10-12 日 山梨 シンポジウム 核内受容体レギュロンによるエネルギー代謝調節
諸橋憲一郎、馬場崇
6) 第 48 回日本小児内分泌学会 浜松 9 月 25-27 日 Basic Science Lecture. Ad4BP/SF-1 レギュロンによるエネルギー代謝調節。諸橋 憲一郎、馬場崇
7) 第 87 回日本生化学会 京都 10 月 15-18 日 シンポジウム. Dual Roles of Ad4BP/SF-1 in Steroidogenesis and Glycolysis. Takashi Baba and Ken-ichirou Morohashi
8) 第 22 回日本ステロイドホルモン学会、11 月 3 日、東京 シンポジウム。核内受容体 Ad4BP/SF-1 による細胞内代謝制御。馬場崇、大竹博之、佐藤哲也、宮林香奈子、宍戸祐里菜、Chia-Yih Wang、嶋雄一、木村宏、八木美佳子、石原康宏、日野信次郎、小川英知、中尾光善、山崎岳、康東天、大川恭行、須山幹太、Bon-Chu Chung, 諸橋憲一郎

一般演題
省略

H. 知的財産権の出願・登録状況
1. 特許取得
該当無し
2. 実用新案登録
該当無し
3. その他
該当無し

様式第19

学 会 等 発 表 実 績

委託業務題目「性分化異常、小児内分泌疾患、先天奇形症候群に関する情報収集と解析」
機関名　独立行政法人国立成育医療研究センター

1. 学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
Identification of a missense MAP3K1 mutation in a patient with hypospadias.（ポ	Igarashi M, Horikawa R, Nakabayashi K, Hata K, Ogata T, Fukami M	53th annual ESPE meeting,Dublin	September 18-20, 2014	国外
Mutation analysis of KDM3A (lysine-specific demethylase 3A) in patients with hypospadias.（ポスター）	Kon M, Igarashi M, Izumi Y, Kato-Fukui Y, Mizuno K, Hayashi Y, Kohri K, Kojima Y, Nonomura K, Ogata T,	53th annual ESPE meeting,Dublin	September 18-20, 2014	国外
Genomic Variation in the AZF Region Associated with the Risk of Azoospermia.（ポスター）	Saito K, Yoshida A, Kobori Y, Tanaka Y, Katsumi M, Miyado M, Ogata T, Kubota T, Saito H, Fukami M, Okada H	ASRM 2014 annual meeting,Hawaii	October 18-22, 2014	国外
低ゴナドトロピン性性腺機能低下症58例の網羅的遺伝子解析.（口頭）	泉陽子、鈴木江莉奈、神崎晋、八ツ賀秀一、金城さおり、中林一彦、梅澤明弘、秦健一郎、緒方勤、深見真紀、丸山哲夫、末岡浩、吉村泰典	第32回日本受精着床学会、東京	2014年7月31日-8月1日	国内
複合型下垂体ホルモン不全症患者におけるWDR11スプライスサイト変異の同定.（口頭）	泉陽子、西岡淳子、八ツ賀秀一、鈴木江莉奈、佐野伸一朗、中林一彦、梅澤明弘、秦健一郎、緒方勤、深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
成長ホルモン補充開始後に低血糖発作が改善し、WDR11変異を認めたSepto Optic Dysplasiaの一例.（口頭）	島彦仁、梅木郁美、加賀元宗、上村美季、箱田明子、菅野潤子、泉陽子、深見真紀、藤原幾磨	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
8番染色体片親性アイソダイソミーにより顕在化したCYP11B1遺伝子変異による11β水酸化酵素欠損症例.（口頭）	松原圭子、片岡直樹、荻田聡子、佐野伸一朗、緒方勤、深見真紀、勝又規行	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
非閉塞性無精子症・乏精子症患者におけるY染色体構造解析.(ポスター)	齊藤和毅、勝見桃理、宮戸真美、田中葉子、岡田弘、小堀善友、吉田淳、石川博通、緒方勤、久保田俊郎、深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
無精子症・乏精子症患者のゲノムコピー数変化の同定.（ポスター）	勝見桃理、齊藤和毅、宮戸真美、田中葉子、岡田弘、小堀善友、吉田淳、石川博通、緒方勤、深見真	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
SRY(+)46,XX精巣性性分化疾患4症例における性分化決定因子と転座発症機序の解析.（口頭）	中島信一、大石彰、高田史男、河村秀樹、小野裕之、五十嵐麻希、深見真紀、緒方勤	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
中枢神経奇形を合併した複合型下垂体機能低下症の2例：trio exome解析による新規原因遺伝子同定の試み.（口頭）	渡辺聡、伊達木澄人、近河日智、中富明子、木下英一、吉浦孝一郎、深見真紀、緒方勤、森内浩幸	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
遺伝性女性化乳房症に対するアロマターゼ阻害剤治療効果の検討.（ポス	長崎啓祐、志原大蔵、佐藤英利、小川洋平、宮戸真美、深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
SOX9 frameshift mutation in a patient with acampomelic campomelic dysplasia:the second case.（ポスター）	山口理恵、楢村哲生、加藤芙弥子、永田絵子、中島信一、馬場崇、諸橋憲一郎、五十嵐麻希、深見真紀、緒方勤	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
Uniparental disomy of chromosome 8 leading to homozygosity of a CYP11B1 mutation in a patient with congenital adrenal hyperplasia.（口頭）	Matsubara K, Kataoka N, Ogita S, Sano.S, Ogata T, Fukami M, Katsumata N	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
マウス分娩の開始と完了におけるMamld1機能の解明.（口頭）	宮戸真美、齊藤和毅、勝見桃理、宮戸健二、緒方勤、深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
46,XX精巣性性分化疾患を伴わない母娘例におけるSOX3重複の同定.（ポスター）	五十嵐麻希、三上仁、勝見桃理、泉陽子、緒方勤、深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
非症候性尿道下裂発症における単一遺伝子変異の寄与の解明.（口頭）	今雅史、室谷浩二、長谷川行洋、長崎啓祐、Dung Vu Chi、上岡克彦、大戸佑二、五十嵐登、三井貴彦、鈴木江莉奈、五十嵐麻希、福井由宇子、守屋仁彦、野々村克也、緒方勤、深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内

