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X-Linked Acrogigantism

Synonyms: Chromosome Xq26.3 Duplication Syndrome, X-LAG, XLAG

Donato Iacovazzo, MD[1] and Márta Korbonits, MD, PhD[1]

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Summary

Clinical characteristics

X-linked acrogigantism is the occurrence of pituitary gigantism in an individual heterozygous or hemizygous for a germline or somatic duplication of *GPR101*. X-linked acrogigantism is characterized by acceleration of linear growth in early childhood – in most cases during the first two years of life – due to growth hormone (GH) excess. Most individuals with X-linked acrogigantism present with associated hyperprolactinemia due to a mixed GH- and prolactin-secreting pituitary adenoma with or without associated hyperplasia; less commonly they develop diffuse hyperplasia of the GH- and prolactin-secreting pituitary cells without a pituitary adenoma. Most affected individuals are females. Growth acceleration is the main presenting feature; other frequently observed clinical features include enlargement of hands and feet, coarsening of the facial features, and increased appetite. Neurologic signs or symptoms are rarely present. Untreated X-linked acrogigantism can lead to markedly increased stature, with obvious severe physical and psychological sequelae.

Diagnosis/testing

The diagnosis of X-linked acrogigantism is established in an individual with pituitary gigantism and a germline or somatic duplication of *GPR101* identified by molecular genetic testing.

Management

Treatment of manifestations:

- In patients with radiologic evidence of a pituitary adenoma: transsphenoidal surgery should be considered as first-line treatment as it can provide long-term control of the disease (although often at the cost of permanent hypopituitarism) and prevent excessive tumor growth; in those with persistent disease, GH receptor antagonist treatment should be promptly initiated and tailored to growth velocity and IGF-1 levels.

Author Affiliation: 1 Department of Endocrinology William Harvey Research Institute Barts and the London School of Medicine Queen Mary University of London London, United Kingdom; Email: d.iacovazzo@qmul.ac.uk; Email: m.korbonits@qmul.ac.uk.

- In patients with radiologic evidence of hyperplasia without a pituitary tumor: first-line treatment with GH receptor antagonist should be considered as surgery (which is not usually recommended) can lead to disease remission only by means of a total hypophysectomy, invariably resulting in the need for lifelong pituitary hormone replacement treatment.
- In patients with associated hyperprolactinemia: a dopamine agonist should be employed.

Surveillance: Intensive monitoring of height, growth velocity, and pituitary function tests. Repeat pituitary MRI (with frequency based on presence of hyperplasia/tumor, previous extent of the tumor, treatment modality, clinical status, and disease activity). Routine surveillance for complications of GH excess (based on recommendations for patients with acromegaly).

Genetic counseling

X-linked acrogigantism is inherited in an X-linked manner. The majority of affected individuals represent simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* *GPR101* duplication; of note, all males who are simplex cases have had a somatic mosaic *GPR101* duplication. In the three reported instances of familial X-linked acrogigantism, affected males inherited the *GPR101* duplication from their affected mothers. Females with X-linked acrogigantism have a 50% chance of transmitting the *GPR101* duplication in each pregnancy. While a male with a somatic mosaic *GPR101* duplication that involves germ cells could theoretically transmit the duplication to his daughters, and a male with a germline *GPR101* duplication will transmit the duplication to all of his daughters, to date male-to-female transmission has not been described. A male will not transmit the duplication to his sons. Offspring of either sex who inherit the *GPR101* duplication will be affected. Once the *GPR101* duplication has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

X-linked acrogigantism **should be suspected** in an individual with early-onset pituitary gigantism, defined as acceleration of linear growth due to growth hormone (GH) excess. All individuals with X-linked acrogigantism reported to date have manifested the first signs of the disorder before age four years, with most manifesting the disease during the first two years of life.

Clinical findings

- Accelerated growth velocity (>+2 SD) and/or abnormally tall stature (>+2 SD, adjusted for parental height). Note: When available, country-specific growth curves should be employed.
- Other frequently observed clinical features of GH excess: acral enlargement, coarse facial features, and increased appetite (~1/3 of cases)

Laboratory findings

- GH excess as demonstrated by:
  - Elevated levels of GH that do not suppress during an oral glucose tolerance test (OGTT) (1.75 g/kg of anhydrous glucose; maximum 75 g)
  - Increased circulating age-adjusted IGF-1 levels
- Hyperprolactinemia (seen in 26/28 reported individuals for whom data were available)

Imaging findings consistent with either of the following:

- Pituitary macroadenoma (>10 mm in diameter) with or without associated hyperplasia (in 24 of 30 reported individuals with available data)

- Diffusely (even slightly) enlarged pituitary gland secondary to pituitary hyperplasia without an adenoma (in 6 of 30 reported individuals with available data)

Note: Although none of the reported individuals presented with a microadenoma, this presentation is theoretically possible.

Histopathologic findings. Pituitary adenomas observed in X-linked acrogigantism have a peculiar sinusoidal and lobular architecture with frequent calcifications and follicle-like structures. Sparsely and densely granulated GH-secreting cells are admixed with cells secreting prolactin. Mitotic activity and the proliferation index Ki-67 are generally low [Beckers et al 2015, Iacovazzo et al 2016].

Establishing the Diagnosis

The diagnosis of X-linked acrogigantism is established in an individual with pituitary gigantism and a germline or somatic duplication of *GPR101* identified by molecular genetic testing (see Table 1) [Trivellin et al 2014, Daly et al 2016b, Iacovazzo et al 2016]. Although most (not all) individuals with X-linked acrogigantism have duplications of *GPR101* as well as *ARHGEF6*, *CD40LG*, and *RBMX*, to date it is unclear whether duplication of these other genes or the number of copies of *GPR101* influence diagnosis and/or prognosis.

