The causes and consequences of pituitary gigantism

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Abstract | In the general population, height is determined by a complex interplay between genetic and environmental factors. Pituitary gigantism is a rare but very important subgroup of patients with excessive height, as it has an identifiable and clinically treatable cause. The disease is caused by chronic growth hormone and insulin-like growth factor 1 secretion from a pituitary somatotrope adenoma that forms before the closure of the epiphyses. If not controlled effectively, this hormonal hypersecretion could lead to extremely elevated final adult height. The past 10 years have seen marked advances in the understanding of pituitary gigantism, including the identification of genetic causes in ~50% of cases, such as mutations in the *AIP* gene or chromosome Xq26.3 duplications in X-linked acrogigantism syndrome. Pituitary gigantism has a male preponderance, and patients usually have large pituitary adenomas. The large tumour size, together with the young age of patients and frequent resistance to medical therapy, makes the management of pituitary gigantism complex. Early diagnosis and rapid referral for effective therapy appear to improve outcomes in patients with pituitary gigantism; therefore, a high level of clinical suspicion and efficient use of diagnostic resources is key to controlling overgrowth and preventing patients from reaching very elevated final adult heights.

Height is a fundamental variable among human populations. The rates at which children grow and the final height reached in adulthood are governed by environmental factors that interact with multiple genetically inherited traits[1,2]. Sex and parental height are key contributors to an individual's height. Genome-wide association studies have highlighted various genes and pathways (*IGFBP4*, *SHOX2* and duplications and deletions of chromosome 16p11.2) that have a combined effect on height determination across large human populations[3,4]. In healthy children, height can be predicted to a clinically useful degree on the basis of formulae that incorporate parental height, the physical maturity of the individual (for example, bone age) and the prevailing stature of the local population. Social factors, including improved management of chronic diseases during the 20th century, have contributed to increased mean height in men and women across the globe. Additionally, sufficient early-life nutrition is an important variable that positively influences growth patterns and height measures, both at the individual and the population level. Periods of starvation during childhood reduce growth, which can be countered to some extent by catch-up growth when sufficient nutrition is introduced. Mass migration from rural to urban centres and accompanying socio-economic improvements in health and nutrition are matched by substantial changes in secular trends in height, as seen in Europe and Japan in the 20th century and over the past 40 years in China[5–7].

Abnormal childhood growth patterns and final adult heights are judged in comparison with the mean height characteristics of the local population, which are assessed using national or international reference data sets. As a general rule, those individuals whose height is above or below 2 s.d. from the sex-specific population mean are considered as having atypical height. Among these groups, idiopathic or constitutionally tall or short stature might exist in otherwise healthy people. Procedures to detect and investigate decreased stature or growth in children and adolescents are well established in many nations. However, systematic screening for excessively tall stature is given less priority, which might be because of a number of socio-economic factors (including the fact that greater height is perceived as a positive trait associated with economic advantages)[8,9]. Height is a complicated theme in medicine, however, and thresholds and considerations about what constitutes normal and tall stature have changed over time in line with evolving social mores. This change is well illustrated by the fact that in the 1950s it was considered acceptable to use exogenous oestrogen as 'treatment' to arrest growth in girls with a predicted height >173 cm (REFS[10,11]). As the threshold for being considered 'too tall' increased markedly up to the 1980s, the nature of tall

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Key points

- Nearly 50% of patients with pituitary gigantism have a known underlying genetic cause; therefore, these patients should be strongly considered for genetic counselling and screening.
- Once growth hormone (GH) hypersecretion has been established, efforts should be made to avoid delays in instigating treatment to control levels of GH and insulin-like growth factor 1.
- A shorter time between diagnosis and the commencement of treatment is associated with a decreased final height in pituitary gigantism.
- Pituitary gigantism is a disease that predominantly affects males, but males also have a longer delay in time to diagnosis than females, leading to a low proportion of male patients who have disease control by 18 years of age.
- Somatotropinomas in pituitary gigantism are usually large (macroadenomas) and might be difficult to cure with surgery or medical therapy alone; therefore, multimodal approaches are common in pituitary gigantism.
- The effect of large tumour size and multiple surgeries and radiotherapy is that patients with pituitary gigantism often have hypopituitarism at long-term follow-up.

stature referrals to endocrinologists and their treatment has altered dramatically[11].