特発性思春期早発症女児におけるESR1遺伝子イントロン内欠失多型の検討.（ポスター）	鈴木江莉奈、泉陽子、 緒方勤、 深見真紀	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
妊娠マウスにおける黄体退縮調節因子の同定.（口頭）	宮戸真美、 齊藤和毅、 勝見桃理、 宮戸健二、 緒方勤、深見真紀	第22回日本ステロイドホルモン学会学術集会、東京	2014年11月3日	国内
SOX10 半量不全は、Kallmann 症候群とWaardenburg 症候群を招く.（口頭）	泉陽子、 武者育麻、 鈴木江莉奈、 堀川玲子、 雨宮伸、 緒方勤、 深見真紀、 大竹明	第59回人類遺伝学会、東京	2014年11月19－22日	国内
先天性疾患の遺伝子診断.（口頭）	深見真紀	第59回日本人類遺伝学会ランチョンセミナー、東京	2014年11月19－22日	国内
疾患遺伝子パネルを用いた低ゴナドトロピン性性腺機能低下症の遺伝子診断.（口頭）	鈴木江莉奈、 泉陽子、 神崎晋、 八ツ賀秀一、 金城さおり、 五十嵐麻希、 中林一彦、 梅澤明弘、秦健一郎、 緒方勤、 深見真紀	第59回人類遺伝学会、東京	2014年11月19日－22日	国内
妊娠マウスの卵巣におけるMAMLD1の役割.（ポスター）	宮戸真美、 齊藤和毅、 勝見桃理、 宮戸健二、 緒方勤、 深見真紀	第37回日本分子生物学会年会、神奈川	2014年11月25－27日	国内
ヒト性分化異常症の網羅的遺伝子変異解析.（口頭）	五十嵐麻希、 今雅史、 泉陽子、 福井由宇子、 和田友香、 宮戸真美、 緒方勤、 深見真紀	第37回日本分子生物学会年会、神奈川	2014年11月25－27日	国内
無精子症・乏精子症発症に関与するゲノムコピー数変化の解明.（ポスター）	勝見桃理、 齊藤和毅、 宮戸真美、 田中葉子、 岡田弘、 小堀善友、 吉田淳、 石川博通、 緒方勤、 深見真紀	第37回日本分子生物学会年会、神奈川	2014年11月25－27日	国内
非閉塞性無精子症・乏精子症患者におけるMLPA法を用いたY染色体構造解析.（口頭）	齊藤和毅、 勝見桃理、 宮戸真美、 岡田弘、 小堀善友、 吉田淳、 田中葉子、 石川博通、 緒方勤、 齊藤英和、 久保田俊郎、 深見真紀	第59回日本生殖医学会、東京	2014年12月4－5日および7日	国内
思春期早発症女児2例におけるNMUR2機能低下多型の同定.（口頭）	泉陽子、 鈴木江莉奈、 佐野伸一朗、 中林一彦、 梅澤明弘、 秦健一郎、末岡浩、 田中守、 緒方勤、 深	第59回日本生殖医学会、東京	2014年12月4－5日および7日	国内
Mamld1 deficient female mice exhibit delayed parturition.（口頭）	Miyado M, Miyado K, Saito K, Katsumi M, Ogata T, Fukami M	Young Scientist Meeting for Sexual Differentiation、静	2014年12月4－5日	国内
Systematic mutation analysis of patients with disorders of sex development.（口頭）	Igarashi M, Kon M, Izumi Y, Kato-Fukui Y, Suzuki E, Wada Y, Miyado M, Ogata T, Fukami M	Young Scientist Meeting for Sexual Differentiation、静岡	2014年12月4－5日	国内
Copy number variations associated with a risk of azoospermia and oligospermia.（ポスター）	Katsumi M, Saito K, Miyado M, Tanaka Y, Okada H, Kobori Y, Yoshida A, Ishikawa H, Ogata T, Fukami M	Young Scientist Meeting for Sexual Differentiation、静岡	2014年12月4－5日	国内
思春期早発症女児2例におけるNMUR2機能低下多型の同定.（口頭）	泉陽子、 鈴木江莉奈、 佐野伸一朗、 中林一彦、 梅澤明弘、 秦健一郎、 緒方勤、 深見真紀	第19回日本生殖内分泌学会学術集会、大阪	2015年1月10日	国内
低ゴナドトロピン性性腺機能低下症58例の網羅的遺伝子解析.（口頭）	鈴木江莉奈、 泉陽子、 神崎晋、 八ツ賀秀一、 金城さおり、 五十嵐麻希、 中林一彦、 梅沢明弘、 秦健一郎、 緒方勤、 深見真紀	第19回日本生殖内分泌学会学術集会、大阪	2015年1月10日	国内
Methylome analysis of the 14q32.2 imprinted region in patients with imprinting defects on human chromosome 14.（ポス	Kagami M, Hayano K, Hosomich K, Fukami M, Ogata T, Inoue I	International Symposium on Genome Science 2015、東京	2015年1月20日－21日	国内
SRY遺伝子変異を同定した高度尿道下裂の父息子例.（口頭）	室谷浩二、花川純子、大戸佑二、朝倉由美、白柳慶之、山崎雄一郎、鳴海覚志、長谷川奉延、安達	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
日本人新生児の陰茎長：基準値と人種差比較.（口頭）	石井智弘、松尾宣武、John Takayama、三輪雅之、長谷川奉延	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
線維性骨異形成のみを呈する児におけるGNAS1解析の意義 －McCune-Albright症候群早期発見の可能性.（口頭）	河野智敬、鈴木秀一、小澤綾子、会津克哉、清水健司、大橋博文、鳴海覚志、長谷川奉延、望月弘	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
巨大副腎骨髄脂肪腫を21-水酸化酵素欠損症（21-OHD）の一例.（ポスター）	永井純子、田實麻智子、福井彩子、梅村臣吾、村瀬正敏、山川文子、山田努、山家由子、村瀬孝司、長谷川奉延、本間桂子	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
Denys-Drash症候群の3例：遺伝子型と表現型の相関.（ポスター）	大戸佑二、室谷浩二、花川純子、朝倉由美、白柳慶之、山崎雄一郎、田中祐吉、林美恵、長谷川奉延、安達昌功	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内

鼡径ヘルニアを契機に診断に至った17α水酸化酵素欠損症の1例.（ポスター）	岩橋めぐみ、清水美佳、本間桂子、林美恵、天野直子、長谷川奉延、宮田市郎	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
男性低ゴナドトロピン性性腺機能低下症の成人身長と精液検査に関するアンケート調査.（ポスター）	佐藤直子、田中敏章、長谷川奉延、長谷川行洋、雨宮伸、大薗恵一、菊池透、田中弘之、原田正平、宮田市郎、有阪治	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
尿中ステロイドプロファイルが診断に有用であった成人先天性副腎皮質過形成の一例.（ポスター）	前田英昭、山田英二郎、下田容子、長谷川奉延、本間桂子、佐藤哲郎、岡田秀一、山田正信	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
成人ターナー症候群の核型、合併症およびQOLに関するアンケート調査.（ポスター）	羽二生邦彦、堀川玲子、田中敏章、長谷川奉延、藤田敬之助、横谷進	第87回日本内分泌学会学術総会、福岡	2014年4月24－26日	国内
小児期における男性低ゴナドトロピン性性腺機能低下症の治療現状と男性ホルモンとゴナドトロピン補充療法の治療プロトコール.（口頭）	佐藤直子、長谷川奉延、長谷川行洋、田中敏章	第2回MHH治療研究会、東京	2014年5月24日	国内
新生児・乳児期に診断に至らず、思春期に急激な男性化を認めた5αリダクターゼ欠損症例.（口頭）	相野谷慶子、竹本淳、坂井清英、長谷川奉延	第23回日本小児泌尿器科学会学術集会、神奈川	2014年7月9－11日	国内
嗅覚正常視床下部性性腺機能低下症の1男児例：両アリル性PROKR2変異の本邦初発例.（口頭）	杉澤千穂、佐藤武志、鳴海覚志、谷山松雄、長谷川奉延	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
LMS法による日本人小児（0-7歳）陰茎長の横断的成長曲線の作成：人種間比較と世代間比較.（口頭）	石井智弘、松尾宣武、井ノ口美香子、長谷川奉延	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
日齢90未満の5αリダクターゼ欠損症診断における尿ステロイドプロフィルの有用性と限界.（口頭）	小山雄平、本間桂子、猪瀬美帆子、林美恵、石井智弘、涌井昌俊、村田満、長谷川奉延	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
小児期早期に診断された男性低ゴナドトロピン性性腺機能低下症の治療指針の提案.（口頭）	佐藤直子、長谷川奉延、長谷川行洋、田中敏章	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
男性低ゴナドトロピン性性腺機能低下症におけるテストステロン治療の有効性および造精能への影響.（ポスター）	柴田浩憲、堀尚明、佐々木悟郎、石井智弘、上牧務、安藏慎、玉井伸哉、佐藤清二、松尾宣武、長谷川奉延	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
尿ステロイドプロフィルによる5β-還元酵素欠損症スクリーニングの可能性.（ポスター）	本間桂子、木村昭彦、水落建輝、大竹明、保科隆之、井原健二、武井一、入戸野博、猪瀬美帆子、小山雄平、清水長子、涌井昌俊、村田満、石井智弘、長谷川奉延	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
P450オキシドレダクターゼ（POR）異常症の2例.（ポスター）	古谷曜子、松尾公美浩、長屋建、棚橋祐典、東寛、平澤雅敏、宮本和俊、吉藤和久、本間桂子、長谷川奉延	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
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46,XX/46,XYの核型を持つ性分化疾患の性染色体と性腺組織の関連.（ポス	仁科範子、福澤龍二、石井智弘、長谷川奉延、長谷川行洋	第24回臨床内分泌代謝Update、埼玉	2014年11月28－29日	国内
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思春期早発症臨床の実際.（口頭）	堀川玲子	第117回日本小児科学会、愛知	2014年4月11－13日	国内
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自然に性腺機能低下症が回復した複合型下垂体昨日低下症の2例.（ポスター）	佐藤直子、内木康博、堀川玲子、田中敏章	第48回日本小児内分泌学会学術集会、静岡	2014年9月25－27日	国内
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Dual Roles of Ad4BP/SF-1 in Steroidogenesis and Glycolysis.（口頭）	Baba T, Morohashi K	20th International Symposium on Microsomal and Drug	May 18-22, 2014	国外
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セルトリ細胞における性染色体構成に起因したクロマチン構造変化とその影響評価．（口頭）	宍戸祐里菜, 馬場崇, 大竹博之, 佐藤哲也, 宮林香奈子, 嶋雄一, 大川恭行, 須山幹太, 諸橋憲一郎	第22回日本ステロイドホルモン学会、東京	2014年11月3日	国内
胎仔ライディッヒ細胞の分化誘導系の確立．（口頭）	井上実紀、嶋雄一、宮林香奈子、諸橋憲一郎	第22回日本ステロイドホルモン学会、東京	2014年11月3日	国内
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２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Uniparental disomy of chromosome 8 leading to homozygosity of a CYP11B1 mutation in a patient with congenital adrenal hyperplasia: Implication for a rare etiology of an autosomal recessive disorder.	Matsubara K, Kataoka N, Ogita S, Sano S, Ogata T, Fukami M, Katsumata N	Endocr J	2014年	国外
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Pre-pubertal serum leptin levels and sensitivity to central leptin injection of prenatally undernourished female rats.	Iwasa T, Matsuzaki T, Munkhzaya M, Tungalagsuvd A, Kawami T, Murakami M, Yamasaki M, Kato T, Kuwahara A, Yasui T, Irahara M	Int J Dev Neurosci	2014年	国外
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EXPERT REVIEWS