If the proband:

- Is female and a simplex case (i.e., a single occurrence in a family), the *GPR101* duplication is usually germline (i.e., constitutional).
- Is male and a simplex case, the *GPR101* duplication is usually somatic with variable levels of mosaicism. Although to date no males who are simplex cases have been identified with a *de novo* germline *GPR101* duplication, this remains a possibility.
- Has a family history consistent with an X-linked pattern of early-onset pituitary gigantism, the *GPR101* duplication is likely to be germline.

Molecular testing approaches used to identify germline and somatic duplications can include **single-gene duplication testing** or **chromosomal microarray analysis (CMA)**. Note: Sequence analysis of *GPR101* is not recommended as no pathogenic sequence variants have been identified to date in individuals with X-linked acrogigantism.

- **Single-gene testing.** Gene-targeted duplication analysis of *GPR101* should be performed first on leukocyte DNA. If a *GPR101* duplication is not found on testing of leukocyte DNA, testing of DNA derived from other sources (e.g., pituitary tissue [if available], saliva, skin, tissue from previous surgery) is recommended – especially in simplex males whose phenotype suggests X-linked acrogigantism – as such testing may detect a somatic mosaic *GPR101* duplication not present in leukocyte DNA [Rodd et al 2016]. Note: Copy number variation droplet digital PCR is recommended as this technique can identify *GPR101* duplications and low-level mosaicism with high sensitivity [Daly et al 2016b, Iacovazzo et al 2016].

- **Chromosomal microarray analysis (CMA)** may be used to detect genome-wide duplications (including *GPR101* duplications). However, standard cytogenetic CMA may not correctly identify the *GPR101* duplication in all individuals with X-linked acrogigantism:
    - In one individual with a molecularly confirmed diagnosis of X-linked acrogigantism, the length of the duplication was below the sensitivity of the standard genome-wide array employed [Iacovazzo et al 2016].
    - Low-level mosaicism may not be identified.

  Targeted CMA with a higher density of probes in the Xq26.3 region – if available – can overcome such limitations [Trivellin et al 2014, Iacovazzo et al 2016].

Table 1. Molecular Genetic Testing Used in X-Linked Acrogigantism

Gene [1]	Method	Proportion of Probands [2] with a Pathogenic Variant [3] Detectable by Method
GPR101	Gene-targeted duplication analysis [4, 5]	33/33 [6, 7]
	Standard cytogenetic chromosomal microarray analysis	31/33 [6, 8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. Thirty-three affected individuals have been described to date. Not all 33 were tested using both techniques; the authors have calculated the number of probands whose duplication would have been identified using both techniques.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. These methods will detect from single-exon to whole-gene deletions or duplications; however, breakpoints of large deletions/duplications and/or deletion/duplication of adjacent genes may not be detected by these methods. (Note: *GPR101* has a single coding exon).
6. Trivellin et al [2014], Beckers et al [2015], Daly et al [2016a], Daly et al [2016b], Naves et al [2016], Gordon et al [2016], Iacovazzo et al [2016], Rodd et al [2016], Beckers et al [2017]. Note: The 26 individuals tested using both gene-targeted duplication analysis and standard CMA are represented in both rows of the table.
7. In one male with somatic mosaicism, the duplication was not detected in leukocyte DNA but was detected in other tissues, including the pituitary [Rodd et al 2016].
8. In two individuals, standard CMA did not identify the duplication (because of either its small size or low-level mosaicism) [Iacovazzo et al 2016]. The duplications in these individuals were correctly identified using targeted CMA with higher density of probes in the Xq26.3 region.

Clinical Characteristics

Clinical Description

X-linked acrogigantism is characterized by marked growth acceleration due to growth hormone (GH) excess starting at an early age (see Figure 1, Figure 2, and Figure 3). Most reported affected individuals (24/33) are females; clinical data are available for 30 individuals. In most individuals with X-linked acrogigantism GH excess results from a mixed GH- and prolactin-secreting pituitary macroadenoma (i.e., >10 mm). Less commonly, GH excess is caused by hyperplasia of the GH- and prolactin-secreting pituitary cells [Trivellin et al 2014]; six of 30 individuals with available data had pituitary hyperplasia in the absence of a pituitary adenoma.

The presenting feature in all affected individuals is growth acceleration, which can manifest as early as age two months [Trivellin et al 2014, Beckers et al 2015, Daly et al 2016a, Daly et al 2016b, Gordon et al 2016, Iacovazzo et al 2016, Naves et al 2016, Rodd et al 2016, Beckers et al 2017]. All individuals with X-linked acrogigantism have manifested the first signs of the disorder before age four years, with most manifesting during the first two years of life. There is no difference in the clinical presentation between males and females.

Other manifestations – in order of frequency – include enlargement of hands and feet, coarsening of the facial features, and increased appetite [Beckers et al 2015, Iacovazzo et al 2016]. Body mass index is also frequently increased at the time of diagnosis. Less frequently described findings are acanthosis nigricans, sleep apnea/snoring, excessive perspiration, diastema, abdominal distension, and skin thickening. Neurologic signs or symptoms are rarely present; intellectual disability has been reported in one affected individual only and was not clearly related to the *GPR101* duplication [Naves et al 2016]. While all individuals with X-linked acrogigantism are prepubertal at the time of presentation, untreated older individuals with hyperprolactinemia would be expected to develop signs of hypogonadism and/or delayed puberty.

Untreated X-linked acrogigantism can lead to markedly increased stature with obvious severe physical and psychological sequelae. Moreover – as occurs in individuals with gigantism or acromegaly secondary to other causes – uncontrolled GH excess is associated with a significantly increased risk of cardiovascular, cerebrovascular, metabolic, neurologic, and orthopedic complications as well as decreased life expectancy [Tagliafico et al 2008, Killinger et al 2010, Jayasena et al 2011, Ritvonen et al 2016].

