
from CYP19A1 coding exons by inversion (Figure 3(a)). This
may also enhance the splicing efficiency between CGNL1
exon 1 and CYP19A1 exon 2 and thereby lead to relatively
severe overexpression of the CGNL1-CYP19A1 chimeric
gene, although this hypothesis would not be applicable for
other chimeric genes.

7. Implication for
the Hypothalamus-Pituitary-Gonadal
Axis Function

It is notable that a similar degree of FSH-dominant hypog-
onadotropic hypogonadism is observed in the three types,
although E₁ and E₂ values and E₂/T ratios are much higher
in the inversion type than in the duplication and deletion
types (Table 1). In particular, FSH was severely suppressed
even after GnRH priming in the duplication type [4]. This
implies that a relatively mild excess of circulatory estrogens
can exert a strong negative feedback effect on FSH secretion
primarily at the pituitary. This would be consistent with
the results of animal studies that show strong inhibitory
effect of E₂ on transcription of FSH beta-subunit gene in the
pituitary cells and almost negligible effect on synthesis of LH
beta-subunit and secretion of LH [18, 19]. In this regard,
while T responses to hCG stimulation are normal in the
duplication and the deletion types and somewhat low in the
inversion type, this would be consistent with fairly preserved
LH secretion in the three types and markedly increased
estrogen values in the inversion type. In addition, whereas
fertility and spermatogenesis are normally preserved in
the three types, this would be explained by the FSH-dominant
hypogonadotropic hypogonadism, because FSH plays only a
minor role in male fertility (spermatogenesis) [20].
8. Conclusions

Current studies argue that AEXS is caused by overexpression of CYP19A1 due to three different types of cryptic genomic rearrangements including duplications, deletions, and inversions. It seems that transcriptional activity and structural property of the fused promoter constitutes the underlying factor for the clinical variability in most features of AEXS except for FSH-dominant hypogonadotropic hypogonadism. Thus, AEXS represents a novel model for gain-of-function mutation leading to human genetic disorders.

References


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