Understanding the pathological manifestations of aromatase excess syndrome: lessons for clinical diagnosis

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Aromatase excess syndrome is characterized by pre- or peripubertal onset of gynecomastia due to estrogen excess because of a gain-of-function mutation in the aromatase gene (*CYP19A1*). Subchromosomal recombination events including duplication, deletion, and inversion has been identified. The latter two recombinations recruit novel promoters for *CYP19A1* through a unique mechanism. Gynecomastia continues for life, and although the general condition is well preserved, it may cause psychological issues. Minor symptoms (variably advanced bone age and short adult height), if present, are exclusively because of estrogen excess. Serum estradiol levels are elevated in 48% of affected males, but are not necessarily useful for diagnosis. Molecular analysis of *CYP19A1* mutations is mandatory to confirm aromatase excess syndrome diagnosis. Furthermore, the use of an aromatase inhibitor can ameliorate gynecomastia.

KEYWORDS: aromatase excess syndrome • CYP19A1 mutation • gynecomastia

Aromatase excess syndrome (AEXS; Mendelian Inheritance in Man database no. 139300), formerly known as familial gynecomastia, is a rare genetic disease characterized by the pre- or peripubertal onset of gynecomastia. Symptoms are exclusively related to estrogen excess and are not life-threatening unlike those of common gynecomastia, which has a variety of well-established etiologies, especially secondary gynecomastia. Only 10 years have passed since the initial discovery of genetic recombination events relevant to AEXS [1].

Although AEXS is rare, this condition has been alluded to in the literature since the early 1960s [2,3] as familial gynecomastia without hypogonadism. By the mid-1980s, researchers established that massive extraglandular conversion of plasma androgens caused hyperestrogenemia in affected boys [4,5]. Following the molecular cloning of the aromatase (estrogen-synthesizing enzyme) gene (*CYP19A1*) in the early 1990s, aberrant aromatase expression was confirmed in the lymphocytes of an affected young male patient [6]. In 2003, a subchromosomal inversion of *CYP19A1* as a causative mutation of AEXS was identified [1,7]. Familial gynecomastia was renamed AEXS because it was established that this disorder is an independent entity of an autosomal genetic disease caused by a gain-of-function mutation in *CYP19A1*.

Since 2003, 12 mutant alleles have been identified in 15 families composed of 30 affected males. After a brief introduction to aromatase, we review the clinical features of AEXS with regard to its pathophysiology, diagnosis and treatment and briefly discuss the characteristics of this disease, primarily based on the clinical features of genetically defined cases [1,7–10].

Aromatase: gene structure, expression & enzymatic activities

Enzymatic activities & gene structure

Aromatase is a key player in estrogen synthesis and converts androgen to estrogen. Aromatase is a member of the cytochrome P450 superfamily that catalyzes the aromatization of the A-ring of androstenedione to produce estrone as well as the aromatization of the A-ring of testosterone

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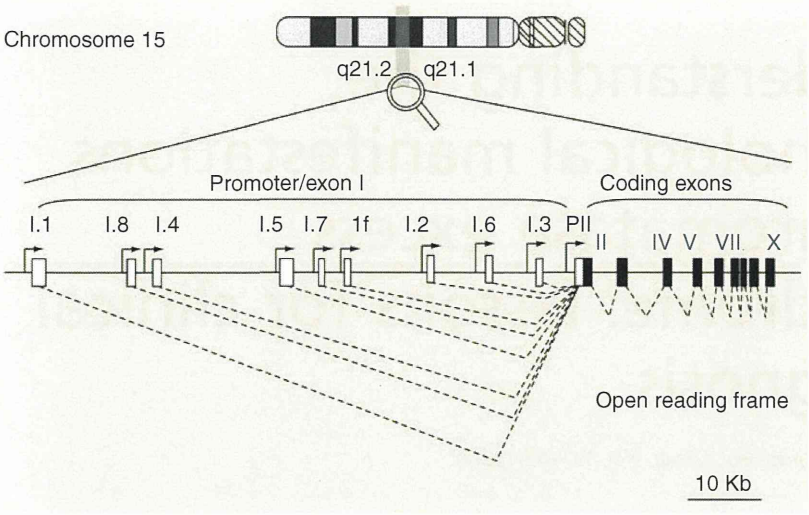

Figure 1. *CYP19A1* structure. Open boxes represent aromatase exon Is and L-shaped arrows in front of the boxes represent corresponding promoters. Closed boxes represent aromatase exons II–X encoding the open reading frame. Broken lines represent the splicing patterns.

to produce estradiol. The reaction proceeds in collaboration with nicotinamide adenine dinucleotide phosphate-cytochrome P450 reductase, which is conjugated with aromatase and supplies nicotinamide adenine dinucleotide phosphate, an essential coenzyme for hydroxylation to aromatase.

Aromatase is composed of 503 amino acids and an iron-containing heme group. The enzyme is found in the cytoplasm or endoplasmic membrane with the glycosylated N-terminal residue inside the lumen of the endoplasmic reticulum.

Aromatase is encoded by *CYP19A1*, which is located on chromosome 15q21.1. The entire gene spans 123 kb and is composed of at least 10 coding exons and upstream 5′ noncoding exons (exon Is) (Figure 1) [11–14]. Each exon I possesses a unique upstream promoter sequence that allows tissue-specific alternative use, and therefore, tissue-specific regulation. For example, the most proximal promoter (PII) is almost exclusively expressed in the gonadal tissues, whereas exons 1f and I.4, which are located upstream of PII, are almost exclusively expressed in the brain and adipose tissues, respectively. The most upstream promoter (I.1) is exclusively expressed in the placenta.

Primary transcripts from exon Is are spliced to a common splicing acceptor site located in exon II so that the secondary mRNAs share exons II–X, which encode the full-length aromatase enzyme. Thus, all *CYP19A1* mRNAs encode the same protein, irrespective of exon I, which contains the transcriptional start site.

Aromatase expression in heath & disease

Aromatase is highly expressed in the gonadal tissue, and the resulting estrogen plays an essential role in reproduction through modulation of endocrine action on the uterine, breast and brain tissues. The brain itself expresses aromatase, and locally synthesized estrogen plays a role in controlling gonadotropin secretion as well as other functions in the brain.

It is well known that aromatase is expressed more widely outside the gonadal tissue than previously believed, including the adipose, breast, bone and uterine tissues, as well as vessels [15,16]. Aromatase is expressed in these tissues at low basal levels and induced by local factors (cytokines, prostaglandins and steroids) in a limited temporospatial manner. Unlike the gonadal tissues, these tissues do not express CYP17A1, a key enzyme that synthesizes steroid hormones from cholesterol *de novo*, and thus, circulating androgen is the sole source of *in situ* estrogen synthesis.

Peripheral tissues expressing aromatase are also positive for the estrogen receptor, which is the target of estrogen. Estrogen synthesized in these tissues *in situ* acts directly on estrogen-producing or neighboring cells in an autocrine/paracrine manner, so that the biological effect *in situ* is more potent than expected from the amount of synthesis. *In situ* estrogen secretion in these tissues possibly plays physiological roles on breast development and bone closure. More importantly, over- and/or dysregulated expression of *in situ* aromatase plays a role in the pathogenesis of various diseases, such as breast cancer, endometrial cancer, endometriosis and uterine fibroid development [16–19].

The placenta is considered an endocrine organ because it synthesizes massive amounts of estrogen. Examinations of aromatase deficiency have revealed that placental aromatase protects the fetus from virilization through the clearance of potentially hazardous adrenal androgen [20]. In line with this concept, aromatase is expressed in the placenta of only those higher primates that secrete adrenal androgens.