Despite societal changes in the perception of tall stature, there remains an important challenge in identifying pathological causes of increased growth and gigantism (BOX 1). As statural growth is a dynamic process that fluctuates normally with physiological development, gigantism has to be defined in a number of ways to cover not only final adult height but also growth during childhood and growth that diverges from normal patterns. Excessive height is generally defined as an individual with a height >+2 s.d. scores above the appropriate mean height for their sex and ethnic population of origin. In addition, excessive height is assessed in terms of individuals who are >+2 s.d. in excess of their calculated mid-parental height (there are a variety of methods to estimate target and mean parental heights, each with their own limitations)[12–15]. A child who exceeds their relevant growth curve for the local population might not initially meet the clear criteria of >+2 s.d. excess in height, but this finding might be an early indication of an underlying abnormality in height development.

Many cases of tall stature in childhood or adolescence are not related to an identifiable abnormality and represent individuals with familial or constitutional tall stature, whereas the diagnosis of gigantism is generally reserved for suspected pathological cases. An increasing number of genetic abnormalities have been identified that affect key players in statural growth, including connective tissue or bone diseases and hormonal abnormalities[16–18]. Gigantism can be an individual feature of complex syndromes, such as Sotos syndrome or Marfan syndrome, and each one of these has a series of specific associations and required investigations[15,19].

The assessment and management of tall stature as a general topic has been reviewed extensively elsewhere[12–15,20–23]. During post-infancy childhood and adolescence, the somatotropic axis has a central role in determining growth velocity, and disorders of growth hormone (GH) and insulin-like growth factor 1 (IGF1) secretion and signalling are important causes of pathological height disorders. Pituitary gigantism is caused by chronic oversecretion of GH and IGF1, caused by a somatotrope adenoma or hyperplasia that forms before the fusion of the epiphyses. As pituitary gigantism is a disease that generally starts during childhood and adolescence, it affects a population of patients in which abnormal growth (due to the pituitary tumour) occurs against a background of normal growth spurts. Particularly in patients going through puberty, it can be a very challenging clinical problem to differentiate normal from abnormal growth.

As compared with other forms of gigantism, pituitary gigantism is of particular clinical importance because the tumour and related hormonal hypersecretion are amenable to treatment. Early recognition of the disease is vital to maximize the opportunity for effective investigation, diagnosis and treatment. Research advances over the past 10 years have fundamentally changed our understanding of the causes of pituitary gigantism. From being an obscure disorder in the past, today the genetic pathophysiology of nearly half of patients with pituitary gigantism is known[24–26]. This genetic information has also led to a better appreciation of why pituitary gigantism is an aggressive disease. The causative genes, when disrupted, alter the function of pituitary somatotropes, leading to hyperplasia, aggressive tumour formation and hypersecretion of GH. This hormonal excess often responds poorly to existing treatments, a molecular effect that translates into a clinically relevant challenge when attempting to optimize management. Our international studies have addressed the effect that this aggressive disease has on patients, who have a high symptom burden owing to early-onset resistant pituitary somatotrope tumorigenesis and difficult-to-control hypersecretion of GH and IGF1 (REF.[25]).