Genotype-Phenotype Correlations

To date, no genotype-phenotype correlations are evident as the clinical phenotype of the single individual harboring a smaller duplication (encompassing *GPR101* only) was identical to the phenotype of other individuals whose duplications encompass *GPR101* and the neighboring genes on Xq26.3 [Iacovazzo et al 2016].

While a limited number of simplex males with X-linked acrogigantism have been reported to date, no differences have been observed between individuals with germline duplications and those with somatic mosaic duplications [Daly et al 2016b, Iacovazzo et al 2016].

Penetrance

All heterozygous females and hemizygous males described to date were affected.

In females who are simplex cases, the *GPR101* duplications arose *de novo* as demonstrated by the normal dosage of *GPR101* in samples from the unaffected parents. Moreover, in the three families described, all males who inherited the duplication from their affected mother were affected. Thus, based on currently available data the penetrance for X-linked acrogigantism appears to be 100%.

Nomenclature

The abbreviation X-LAG has traditionally been used in the medical literature as an abbreviation for X-linked acrogigantism and the abbreviation XLAG for X-linked lissencephaly with ambiguous genitalia.

Prevalence

X-linked acrogigantism is extremely rare. To date, 33 individuals with a molecularly confirmed diagnosis have been reported [Trivellin et al 2014, Beckers et al 2015, Daly et al 2016a, Naves et al 2016, Daly et al 2016b, Gordon et al 2016, Iacovazzo et al 2016, Rodd et al 2016, Beckers et al 2017].

In two series of individuals with pituitary gigantism who underwent genetic testing, X-linked acrogigantism accounted for 10% of 143 affected individuals [Rostomyan et al 2015] and 8% of 153 affected individuals [Iacovazzo et al 2016].

X-linked acrogigantism accounts for approximately 20% of females with pituitary gigantism [Iacovazzo et al 2016] and approximately 65% of individuals whose symptoms appeared at or before age five years [Korbonits, unpublished data].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with duplication of *GPR101*.

Differential Diagnosis

Pituitary gigantism can be nonsyndromic or can be associated with other manifestations as part of a syndrome (Figure 4) [Caimari & Korbonits 2016].

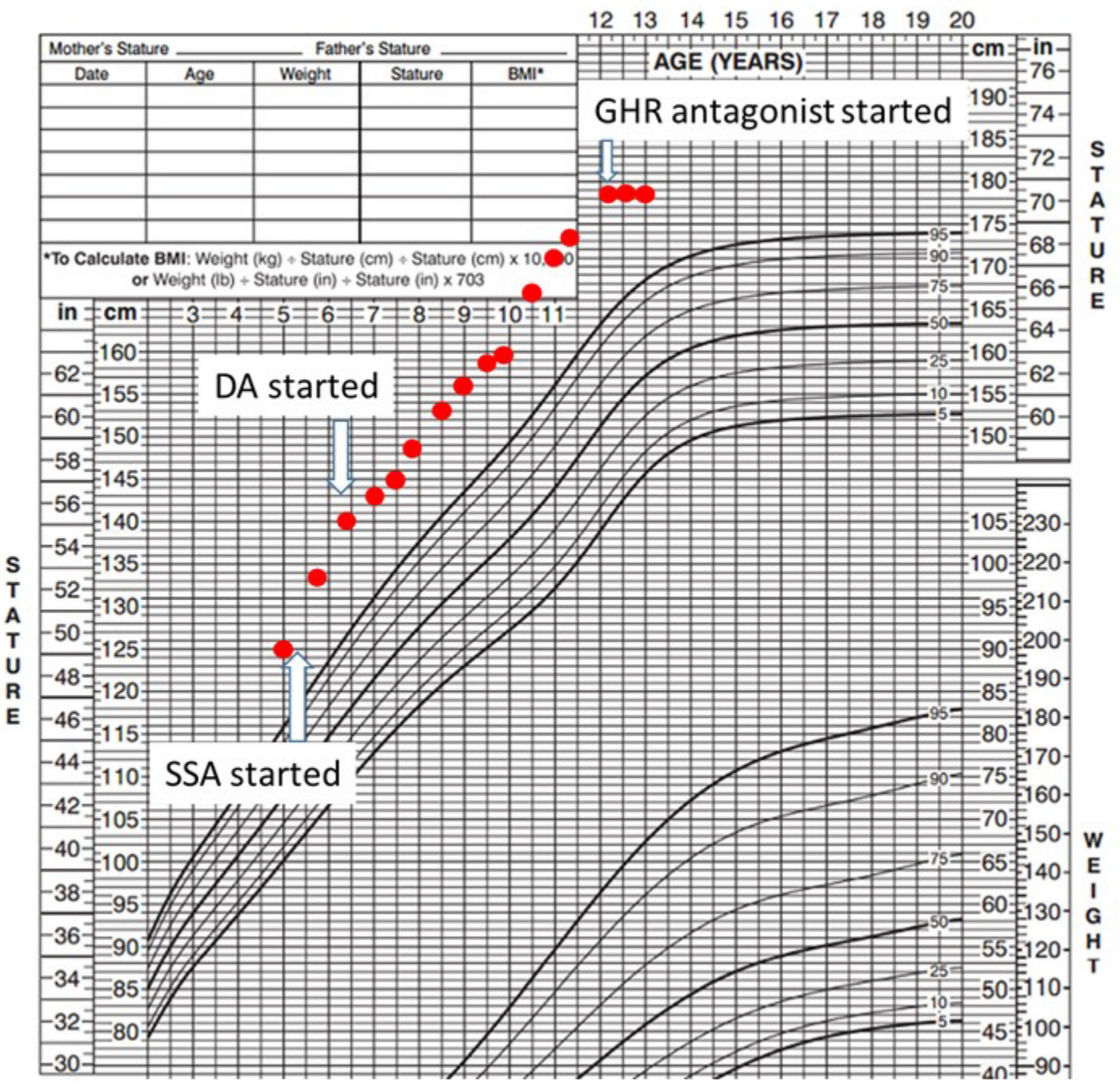

Figure 1. Growth curve of a female patient with molecularly confirmed X-linked acrogigantism who presented at age five years with abnormally tall stature. Her growth proceeded at a rapid pace despite treatment with somatostatin analogs (SSA) and dopamine agonists (DA) and was only controlled with the use of the GH receptor (GHR) antagonist.