Clinical features of AEXS

The most characteristic feature of AEXS is the pre- or peripubertal onset of gynecomastia in response to increasing estrogen production. Additional symptoms, which may or may not be associated, are also related to estrogen excess and include accelerated bone growth during the peripubertal period, resulting in reduced adult height and hypogonadotropic hypogonadism. Sparse facial hair and a high-pitched voice are also characteristics in some cases.

Gynecomastia

The source of estrogen excess in gynecomastia is circulating androgens from the adrenal glands, and the earliest onset of

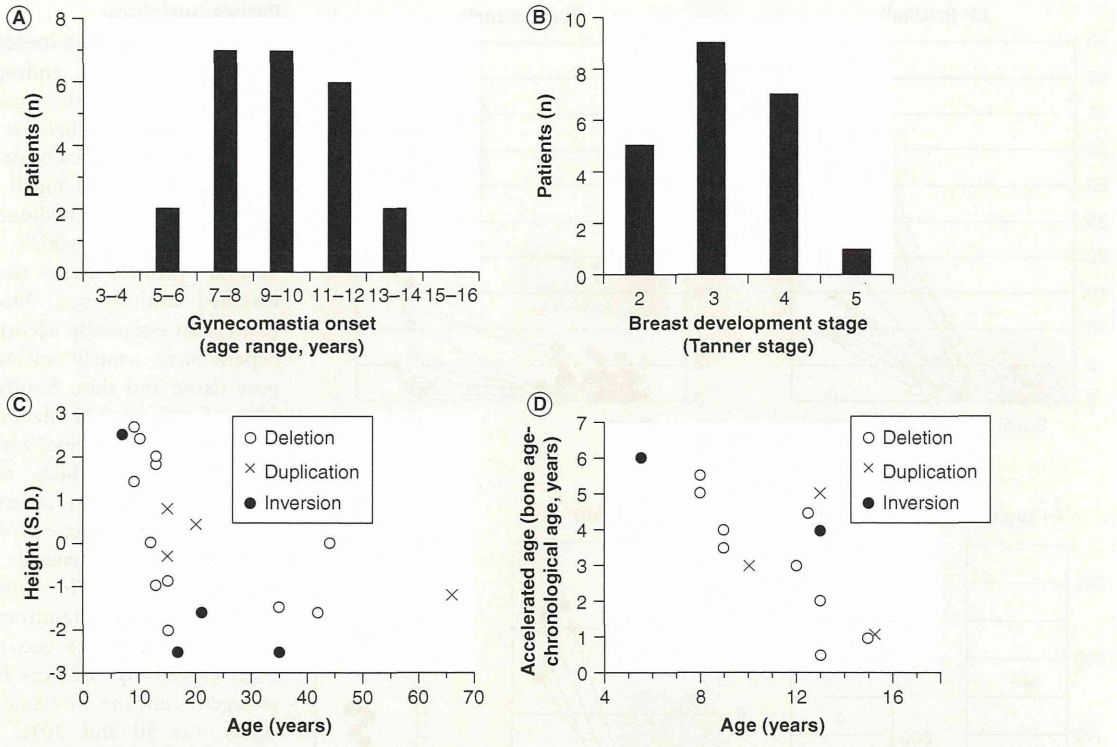

Figure 2. Clinical features of 30 male patients with molecularly diagnosed aromatase excess syndrome. (A) Distribution of gynecomastia onset. **(B)** Distribution of developmental stage of gynecomastia at the time of the initial visit. Severity of gynecomastia is expressed using the Tanner staging system for morphological description of the female breast. **(C)** Chronological change in height. Height expressed in standard deviation for age is plotted against chronological age. Closed circles, deletion-type mutations; open circles, duplication-type mutations; open triangles, inversion-type mutations. **(D)** Acceleration of bone growth. Differences between bone age and chronological age (years) are plotted against chronological age. Acceleration of bone growth becomes evident before 10 years of age.

gynecomastia occurs around the adrenarche period (7–14 years) (Figure 2A) [4]. No case of adult-onset gynecomastia has ever been reported. Onset of gynecomastia somewhat varies among individuals (Figure 2B), but shows an apparent consistency within the same family, indicating genotypic influence on disease severity [8].

Gynecomastia is not only a physical but also a mental health problem for patients and their families, even in mild cases. In a cohort of 30 males, 20 underwent mastectomy between the ages of 12 and 19 years, with most cases undergoing surgery by the age of 16 years. Among patients aged ≥12 years only, mastectomy was performed in 81% cases, including cases with relatively mild gynecomastia. Early diagnosis and prophylactic treatment can avoid the need for surgical intervention. Therefore, genetic screening is warranted for members of affected families before symptom onset.

Bone growth/height

Estrogen excess during the prepubertal period initially accelerates bone growth and bone age, and subsequently, induces premature epiphyseal closure (Figure 2C & 2D). As seen in other instances of precocious puberty, patients are taller than their age-matched peers until the early teenage period, after which height is in the subnormal adult range between -2.5 and 0 standard deviations of normal.

Fertility

Patients with AEXS may show mild hypogonadotropic hypogonadism. Decreased testosterone levels are consistent in patients with AEXS of all ages. Testicular volume is subnormal in teens, but normal in adults. Gender identity is not compromised. Although infertility has not been reported, mild oligozoospermia was noted in one patient, but fecundity in this patient remains unknown because he had no desire to have children at the time of examination.

Serum follicle-stimulating hormone (FSH) levels are consistently suppressed (Figure 3), but luteinizing hormone (LH) and testosterone production in response to human chorionic gonadotropin is fairly preserved. The low basal testosterone levels do not seem to be a consequence of compromised testicular function, but rather a consequence of enhanced conversion to estrogen.

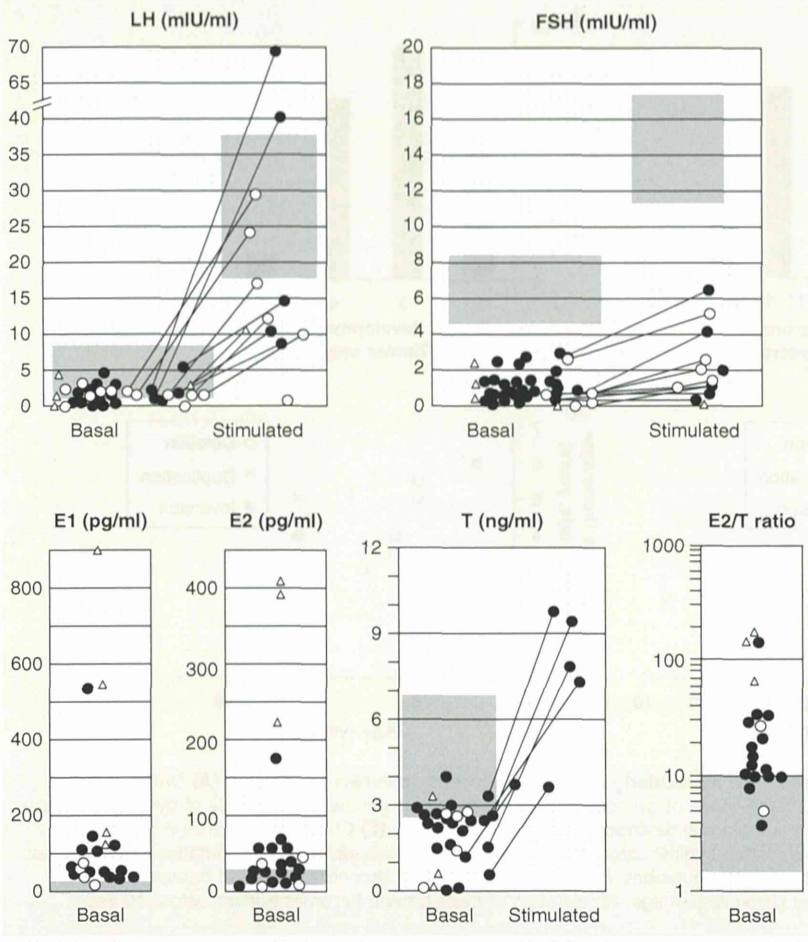

Figure 3. Hormonal profiles of 30 male patients with molecularly diagnosed aromatase excess syndrome. Isolated marks represent basal luteinizing hormone, follicle-stimulating hormone, estradiol, and testosterone levels and estradiol/testosterone ratio in each individual. Closed circles, deletion-type mutations; open circles, duplication-type mutations; open triangles, inversion-type mutations. The gray zones represent approximate normal reference ranges of adolescents. Paired marks tethered by a solid bar represent the gonadotropin levels before and 30 min after 100 μg of LH-releasing hormone loading. Paired marks in the testosterone chart represent levels before and after injection of human chorionic gonadotropin.
LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; LHRH: LH-releasing hormone.
Data taken from [1,7–10].