Clinical characteristics and diagnosis

Historical context. Gigantism is an intrinsically familiar cultural concept. Human societies, despite their apparent heterogeneity, share common themes and archetypes among their legends, myths and origin stories. The figure of the giant is typical of such stories, often as a martial character with mythical, superhuman size and strength[27]. These legends have, in turn, led to a public fascination with real individuals of great stature, who were historically objects of spectacle in circuses or toured for money (FIG. 1). Burgeoning scientific interest from anatomists and others led to unusual skeletons being preserved in collections, and numerous examples of human remains with pituitary gigantism exist in museum or anatomy collections around the world today[28,29]. By the end of the 19th century, medical science was concerned with understanding the pathological mechanisms underlying the disease. The issue of how and why giants grew to their huge size led to some impressive feats of descriptive science, including ruminations on the role of the pituitary enlargement seen in cases of what would be called acromegaly. For instance, in July 1884, the Swiss physician-researchers Fritsche and Klebs published the treatise entitled *Ein Beitrag Zur Pathologie Des Riesenwuchses. Klinische Und Pathologisch -Anatomische Untersuchungen*, in which they described the comprehensive clinical and anatomical findings regarding a

Somatotropic axis
The hormonal system, including the hypothalamus, pituitary and peripheral tissues, that controls growth hormone secretion from the anterior pituitary gland and insulin-like growth factor 1 mainly from the liver.

Somatotrope adenoma
A benign tumour of the growth hormone-producing cells of the anterior pituitary gland.

Epiphyses
Proximal and distal end portions of long bones that contain cartilaginous growth plates at which longitudinal bone growth occurs until growth plate closure and epiphyseal fusion with the rest of the bone.

Box 1 | **Causes of tall stature, overgrowth and gigantism**

Idiopathic tall stature

- Physiological or non-pathological causes of tall stature (majority of investigated cases)
  - Constitutional tall stature
  - Familial tall stature
  - Non-familial tall stature
  - Constitutional advancement of growth

Pathological causes

- Tumoural causes
- Pituitary gigantism due to tumoural growth hormone (GH) excess
- Other endocrine causes
  - Precocious puberty
  - Hyperthyroidism
  - Hypogonadism (including genetic forms, such as aromatase deficiency)
  - Familial glucocorticoid deficiency
- Chromosomal disorders
  - Klinefelter syndrome (47, XXY)
  - 47, XXX
  - 47, XYY
- Childhood obesity
- Metabolic causes
  - Homocystinuria
- Syndromes associated with tall stature or overgrowth
  - Beckwith–Wiedemann syndrome
  - Marfan syndrome
  - Loeys–Dietz syndromes
  - Fragile X syndrome
  - Sotos syndrome
  - Weaver syndrome
  - Simpson–Golabi–Behmel syndrome

Rare syndromes and occasional associations

- Lujan–Fryns syndrome
- 19p13.13 deletion syndrome
- Gorlin–Goltz syndrome (patched 1 (*PTCH1*) mutations)
- Camptodactyly, tall stature and hearing loss (CATSHL) syndrome (fibroblast growth factor receptor 3 (*FGFR3*) gain-of-function mutations)
- *NPR2* (encodes atrial natriuretic peptide receptor 2) gain-of-function mutation

man with acrogigantism, Peter Rhyner[30]. In addition, the authors described related findings from the literature and the skull of a giant from Zurich, in which the typical changes of acromegaly could be seen. Although Klebs noted that the enlargement of the pituitary "is a constant accompaniment … of general gigantism", he attributed it to a general process causing gigantism rather than the core of the problem itself.

The description of acromegaly by Pierre Marie in 1886 stimulated an uptick in interest in acromegaly and pituitary gigantism[31]. The link between the pituitary gland and acromegaly was not established when acromegaly was first described by Marie and required further investigation by de Souza Leite and others before pituitary tumours were established as an invariable association[32] (reviewed by de Herder in REF.[33]). This period was followed by the publication of large bodies of work on acromegaly, including specific reports of cases of gigantism throughout the world[34–36]. There remained for a time a divergence of opinion on whether acromegaly and pituitary gigantism represented a continuum or two separate entities. Marie initially favoured a separate nature for the two conditions, whereas others such as Launois eventually successfully argued for a common cause[36–38]. In hindsight, the very common germline genetic causes we now know to be present in pituitary gigantism leading to severe, early-onset disease suggest that the differences Marie and others appreciated between gigantism and adult acromegaly were not entirely baseless. Interestingly, patients with pituitary gigantism also number among the earliest patients to be treated with neurosurgery and radiotherapy[39,40].