Approximately 50% of all individuals with pituitary gigantism have a known predisposing genetic variant [Rostomyan et al 2015, Iacovazzo et al 2016].

The very young age at disease onset, female preponderance, and the absence of extrapituitary manifestations can help with the differential diagnosis of X-linked acrogigantism (Table 2).

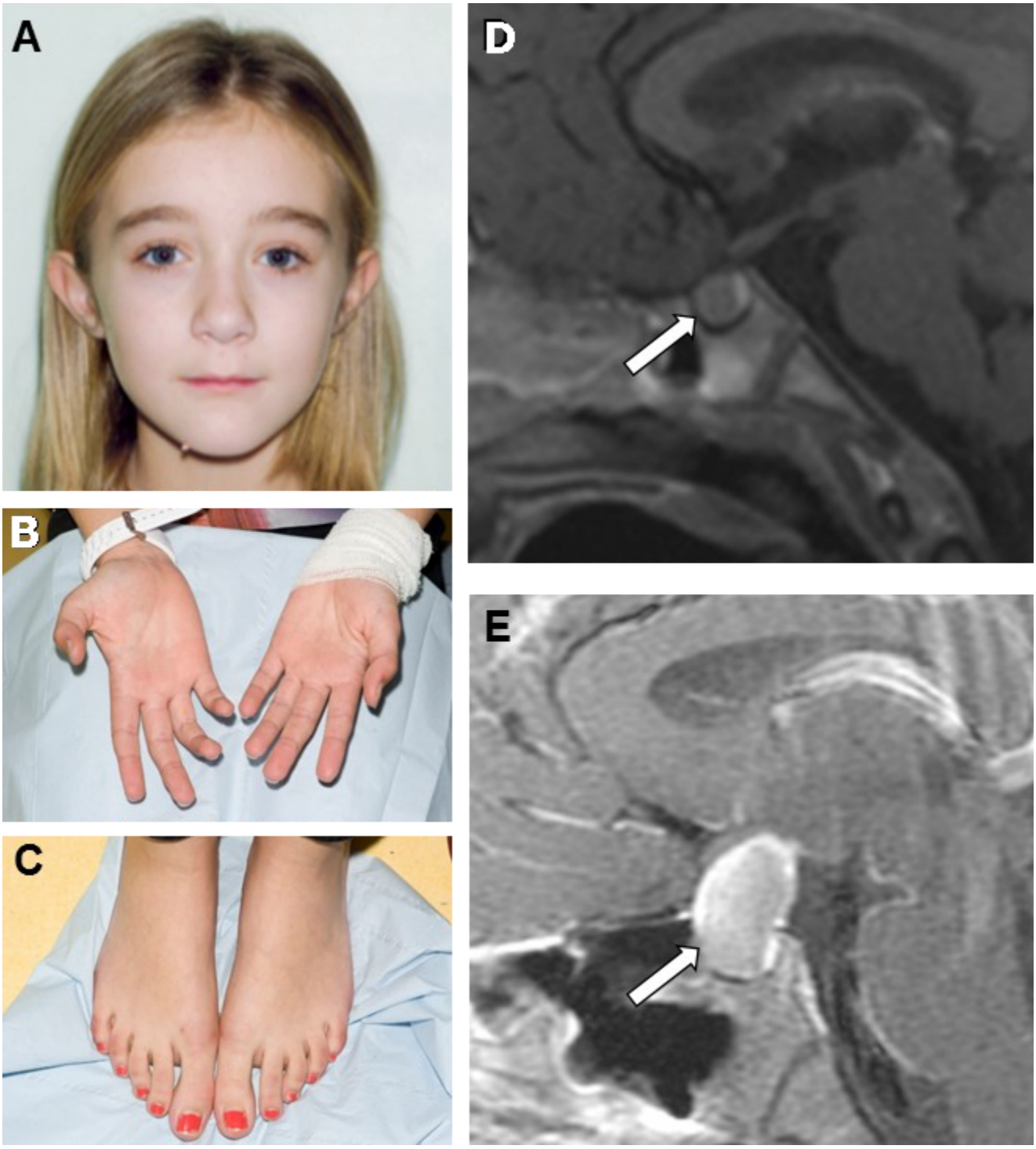

Figure 2. Clinical and radiologic features of individuals with molecularly confirmed X-linked acrogigantism

A-D. Girl (same patient as in Figure 1) age five years who presented with abnormally tall stature and no significant coarsening of the facial features