Female patients

Phenotypic characteristics of females with AEXS are not well defined [21], since only eight women among seven families have been molecularly diagnosed with AEXS [7,8,10,21,22]. Six of these women had one or more of the following symptoms: premature thelarche, early menarche, accelerated bone age at puberty, short adult stature, macromastia, irregular uterine bleeding and an enlarged uterus, while two women were phenotypically normal. One woman underwent reductive surgery for macromastia. Thus, symptoms of gynecomastia in females seem relatively mild compared to those in males.

Pathophysiology

Estrogen & androgen metabolism

The rate of plasma androgen conversion to estrogen in the entire body was measured using radioactive tracers. In four boys with clinically defined familial gynecomastia, as much as 16–48% of plasma androstenedione was converted to estrone, which was 15- to 50-fold greater than that in age-matched controls [4,5]. Moreover, this conversion essentially occurred in extrahepatic sites, namely subcutaneous adipose tissue and skin. Similarly, 55 and 59% of androstenedione was converted to estrone in two boys with genotype-defined AEXS, which was 40-fold greater than that in controls [1]. The conversion from testosterone to estradiol was also enhanced by 50-fold in these boys. The interconversion between androgens (androstenedione to testosterone and vice versa) was 8 and 5%, respectively, whereas that between estrogens (estrone to estradiol and vice versa) was 50 and 90%, respectively, but they were not statistically different from those of controls.

These studies demonstrated that excessive aromatization is responsible for the increase in estrogen associated with the decrease in androgen in circulating blood. These studies also demonstrated that a major source of estrogen is adrenal androgen (androstenedione), and therefore, the primary product is estrone. The contribution of testicular androgen (testosterone) and its product (estradiol) is small (<0.04% of net estradiol production is formed by the testes).

Aromatase overexpression

The initial metabolic studies excluded the possibility that the testis, adrenal gland and liver are responsible for excess aromatization [4,5,23]. Instead, peripheral tissues, including the skin and subcutaneous fat, were considered as a possible site of conversion [24–26], partly because of the curious resemblance to henny-feathered male Sebright Bantam chickens, which synthesize estrogen in all body tissues at high levels, especially the chest skin, resulting in female-type feathering [5,27–29].

Aberrant expression of aromatase has been demonstrated in humans [1,6–8,30]. Patient-derived skin fibroblasts showed an increase in aromatase activity of 11- to 24-fold and an increase

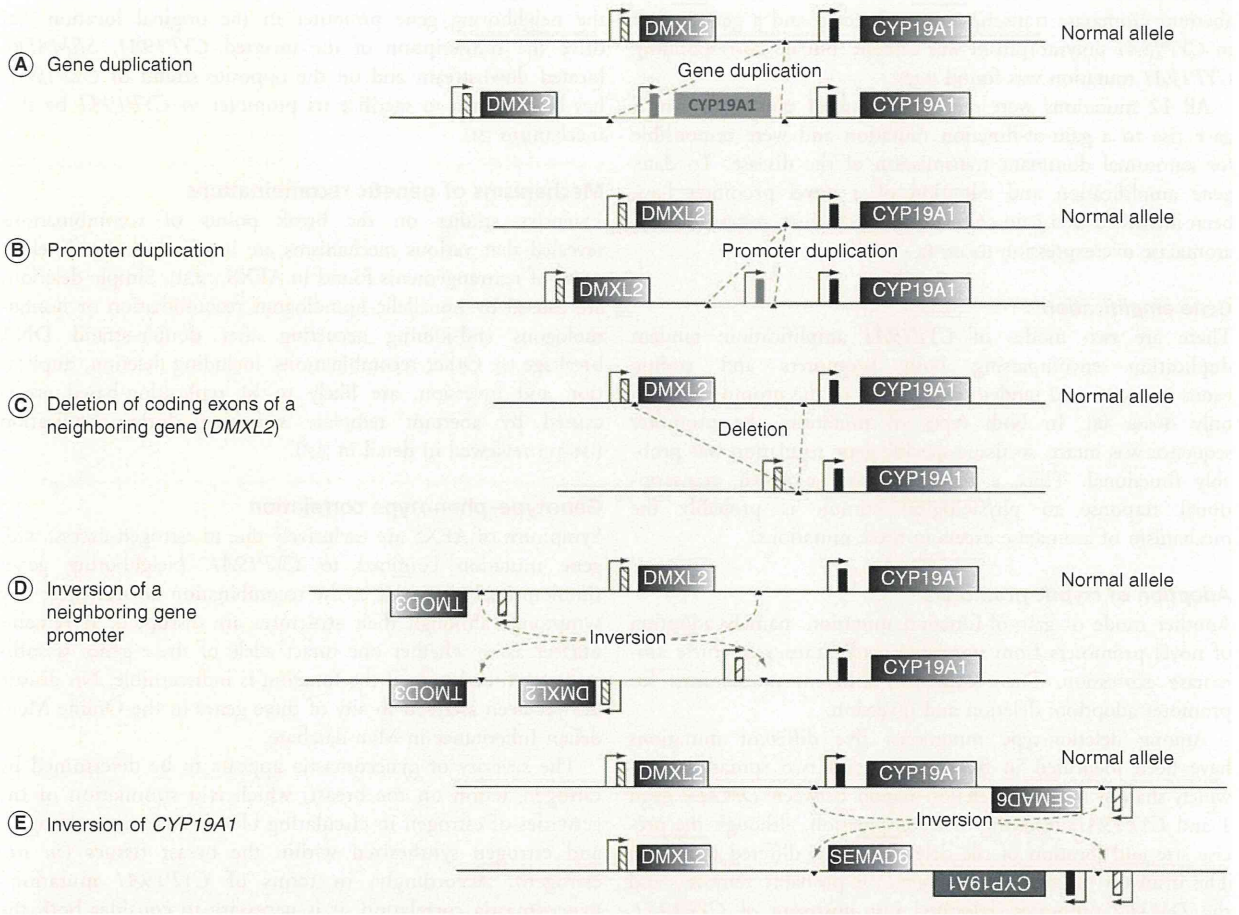

Figure 4. Schematic representations of DNA recombination events that give rise to gain-of-function mutations in familial aromatase excess syndrome. *CYP19A1* exons II–X are expressed in one box. The arrows and following closed boxes represent one of multiple *CYP19A1* promoters. The arrows indicate transcriptional direction. Similarly, the structure of *DMXL2*, a neighboring gene of *CYP19A1* on the same (minus) strand as *CYP19A1*, is represented by a gray box (coding exons) and a shaded box (exon 1) associated with an arrow (promoter). *DMXL2* exon 1 contains the 5′ end of the open reading frame. *TMOD3* and *SEMAD6* represent upstream and downstream neighboring genes of *CYP19A1*, on the opposite strand of *CYP19A1*, and are involved in inversion mutation. Inversion mutation may be combined with any type of other recombinations listed above to form the more complex DNA recombinations. For details, please refer to [33].
AEXS: Aromatase excess syndrome.

in aromatase mRNA levels of 14- to 24-fold compared to normal controls [1].

Recent studies have revealed that promoters of so-called housekeeping genes are recruited for the aberrant expression of aromatase in AEXS [1,7,8]. Thus, aromatase is probably expressed continuously and ubiquitously in all somatic cells, as are housekeeping genes, which is in contrast to the continuous downregulation and temporospatial upregulation of aromatase in normal subjects [12,14,16]. Prolonged and wide expression can explain why even a slight increase in the basal expression level causes detectable changes in androgen and estrogen levels in circulating blood.

Epstein–Barr virus-transformed lymphocytes have been used as an alternate to primary cells for DNA analysis. Lymphocytes can also serve as research material for mRNA analysis because they may express aromatase through aberrant promoters [1,6–8].

Genetics

Genotypes

AEXS is a genetic disease exclusively caused by *CYP19A1* mutations. No other genes so far have been reported to cosegregate with *CYP19A1* in AEXS. A total of 12 types of gain-of-function mutations in *CYP19A1* have been identified among 15 families [1,7–10]. In the literature, there are at least four reports of families with suspected *CYP19A1* mutations: two were clinically defined cases reported before the molecular cloning of *CYP19A1* and, therefore, lack information regarding genomic mutations [4,5], whereas, in the other two cases,

aberrant aromatase transcripts were detected and a genetic link to *CYP19A1* polymorphism was evident, but no corresponding *CYP19A1* mutation was found [6,22].