Diagnosis. Pituitary gigantism is caused by excess levels of GH due to a pituitary somatotrope adenoma or hyperplasia occurring in childhood or adolescence. Although the clinical focus in a case of pituitary gigantism is on excessive height in the first instance, the pathological effects of excess levels of GH and IGF1 are systemic and involve multiple organs. The clinical assessment of a patient with pituitary gigantism must consider all aspects of local tumour effects and deleterious effects on vital organs (such as the heart), in addition to the pressing concerns regarding excessive height. The more typical presentation of a somatotrope adenoma in adults is in the form of acromegaly, which provides important similarities and contrasts with the presentation of pituitary gigantism (TABLE 1). Acromegaly characteristically presents sporadically (that is, in a non-familial setting) in the fifth decade of life and is slightly more frequent in women than in men[41–43]. A diagnosis of acromegaly is usually preceded by a period of occult disease (about 9 years), during which patients have gradually worsening symptoms (coarsening of the face, enlargement of hands and feet and increased sweating and headaches). The mean adenoma size at presentation in acromegaly is 15 mm (REF.[43]).

By contrast, pituitary gigantism mainly affects men, who make up 78% of patients in the largest international series[25]. The reason for this marked difference is unknown but presumably is due to exacerbation of the sexual dimorphic pubertal growth patterns by excess GH and IGF1. Females with gigantism were significantly younger at diagnosis than males (median: 15.8 years versus 21.5 years; $P < 0.05$). This difference was also seen at the age of onset of rapid growth, which occurred at 11 years in females and 13 years in males ($P < 0.05$)[25]. A number of factors could explain this difference. One is the preponderance of women with X-linked acrogigantism (X-LAG) syndrome, which is a particularly early-onset and severe form of pituitary gigantism[44]. Additionally, the earlier onset of puberty in girls and the lower final adult height in women could lead to excessive height being noted and referred for investigation earlier in girls than in boys. A major consequence of this time difference in onset or detection is the delay between the first occurrence of excessive height until diagnosis of pituitary gigantism in males[25]. Males had a 3.7-year longer delay in diagnosis than females (6.2 years versus 2.5 years; $P < 0.05$). The overall effect of these differences was that only a minority (37.3%) of male patients had been diagnosed by the end of their teenage years, compared with a majority of females (61.9%; $P < 0.05$). In terms

Fig. 1 | **An historical patient with pituitary gigantism. a** | Contemporary publicity image dating from 1899, advertising an appearance at the London Pavilion by Julius Koch (stage name was Giant Constantin, or *Le Geant Constantin*). **b** | In contrast to the idealized publicity image, this panel shows a photograph in which the coarsened facial features and enlarged hands and feet are more clearly seen. The man measured up to 259 cm in height and was later determined to have pituitary gigantism and to harbour a large pituitary macroadenoma on autopsy. A study in 2017 demonstrated an increased copy number of *GPR101* in DNA from the bone of Julius Koch, which is indicative of X-linked acrogigantism syndrome[104]. Part **a** reproduced from https://wellcomecollection.org/works/jpy3unnm, CC-BY-4.0. Part **b** is adapted with permission from REF.[104], Society for Endocrinology.

of height at diagnosis, however, sex-related differences were not as marked. *Z*-Scores were identical in both sexes (+3.1 s.d.) at diagnosis. Similarly, no statistically significant difference existed between males and females with pituitary gigantism with respect to variation from mean parental height[25].