B,C. At age 11 years with evidence of enlargement of the hands and feet

D. MRI at initial presentation showing mild pituitary enlargement (arrow) consistent with pituitary hyperplasia

E. Girl age 5.7 years; MRI at initial presentation showing a pituitary macroadenoma with suprasellar extension (arrow)

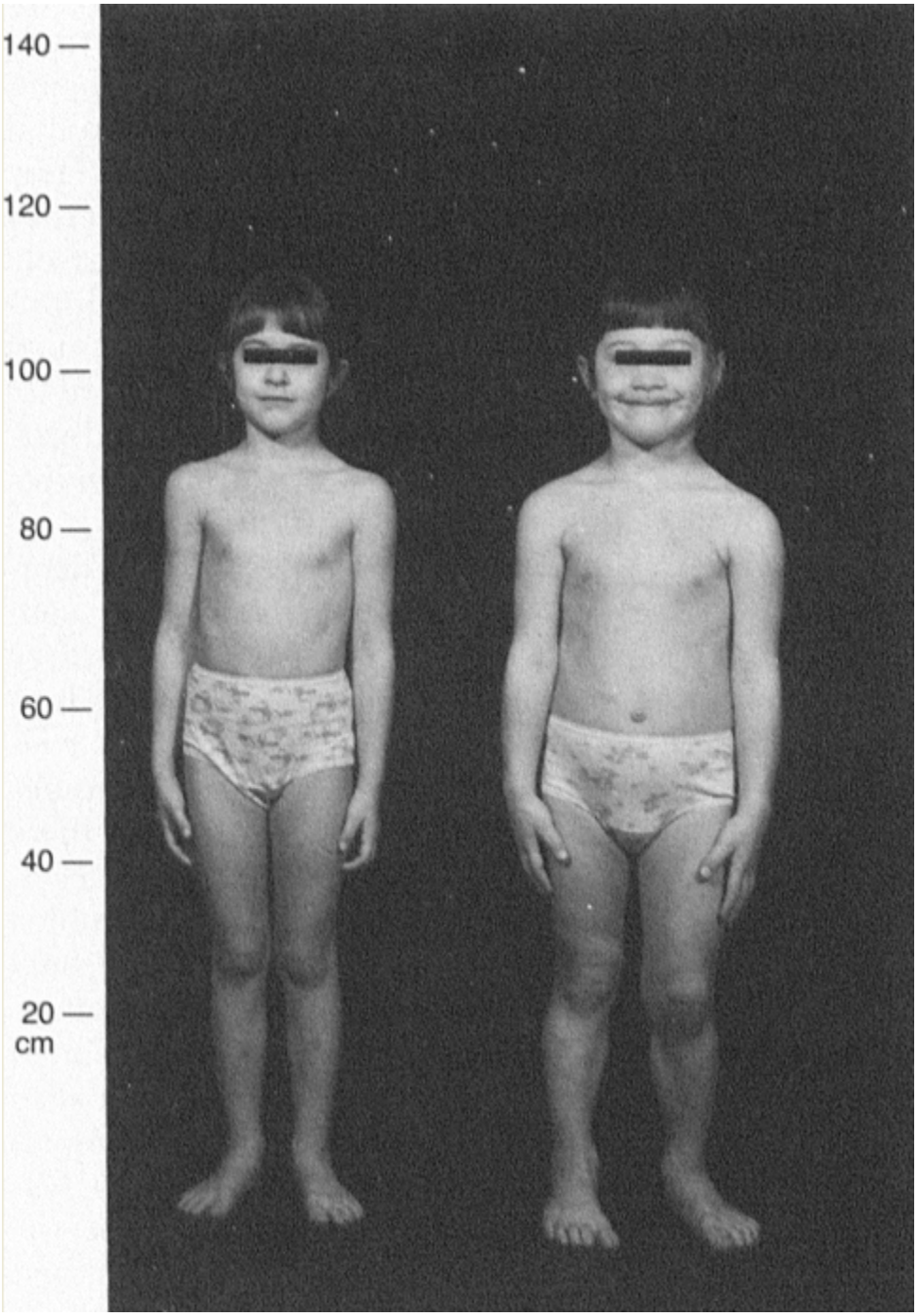

Figure 3. Patient age three years (right) at initial presentation, with her unaffected sister, age six years (left). The diagnosis of X-linked acrogigantism was made at age 28 years [Iacovazzo et al 2016].

From Moran et al [1990]; republished with permission of Massachusetts Medical Society

Table 2. Disorders to Consider in the Differential Diagnosis of Pituitary Gigantism

Disease Name	Gene	Prevalence of Pituitary Disease by Sex	Age of Onset of GH Excess	Clinically Evident GH Excess (% of Affected Persons)	Pituitary Findings	Extrapituitary Manifestations
McCune-Albright syndrome [1]	*GNAS* [2]	Equal	Variable (~30% diagnosed < age 16 yrs)	~20% [3]	GH-secreting pituitary adenoma or mixed GH- & prolactin-secreting pituitary adenoma &/or hyperplasia of GH- & prolactin-secreting pituitary cells	Polyostotic fibrous dysplasia, café au lait spots, precocious puberty, other manifestations
Multiple endocrine neoplasia type 1 [1]	*MEN1*	↑ Female [4]	Typically adult-onset; gigantism is rare	2%-5%	GH-secreting pituitary adenoma, mixed GH- & prolactin-secreting pituitary adenoma; pituitary hyperplasia secondary to a GHRH-secreting neuroendocrine tumor; other pituitary adenoma subtypes can occur: prolactinoma, NFPA, corticotropinoma.	Primary hyperparathyroidism, pancreatic neuroendocrine tumors, other manifestations
Carney complex [1]	*PRKAR1A* [5]	Equal	Typically adult-onset, but gigantism can occur	~10% [6]	GH-secreting pituitary adenoma or mixed GH- & prolactin-secreting pituitary adenoma &/or hyperplasia of GH- & prolactin-secreting pituitary cells; corticotropinomas described in 2 persons [7]	Skin hyperpigmentation, myxomas, PPNAD, other manifestations
AIP-related familial isolated pituitary adenoma [8]	*AIP*	↑ Male	Typically 2nd decade of life	~80%	GH- or mixed GH- & prolactin-secreting pituitary adenoma; pituitary hyperplasia rare; characteristically, can present w/pituitary apoplexy [9]; other pituitary adenoma subtypes can occur: prolactinoma, NFPA, corticotropinoma, thyrotropinoma	No

Table 2. continued from previous page.