All 12 mutations were recombinations of one allele, which gave rise to a gain-of-function mutation and were responsible for autosomal dominant transmission of the disease. To date, gene amplification and adoption of a novel promoter have been identified as a gain-of-function mechanism responsible for aromatase overexpression (Figure 4).

Gene amplification

There are two modes of *CYP19A1* amplification: tandem duplication encompassing both promoters and coding exons (Figure 4A) and tandem duplication of the promoter region only (Figure 4B). In both types of mutation, the promoter sequence was intact, so tissue-specific gene regulation was probably functional. Thus, a regulated, but enhanced, transcriptional response to physiological stimuli is probably the mechanism of aromatase excess in these mutations.

Adoption of cryptic promoters

Another mode of gain-of-function mutation, namely adoption of novel promoters from unrelated genes, causes eccentric aromatase expression. There exist two different mechanisms for promoter adoption: deletion and inversion.

Among deletion-type mutations, five different mutations have been identified in five families and two sporadic cases, which share a minimal deletion region between *DMXL2* exon 1 and *CYP19A1*, resulting in recombination, although the precise size and location of the deleted regions differed (Figure 4C). The insulator between the two genes is probably removed and the *DMXL2* promoter, relocated just upstream of *CYP19A1*, drives transcription all the way downstream to *CYP19A1*, resulting in an increase in the recombinant *DMXL2 exon 1-CYP19A1* transcript. The *DMXL2* promoter drives aromatase transcription in an unlimited spatiotemporal manner compared to tissue- and time-limited expression of authentic promoters of *CYP19A1*. Constitutive expression may explain why the *DMXL2-CYP19A1* recombinant, albeit a low translational efficacy as described later, causes an increase in net estrogen production.

In the last type of gain-of-function mutation, *CYP19A1* recruits a cryptic promoter through inversion (Figure 4E & 4F), which is a truly original mechanism of a gain-of-function mutation [1]. There exist several genes upstream of *CYP19A1*, but on the opposite strand of *CYP19A1*, so that the promoters of these neighboring genes are in the opposite direction to *CYP19A1* and are transcribed unrelatedly to *CYP19A1*. If the promoter is inverted upstream of *CYP19A1* and directs to *CYP19A1*, it in turn can drive *CYP19A1* transcription. Four genes (*TMOD3*, *MAPK6*, *TLN2* and *CGML1*) are reportedly involved in this mechanism. Conversely, inversion of *CYP19A1* itself, instead of the neighboring genes, creates the same situation. *CYP19A1* is inverted *in situ* and ligated just downstream of the neighboring gene promoter in the same direction. Now, the neighboring gene promoter in the original location can drive the transcription of the inverted *CYP19A1*. *SEMAD6*, located downstream and on the opposite strand of *CYP19A1*, has been shown to sacrifice its promoter to *CYP19A1* by this mechanism [31].

Mechanisms of genetic recombinations

Extensive studies on the break points of recombinations revealed that various mechanisms are involved in the development of rearrangements found in AEXS [7,8,31]. Simple deletions are caused by nonallelic homologous recombination or nonhomologous end-joining occurring after double-strand DNA breakage [8]. Other recombinations, including deletion, duplication and inversion, are likely to be replication-based errors caused by aberrant template switching during replication ([31–33]; reviewed in detail in [33]).

Genotype–phenotype correlation

Symptoms of AEXS are exclusively due to estrogen excess, with gene mutation confined to *CYP19A1*. Neighboring genes simultaneously involved in the recombination do not cause any symptoms, although their structures are disrupted. It remains unclear as to whether one intact allele of these genes is sufficient for function or if the function is indiscernible. No disease has yet been ascribed to any of these genes in the Online Mendelian Inheritance in Man database.

The severity of gynecomastia appears to be determined by estrogen action on the breast, which is a summation of the activities of estrogen in circulating blood (endocrine estrogen) and estrogen synthesized within the breast tissues (*in situ* estrogen). Accordingly, in terms of *CYP19A1* mutation–gynecomastia correlation, it is necessary to consider both the transcriptional potency of the novel promoter sequence itself and the breast tissue-specific expression levels of the promoter [8,31,32]. Taking this into consideration, phenotype appears to be correlated with functional and structural properties of genomic mutations, at least in mutations that have been identified.

Patients with *CYP19A1* amplification-type mutation exhibit milder gynecomastia than those with the inversion-type mutation because, as described earlier, aromatase in the gene amplification-type mutation is likely still under 'physiological' regulation [33]. In contrast, in inversion-type mutations, aromatase is expressed more broadly and continuously, reflecting the housekeeping gene-like expression profiles of the original genes.

Patients with the deletion-type mutation (*DMXL2* exon 1-*CYP19A1* fusion) manifest milder gynecomastia than those with the inversion-type mutation [33]. The fusion genes of the deletion-type possess two transcription start sites: one within *DMXL2* exon 1 and the other within *CYP19A1* exon 2. The former is the natural transcription start site of *DMXL2*, but produces a premature termination codon in the fusion genes, resulting in nonsense-mediated mRNA decay. The transcript derived from the downstream transcription start site only

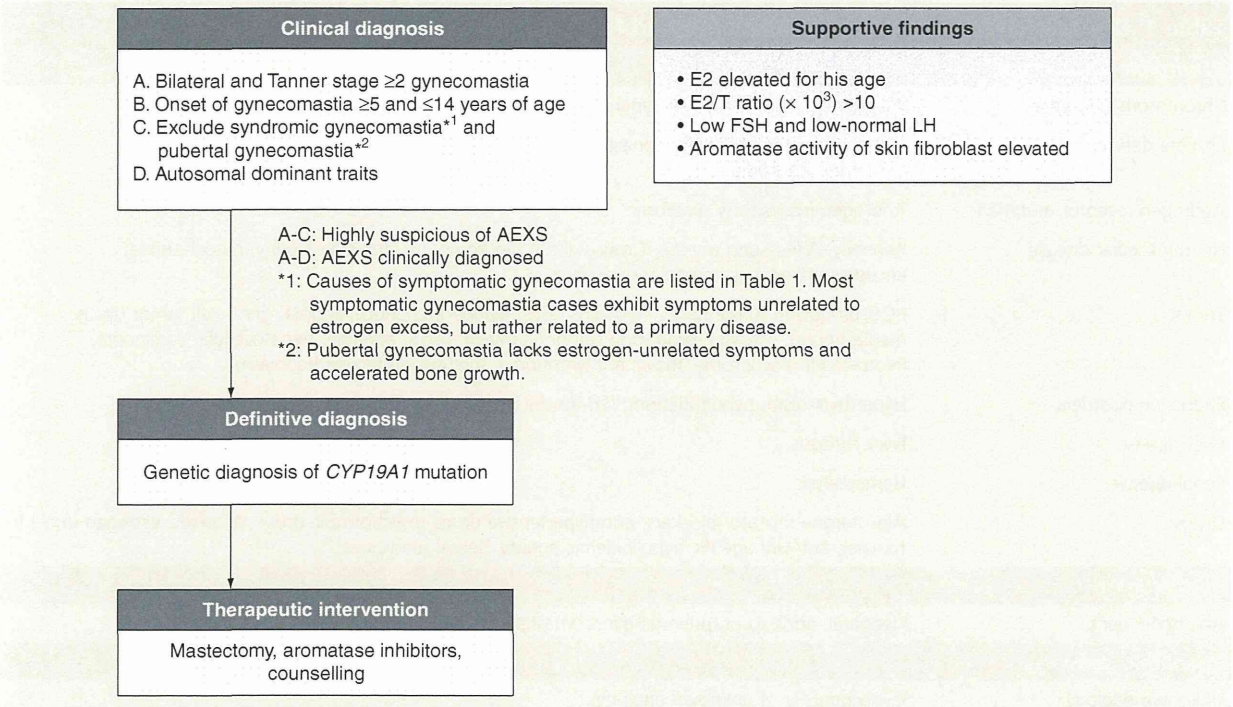

Figure 5. A diagnostic and therapeutic schema. Physical examination for estrogen-unrelated symptoms is crucial for exclusion of aromatase excess syndrome diagnosis.
AEXS: Aromatase excess syndrome.

produces the aromatase protein, although it is a minor species of the fusion gene transcript.