Disease Name	Gene	Prevalence of Pituitary Disease by Sex	Age of Onset of GH Excess	Clinically Evident GH Excess (% of Affected Persons)	Pituitary Findings	Extrapituitary Manifestations
X-linked acrogigantism [8]	*GPR101*	↑ Female	Early onset (in all cases < age 4 yrs)	100%	Mixed GH- & prolactin-secreting pituitary adenoma &/or hyperplasia of GH- & prolactin-secreting pituitary cells; pituitary apoplexy not described	No

GH = growth hormone; GHRH = growth hormone-releasing hormone; NFPA = nonfunctioning pituitary adenoma; PPNAD = primary pigmented nodular adrenal disease

1. Syndromic

2. McCune-Albright syndrome is caused by early embryonic postzygotic somatic activating mutation of *GNAS*

3. Subclinical growth hormone excess has been described.

4. Vergès et al [2002], de Laat et al [2016]

5. Approximately 20% of families with Carney complex have been linked to 2p16. One individual with Carney complex (<1% of families with Carney complex) had a germline rearrangement resulting in four copies of *PRKACB* [Forlino et al 2014]; the authors propose that this is a Carney complex-causing gain-of-function variant.

6. Most patients have subclinical GH excess.

7. Hernández-Ramírez et al [2017], Kiefer et al [2017]

8. Nonsyndromic

9. Xekouki et al [2013]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and further management needs in an individual diagnosed with X-linked acrogigantism, the following evaluations are recommended:

- Consultation with a specialist in pediatric endocrinology or endocrinology
  - Clinical assessment with special attention to signs and symptoms of growth hormone (GH) excess and hyperprolactinemia.
  - Endocrine tests including spot GH (with dilution if above detection limit of the assay), IGF-1, and prolactin to assess for disease activity. LH, FSH, estradiol/testosterone, TSH, fT4, and 9 a.m. cortisol (and if needed dynamic testing) should also be checked in order to detect associated hypopituitarism.
- Visual field evaluation to assess for mass effects due to an expanding pituitary tumor. Young children may need informal testing (e.g., observing eye movements toward small objects in different areas of the visual field).
- Pituitary MRI for evidence of pituitary hyperplasia or a pituitary tumor. In case of a pituitary tumor, extrasellar extension should be evaluated.
- Consultation with a clinical geneticist and/or genetic counselor

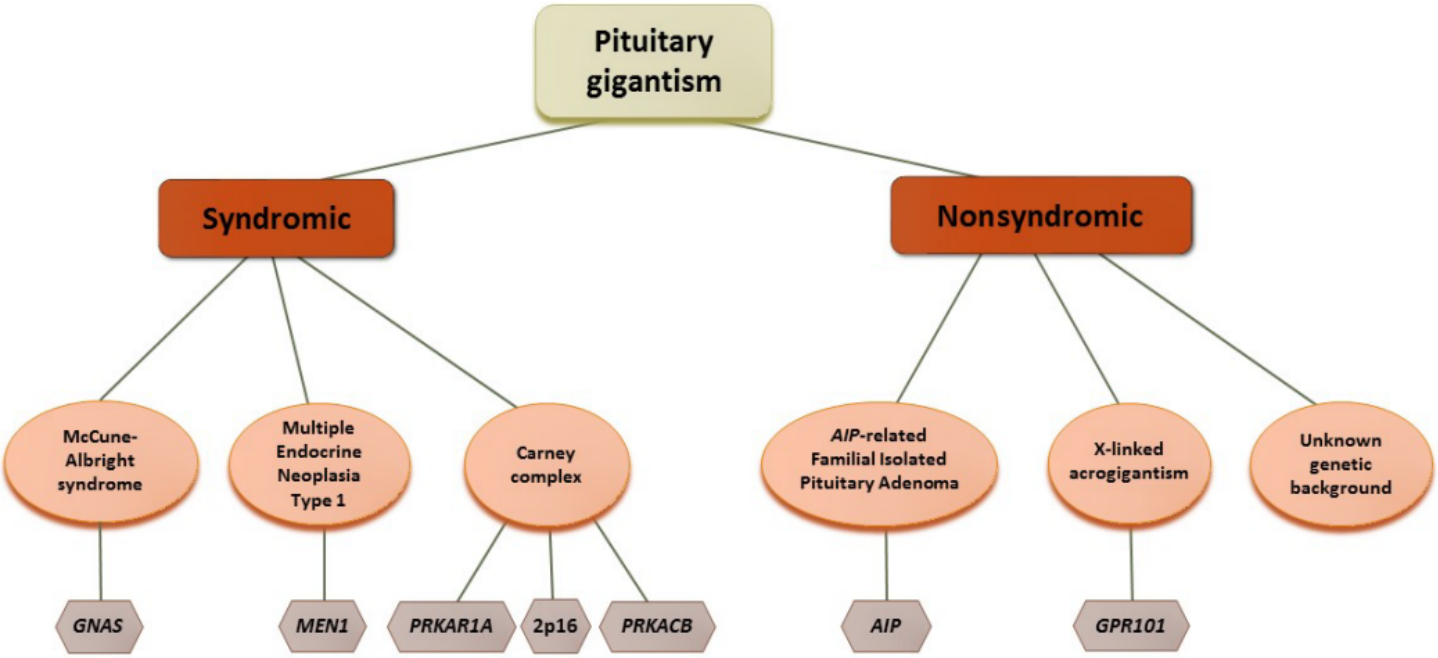

Figure 4. Syndromic and nonsyndromic genetic causes of pituitary gigantism

Treatment of Manifestations

GH Hypersecretion

Pituitary gigantism secondary to X-linked acrogigantism can be treated medically, surgically, and/or with radiotherapy.

Pituitary adenoma. When MRI findings suggest the presence of a pituitary adenoma in patients with molecularly confirmed X-linked acrogigantism, either transsphenoidal surgery or GH receptor antagonist therapy could be a first-line treatment option.

- **Transsphenoidal surgery** may provide long-term control of GH hypersecretion [Beckers et al 2015, Iacovazzo et al 2016], although frequently at the cost of post-surgical hypopituitarism.

  In case of persistent GH excess following surgery, the following are options:

  - Prompt initiation of GH receptor antagonist treatment with doses tailored to linear growth and IGF-1 levels. In most instances this treatment effectively controls GH excess and accelerated growth [Beckers et al 2015, Iacovazzo et al 2016]. Of note, the combination of the GH receptor antagonist with a somatostatin analog could allow use of lower doses of the GH receptor antagonist.
  - Repeat surgery or radiotherapy (conventional or radiosurgery). Note that because the effects of radiotherapy are often not immediately apparent, GH receptor antagonist therapy should be used while waiting to assess the efficacy of radiotherapy.

- **GH receptor antagonist therapy** (with or without somatostatin analogs) could be considered as first-line treatment in selected patients (those with adenomas that do not reach or compress the optic chiasm), followed by close monitoring of the pituitary tumor by serial MRI. Transsphenoidal surgery should be performed in the event of tumor growth.

Pituitary hyperplasia. When imaging shows pituitary hyperplasia (i.e., a diffusely enlarged pituitary gland without clear evidence of a pituitary tumor), GH receptor antagonist therapy (with or without somatostatin

analogs) can effectively control the disease [Iacovazzo et al 2016, Rodd et al 2016] and should be considered as first-line treatment. Note that surgery is not currently recommended because treatment requires total hypophysectomy with resulting lifelong pituitary hormone replacement therapy.

Hyperprolactinemia

Dopamine agonists (in appropriate dosages) can significantly reduce or normalize the prolactin levels and should be employed in patients with associated hyperprolactinemia [Iacovazzo et al 2016].

Surveillance

Patients with X-linked acrogigantism require the following:

- Intensive monitoring of height and growth velocity, and frequent clinical assessment for other manifestations of GH excess (including enlargement of the extremities, hyperhydrosis, headache, joint pain) and/or enlargement of a pituitary adenoma (visual field deficits)
- Intensive monitoring of pituitary function tests (spot GH, IGF-1, prolactin) to determine disease activity and response to treatment. Note: Frequency depends on control of GH excess, clinical status, compliance with treatment, treatment modality, and presence of comorbidities.
- Periodic evaluation of basal hormone tests (9 a.m. cortisol, TSH, fT4, LH, FSH, estradiol/testosterone), and, if necessary, dynamic testing (e.g., growth hormone stimulation tests, ACTH stimulation test) to evaluate for hypopituitarism. Note: Patients treated with radical neurosurgery and/or radiotherapy may develop GH deficiency and should receive GH replacement treatment as appropriate.
- Repeat pituitary MRI. Note: Frequency depends on previous extent of the tumor, treatment modality, clinical status, and disease activity.

The established guidelines regarding surveillance for associated comorbidities and risk of secondary neoplasms for patients with acromegaly [Melmed et al 2013] should be applied to patients with X-linked acrogigantism. These include the following:

- Evaluation for associated comorbidities of GH excess (including hypertension, diabetes mellitus, sleep apnea, cardiovascular disease, osteoarthritis).
- Although this complication has not been reported in X-linked acrogigantism, adults with active acromegaly (increased GH and age-adjusted IGF-1 levels) are at higher risk of developing colonic neoplasms. Thus, colonoscopy at age 40 years is advised with further surveillance at three- to ten-year intervals depending on the presence/absence of abnormalities in the initial colonoscopy and levels of GH and IGF-1 [Cairns et al 2010].

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Considering the need for multimodal treatment and the associated high frequency of hypopituitarism, women with X-linked acrogigantism may need specific fertility treatment in order to conceive.

As medical treatment does not result in significant tumor shrinkage in patients with X-linked acrogigantism, the authors recommend that women with macroadenomas undergo surgery to reduce the adenoma size prior to consideration of pregnancy.

Women with X-linked acrogigantism who have a pituitary macroadenoma may experience clinically significant enlargement of the adenoma during pregnancy. Thus, they should be questioned about symptoms that could

indicate tumor growth (increased frequency of headaches, visual changes) and monitored clinically with serial visual field testing. In the presence of symptoms or new visual field abnormalities, an MRI should be performed.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

X-linked acrogigantism is inherited in an X-linked manner; however, most individuals with X-linked acrogigantism have a *de novo* genetic alteration not inherited from a parent.

Risk to Family Members

Parents of a female proband

- All female probands reported to date have a *de novo GPR101* duplication; vertical transmission of a *GPR101* duplication from an affected parent to a daughter has not been reported.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo GPR101* duplication include clinical evaluation and molecular genetic testing.

Parents of a male proband

- If a male is the only affected family member (i.e., a simplex case), the affected male most likely has somatic mosaicism for a *GPR101* duplication and his mother is not heterozygous for the duplication. To date, all reported males who are simplex cases have a *de novo* somatic mosaic *GPR101* duplication.
- If a male proband has an affected sib, his mother is most likely heterozygous for the *GPR101* duplication. In the three reported instances of familial X-linked acrogigantism, affected males inherited the *GPR101* duplication from affected mothers [Trivellin et al 2014, Gordon et al 2016]. Note: If the *GPR101* duplication cannot be detected in the leukocyte DNA of a mother with more than one affected child (one of whom is male), she most likely has germline mosaicism (maternal germline mosaicism has not been reported in X-linked acrogigantism but is a theoretic possibility).
- Clinical evaluation of the mother and review of the family history may help distinguish male probands with a *de novo* somatic mosaic *GPR101* duplication from those with an inherited germline *GPR101* duplication. Molecular genetic testing of maternal leukocyte DNA can determine if the mother is heterozygous for the *GPR101* duplication.
- The father of an affected male will not have the disorder nor will he be hemizygous for the *GPR101* duplication; therefore, he does not require further evaluation/testing.

Sibs of a female proband

- Risk to sibs depends on the genetic status of the parents.