Among five deletion-type mutations (*DMXL2* exon 1-*CYP19A1*), the largest deletion exhibits milder gynecomastia than that caused by the others [9]. The largest deletion simultaneously affects seven of 10 upstream promoters of *CYP19A1* in a mutant allele, whereas all promoters are intact in the remaining four deletion-type mutations. Deletion of the *CYP19A1* promoters in *DMXL2* exon 1–*CYP19A1* recombinants ameliorates gynecomastia, indicating that, in addition to the cryptic *DMXL2* promoter, upstream seven genuine *CYP19A1* promoters in a recombinant allele contribute to the development of gynecomastia. However, it remains unclear whether this is just due to a gene dose effect of the promoters or unrecognized interactions among promoters in tandem position.

Diagnosis

Diagnostic scheme

AEXS is simply defined as the pre- or peripubertal onset of gynecomastia caused by estrogen excess due to a gain-of-function mutation in *CYP19A1*. AEXS may be associated with minor symptoms, but the general condition is well preserved, at least in the cases that have been identified until date.

A diagnostic approach has been proposed in a study supported by the Japanese government (Figure 5) [34]. AEXS is clinically suspected based on the four criteria of gynecomastia defined below. A suspected diagnosis of AEXS is not difficult in a typical case with well-developed gynecomastia for physicians who recognize this entity as a hereditary and benign disease. Conventional laboratory tests, including measurement of serum estradiol levels, are useful to reconfirm endocrinological pathology, but should not be used for exclusive diagnosis of this disease, especially in cases with indistinct symptoms. After clinical suspicion of the disease using a combination of inclusion and exclusion criteria (Table 1), AEXS should be established through the identification of a *CYP19A1* mutation. Genetic analysis is essential to diagnose a sporadic case of mild gynecomastia in young males and also a family with female proband only.

Clinical diagnosis

Four criteria for the clinical diagnosis of AEXS are as follows: bilateral gynecomastia (≥ stage 2), pre- or peripubertal onset of gynecomastia (≥5 and ≤14 years old), exclusion of other well-known causes of gynecomastia (symptomatic gynecomastia, Table 1) and pubertal gynecomastia, and having a genetic trait (autosomal dominant). The first three criteria are indispensable for clinical diagnosis. The fourth criterion, a genetic trait, is not obligatory, but rather pathognomonic. Detection of a maternal genetic trait may be difficult to discern in a small family. A genetic trait is absent in sporadic cases.

Table 1. Diseases and conditions to be distinguished from aromatase excess syndrome.

Syndromic (secondary)	
Chromosomal anomaly	Klinefelter syndrome, Swyer syndrome
Enzyme deficiency	17β-hydroxysteroid dehydrogenase, 21-hydroxysteroid dehydrogenase, 17α-hydroxylase deficiency syndrome
Androgen receptor mutation	Androgen insensitivity syndrome
Neuromuscular disease	Kennedy–Alter–Sung disease, Crow–Fukase syndrome, myotonic dystrophy, mitochondrial encephalomyopathy, muscular dystrophy
Tumor	hCG-producing tumor (lung, stomach, testis, bladder), choriocarcinoma, germ cell tumor (testis, mediastinum), estrogen-producing tumor (stomach, testis, adrenal), hepatocellular carcinoma, Peutz–Jeghers syndrome, malignant lymphoma, multiple endocrine neoplasm
Endocrine disorders	Hyperthyroidism, hypogonadism, GH insufficiency, ACTH deficiency, hyperprolactinemia
Liver disease	Liver cirrhosis
Renal disease	Hemodialysis
Drugs	Aldosterone receptor blockers, anti-hypertensive drugs, psychotropic drugs, antacids, estrogen (male to female), anti-HIV agents, hypolipidemic agents, herbal medicines
Physiological	
Age dependent	Neonatal, adolescent (pubertal gynecomastia), old age
Idiopathic (primary)	
Unknown etiology	Gynecomastia of unknown etiology

ACTH: Adrenocorticotropic hormone; GH: Growth hormone; hCG: Human chorionic gonadotropin; HIV: Human immunodeficiency virus.

Other useful clues for diagnosis are that a patient (proband) presents AEXS by late puberty and appears healthy, other than features of gynecomastia, even when associated with minor symptoms.

The associated symptoms (small testis, high-pitched voice, sparse facial hair, variably advanced bone age and short adult height) are exclusively related to estrogen activities. The absence of estrogen-unrelated symptoms is useful to distinguish symptomatic gynecomastia that occur secondary to a variety of diseases (Table 1). In symptomatic gynecomastia, patients exhibit symptoms or signs derived from a primary disease, which is unrelated to estrogen activities and often pathognomonic for a primary disease. For example, patients with partial androgen insensitivity syndrome exhibit variable degrees of undervirilization of the external genitalia and patients with gynecomastia associated with Klinefelter syndrome exhibit a tall stature and hypogonadism. Patients with estrogen-producing tumors show gynecomastia associated with other symptoms of excess estrogen, resembling AEXS, but is differed from AEXS by the detection of the tumor by imaging. Thus, the presence of symptoms unrelated to estrogen may indicate the absence of AEXS.

Pubertal gynecomastia should also be differentiated from mild AEXS [35]. Pubertal gynecomastia is characterized by physiological breast enlargement in an otherwise normal healthy boy, and usually appears by the age of 14–14.5 years and stops enlarging spontaneously within 6 months and resolves in 1–3 years [36]. Plasma estrogen and testosterone levels are normal in these boys, although there exists the possibility of an imbalance in hormonal levels, including the relative amount of estrogen excess to androgen. Accelerated growth and bone maturation rates have not been reported for pubertal gynecomastia [37].

Pubertal gynecomastia may be difficult to distinguish from sporadic cases of AEXS with mild symptoms, because both lack symptoms of underlying specific etiologies. In an indistinguishable case, it may be advisable to observe symptoms and suspend clinical diagnosis for 1 year or more, as long as the symptoms are mild.

Endocrinological abnormalities

Circulating estrone levels are elevated in 17 out of 18 cases measured, and estradiol levels are elevated in only 13 out of 27 cases and is at normal levels in the remaining 14 cases, which is consistent with the finding that estrone instead of estradiol is the major estrogen produced in male patients with AEXS. Circulating androstenedione and testosterone levels are low or subnormal for chronological age in more than one-half of the patients. The estradiol (pg/ml)/testosterone (ng/ml) ratio, as a reflection of aromatization, becomes high in many cases, but not all: the ratio is >10 in 75% of AEXS cases (Figure 3).

FSH levels are consistently low and response to LH-releasing hormone (LHRH) is poor (Figure 3). LH levels are within low normal limits, and response to LHRH varies from normal to subnormal.