- All females reported to date have had a *de novo GPR101* duplication, suggesting a low risk to sibs; however, risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of germline mosaicism in one of the parents.

Sibs of a male proband. Risk to sibs depends on the genetic status of the mother:

- If the mother of a male proband is not affected and the proband represents a simplex case (i.e., a single occurrence in a family), sibs are presumed to be at low risk as all simplex males reported to date have a somatic mosaic *GPR101* duplication. However, risk to sibs is slightly greater than that of the general population (though still <1%) because of the theoretic possibility of maternal germline mosaicism.
- If the mother of the proband is affected/has the *GPR101* duplication, the chance of transmitting it in each pregnancy is 50%. Female and male sibs who inherit the *GPR101* duplication will be affected (see Penetrance).

Offspring of a female proband. Each child of a female with X-linked acrogigantism has a 50% chance of inheriting the *GPR101* duplication.

Offspring of a male proband

- If a male proband has a somatic mosaic *GPR101* duplication that involves germ cells, he could theoretically transmit the duplication to his daughters (who would be affected).
- A male proband with a germline *GPR101* duplication will transmit the duplication to all of his daughters (who will be affected).
- A male proband will not transmit the duplication to his sons.

Other family members. Given that most probands with X-linked acrogigantism reported to date have the disorder as a result of a *de novo GPR101* duplication, the risk to other family members is presumed to be low.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of genetic status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *GPR101* duplication has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Familial Isolated Pituitary Adenoma (FIPA) Patients**

United Kingdom

Email: info@fipapatients.org

qmul.ac.uk/fipa-patients

- **AMEND Research Registry**

  Association for Multiple Endocrine Neoplasia Disorders

  United Kingdom

  amend.org.uk

- **FIPA Consortium Registry**

  Patients with familial pituitary adenoma or childhood onset pituitary disease and their families are encouraged to contact the registry.

  Email: info@fipapatients.org

  fipapatients.org/contact

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. X-Linked Acrogigantism: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GPR101	Xq26.3	Probable G-protein coupled receptor 101	GPR101 @ LOVD	GPR101	GPR101

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for X-Linked Acrogigantism (View All in OMIM)

300393	G PROTEIN-COUPLED RECEPTOR 101; GPR101
300942	CHROMOSOME Xq26.3 DUPLICATION SYNDROME

Molecular Pathogenesis

The individuals originally described with X-linked acrogigantism harbored duplications of chromosome Xq26.3 with a smallest region of overlap (SRO) encompassing four genes (*ARHGEF6*, *CD40LG*, *GPR101*, and *RBMX*) [Trivellin et al 2014]. Of these genes, only *GPR101* was significantly overexpressed in the pituitary samples of affected individuals.

More recently, an individual with a typical phenotype and a complex genomic rearrangement was described [Iacovazzo et al 2016]. In this individual, high-density chromosomal microarray analysis revealed a proximal duplication followed by a normal copy segment and a distal duplication. The distal duplication allowed the definition of a novel SRO encompassing *GPR101* only, and not the neighboring genes on Xq26.3, thus proving the pathogenic role of *GPR101*.

Microhomologies, small insertions, or complex genomic rearrangements were identified at the breakpoint junctions in most individuals with X-linked acrogigantism. These mutational signatures suggest fork stalling and template switching/microhomology-mediated break-induced replication (FoSTeS/MMBIR) as the causative

mechanism [Trivellin et al 2014, Daly et al 2016b]. In one individual, the duplication was generated via an *Alu-Alu* mediated rearrangement [Iacovazzo et al 2016].

GPR101

Gene structure. *GPR101* comprises a single coding exon (NM_054021.1) and encodes an orphan G-protein coupled receptor that is 508 amino acids long (NP_473362.1). Four *GPR101* isoforms were identified, characterized by different 5' untranslated regions (UTRs) and a common 3'UTR [Trivellin et al 2016]. Based on *in silico* analyses, the putative *GPR101* promoter is localized within 2 kb upstream of the transcription start site [Trivellin et al 2016]. For a summary of gene information, see Table A.

Pathogenic variants. All individuals with X-linked acrogigantism harbor duplications of Xq26.3 (size ~500 kb). Such duplications are unique and have variable boundaries in individuals who represent simplex cases, while they are identical when transmitted within a family. Although in most cases the duplication affects four genes (*ARHGEF6*, *CD40LG*, *GPR101*, and *RBMX*), the SRO among all individuals reported with X-linked acrogigantism encompasses *GPR101* only.

Normal gene product. *GPR101* encodes a 508-amino acid protein. For a summary of protein information, see Table A.

For information on *GPR101* variants of uncertain significance, click here (pdf).

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Chapter Notes

Author Notes

Website: www.fipapatients.org

The FIPA patients website, established by Dr Korbonits in collaboration with the FIPA Consortium, is an information resource for patients and families with familial isolated pituitary adenoma (FIPA) and other rare conditions predisposing to pituitary adenomas. It also provides general information for medical professionals on research in this field, including links to relevant publications.

The authors welcome comments and inquiries to info@fipapatients.org.

Contact information for the laboratories that originally reported the genetic etiology of X-linked acrogigantism and continue to actively conduct research on the condition is provided below:

Dr Constantine A Stratakis' laboratory
NIH/NICHD, DEB, SEGEN
10 Center Drive, CRC, Rm 1E-3216
Bethesda, MD 20892-1862 USA
Email: stratakc@cc1.nichd.nih.gov; giampaolo.trivellin@nih.gov

Phone: 301-402-1998; 301-451-8034
Website: Pediatric Gigantism and Acromegaly

Prof Albert Beckers' laboratory
Department of Endocrinology CHU Sart Tilman B35
Domaine Universitaire du Sart-Tilman
University of Liège, 4000 Liège, Belgium
Email: albert.beckers@chu.ulg.ac.be; adrian.daly@ulg.ac.be
Phone: 0032 4 3667083

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