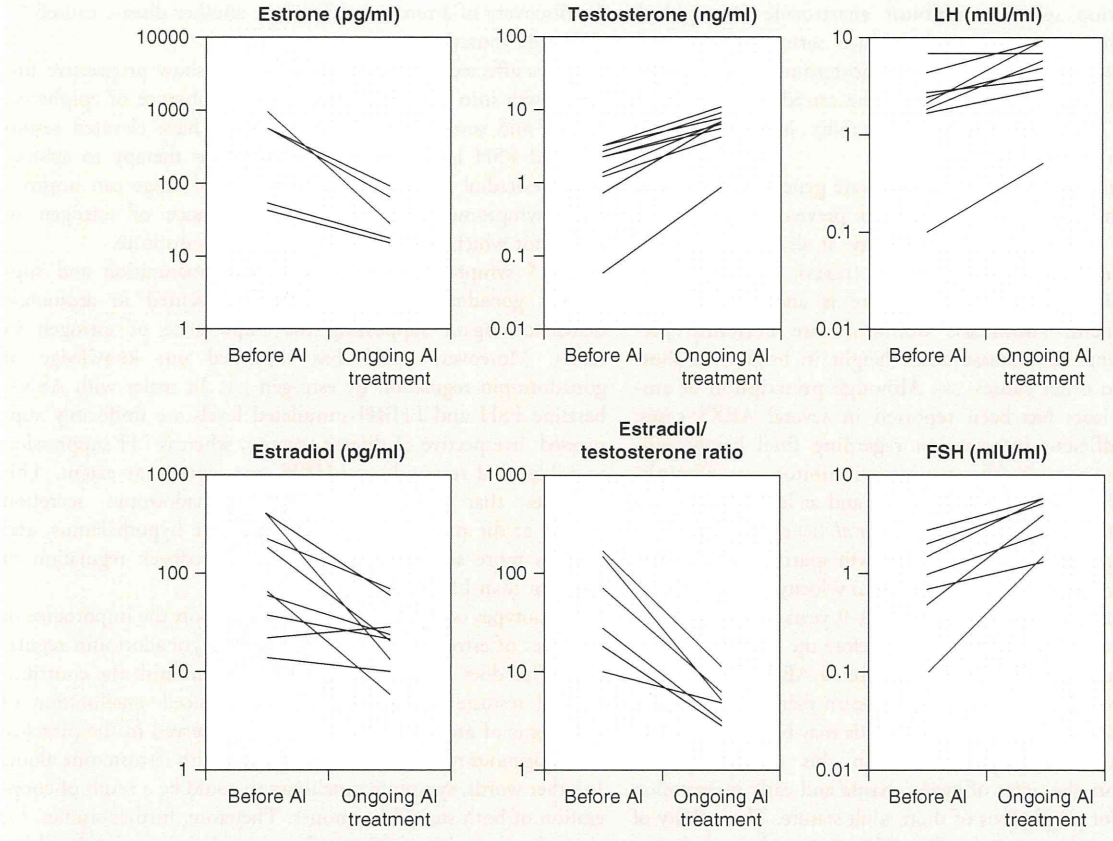

Figure 6. Effect of aromatase inhibitors on serum hormone levels.
The estradiol/testosterone ratio was calculated from measurements and expressed as weighted concentrations.
AI: Aromatase inhibitors; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.
Data taken from [8,31,32].

Endocrinological abnormalities become apparent in patients with severe gynecomastia. Conversely, it is subtle in patients with mild gynecomastia; thus endocrinological data are not useful for diagnosis. Notably, normal levels of circulating estrogen, especially estradiol, are not sufficient to exclude the possibility of AEXS.

Cytogenetic analysis

Cytogenetic analysis to identify a *CYP19A1* mutation is essential for a definitive clinical diagnosis of patients with suspected AEXS. There is no case report in the literature in which karyotyping has detected any abnormality. A high-resolution comparative genomic hybridization using oligonucleotide probes for the long arm of chromosome 15 is useful for the detection of gene amplification and deletion mutations, and precise break points, which may be individually identified by trials of long-range polymerase chain reaction followed by sequencing [8]. A recombination event can be visualized by fluorescent *in situ* hybridization [1]. It is possible to estimate cryptic promoter sequences based on the structure of the identified recombination, and their function is confirmed by mRNA analysis using 5′-rapid amplification of cDNA ends (5′-RACE). Comparative genomic hybridization cannot detect a simple inversion. Instead, 5′-RACE is used to detect cryptic promoters and associated exons. Breast tissue and skin fibroblasts are the most suitable for study, but mononuclear cells isolated from patient blood samples may be used instead.

Higher levels of aromatase mRNA as well as activity have been reported for fibroblasts isolated from skin biopsy specimens [1,6,8,30]. Immunohistochemistry of the excised breast tissues confirmed aromatase expression of epithelial cells lining the glandular ducts [6]. Examinations of breast tissues specimens may help in the diagnosis if appropriate controls are available; however, it may be indecisive like the serum estradiol level in the diagnosis of AEXS, particularly for AEXS cases with relatively low aromatase activity.

Medical treatment

Aromatase inhibitors, developed for treatment for breast cancer, have been used in 10 male cases of AEXS [1,6,9,21]. The

third generation selective inhibitor anastrozole (1 mg/day) has been shown to consistently reduce serum estrone and estradiol levels and increase serum testosterone levels, thereby resulting in significant reduction in the estradiol/testosterone ratio as an index of aromatizing activity and increase in gonadotropin levels (Figure 6).

Use of aromatase inhibitors can alleviate gynecomastia within 6 months and are possibly useful to prevent recurrence of gynecomastia after reduction mastoplasty. It also promotes virilization and increased testicular volume [21,30,38].

Control of premature bone closure is another target of AEXS treatment. Aromatase inhibitors are currently prescribed off-label to increase adult height in boys with short stature due to other causes [38]. Although prescription of aromatase inhibitors has been reported in several AEXS cases, there is insufficient information regarding final height outcomes. In most cases, an aromatase inhibitor was administered after the onset of gynecomastia and at least several years after the onset of growth spurt. Shihara *et al.* [10] reported a case of a boy who experienced a premature growth spurt, which began at approximately 5 years, achieved maximum velocity in bone growth at 6–7 years, and ended by the age of 8–9 years. His accelerated bone growth started as early as 4 years before the onset of gynecomastia (9 years). His brother also exhibited AEXS with similar growth features. This case raises the concern that treatment initiated after the development of gynecomastia may be too late to prevent premature epiphyseal closure. In this context, genetic diagnosis before the onset of gynecomastia and early intervention is warranted for prophylaxis of short adult stature. The severity of short stature varies among families. Therefore, early intervention should be considered if there exists a family member(s) with short statures.

Long-term aromatase inhibitor use is necessary to prevent the recurrence of gynecomastia. Moreover, untreated hyperestrogenemia may facilitate gynecomastia progression into a more severe stage and may increase the risk of breast cancer. In this context, prolonged use of aromatase inhibitor(s) may be warranted because the use of aromatase inhibitor(s) in an adjuvant setting of breast cancer prevents the development of contralateral breast cancer. Although selective aromatase inhibitors are relatively safe, side effects, such as arthralgia and bone fracture, have been reported following long-term use in women with breast cancer [39]. Male and female bone may respond differently to sex steroid therapy, and it is unpredictable whether side effects that occur in females also affect males with testosterone levels elevated by the use of aromatase inhibitors. No detrimental effects on bone metabolism have yet been reported in males due to long-term use of aromatase inhibitors [40]. Side effects of aromatase inhibitor use in males have not yet been determined [41].

Expert commentary

Reconfirmation of the physiological role of estrogen

AEXS reconfirms the important physiological roles of estrogen on bone physiology and gonadotropin regulation revealed by the discovery of aromatase deficiency, another disease caused by *CYP19A1* mutation.

Males affected by aromatase deficiency show progressive linear growth into adulthood caused by the absence of epiphyseal closure and severe osteopenia, as well as have elevated serum LH and FSH levels. Estrogen replacement therapy to achieve serum estradiol levels in the low-to-normal range can improve these symptoms, suggesting the importance of estrogen in males, for which even testosterone cannot substitute.

AEXS symptoms of accelerated bone maturation and suppressed gonadotropins mirror those presented in aromatase deficiency, again supporting the importance of estrogen in males. Moreover, AEXS has expanded our knowledge of gonadotropin regulation by estrogen [32]. In males with AEXS, baseline FSH and LHRH-stimulated levels are uniformly suppressed, irrespective of disease severity, whereas LH suppression is milder and responds to LHRH to a significant extent. This indicates that estrogen suppresses gonadotropin secretion mainly at the pituitary level, instead of the hypothalamus, and FSH is more sensitive to the negative feedback regulation of estrogen than LH [42–45].

Phenotypes of *CYP19A1* mutations support the importance of the roles of estrogen on bone growth and gonadotropin regulation. This does not necessarily, however, diminish the contribution of testosterone because estrogen-induced amelioration of symptoms of aromatase deficiency was observed in the presence of endogenous testosterone, although not with testosterone alone. In other words, symptom amelioration could be a result of cooperation of both steroid hormones. Therefore, further studies, for example, a model of 17α hydroxylase deficiency lacking both androgen and estrogen, are needed to determine the contribution of testosterone.

Role of in situ *estrogen*

Another noteworthy observation in AEXS is that gynecomastia can occur in patients with estradiol levels within the normal range. Also, Shihara *et al.* [10] demonstrated that a similar prepubertal growth spurt occurred without a detectable elevation in serum estradiol levels. One explanation for this is *in situ* estrogen production. Cryptic promoters of *CYP19A1* mutants may be expressed preferentially in breast tissues or bone so that adrenal androgen is effectively converted to estrone *in situ* [1,8], which is, in turn, converted *in situ* into biologically active estradiol by locally expressed 17β-hydroxysteroid dehydrogenase. A similar pathological role of *in situ* estrogen has been established in breast cancer and suggested for other pathologies, including those of the bone. It would be beneficial to elucidate the role of *in situ* estrogen production in terms of physiological maturation of male bone. The phenotype of bone in AEXS cases, in which the circulating estradiol levels are within the normal range, will offer insight into the significance of *in situ* estradiol production.

Five-year view

Here, we reviewed reports of genomic *CYP19A1* recombination events, including duplication, deletion and inversion, as