Despite the young age of the affected population, patients with pituitary gigantism almost invariably have macroadenomas (pituitary adenoma ≥10 mm diameter) at diagnosis. Our group noted that the mean maximal tumour diameter at diagnosis was 22 mm (range: 14–34 mm) and overall 84.3% of patients had macroadenomas (15% were giant adenomas (>40 mm in maximal diameter))[25]. Despite the young age of the patients at diagnosis (mean: 14 years), these tumours also displayed signs of aggressive growth, in that 77% had extrasellar extension and 54.5% of tumours were already invasive. The burden of signs and symptoms in pituitary gigantism is high (FIG. 2), and patients who are older at diagnosis have a concomitantly higher disease burden, probably owing to a longer exposure to chronic hypersecretion of GH and IGF1. Although genetic mutations tend to cause early, large tumour growth and invasion, patients with pituitary gigantism exhibit this aggressive profile irrespective of whether a known genetic mutation has or has not been diagnosed[25,44,45].

Pituitary adenomas in patients with pituitary gigantism are not only large but also are highly secretory, leading to very elevated levels of GH (median 35.5 ng/ml) and IGF1 (median 254.5% of the upper limit of normal)[25]. Overall, females with pituitary gigantism have significantly higher levels of GH than males owing to the X-LAG syndrome subgroup that is predominantly female and is typified by remarkably elevated GH hypersecretion[25]. Levels of IGF1, although invariably high, do not differ between males and females with pituitary gigantism[25]. In our experience, patients with X-LAG syndrome have substantially higher levels of IGF1 than those with aryl hydrocarbon receptor-interacting protein (*AIP*) mutations or patients with no mutations[25]. Additionally, prolactin hypersecretion frequently accompanies excess levels of GH and IGF1 in the overall (34%) population of patients with pituitary gigantism and is particularly prevalent in patients with X-LAG syndrome (82%)[25].

Genetic causes of pituitary gigantism

Given the clinical profile of early-onset, large pituitary tumours, unsurprisingly, genetic abnormalities are found in nearly half of patients with pituitary gigantism[25,26]. These abnormalities can take the form of germline genetic mutations or pathological copy number variations (CNVs), presenting either constitutionally or as somatic mosaicism (TABLE 2). Genes encoding proteins that are involved in pituitary gigantism also drive tumorigenesis in other groups of patients and can lead to inherited or familial forms of pituitary adenomas[46–49]. These forms include either multiorgan tumour syndromes (for example, multiple endocrine neoplasia type 1 (MEN1) or McCune–Albright syndrome (MAS)) or pituitary-specific conditions, such as familial isolated pituitary adenomas (FIPAs)[50].

Among 143 patients with pituitary gigantism who were studied extensively for genetic abnormalities, we found that 46% of patients had a pathological mutation (including validated pathogenic missense, insertion–deletion and truncating mutations) or CNV (duplications of chromosome Xq26.3, including G protein-coupled receptor 101 (*GPR101*))[25]. The most frequent genetic mutations were *AIP* mutations or deletions, making up 29% of the population of patients with pituitary gigantism. Pituitary gigantism was found in 30% of patients with acromegaly due to *AIP* mutations[51]. A study published in 2015 reported that 56 of 120 (46.7%) patients with pituitary gigantism had *AIP* mutations; however, the study excluded patients with other genetic causes or pituitary tumour syndromes[52]. Family history is important in the investigation of patients with pituitary gigantism owing to the high frequency of genetic causes. FIPA cases made up 22.3% of patients with pituitary gigantism in the largest series, and in nearly all of these cases, either *AIP* mutations or X-LAG syndrome was present[25].

AIP gene. The *AIP* gene, located on chromosome 11q13, encodes a 330-amino acid intracellular (usually cytosolic) protein that is ubiquitously expressed in healthy tissues. AIP has multiple interaction partners, including the aryl hydrocarbon receptor (AHR), which acts as a receptor for dioxin and mediates xenobiotic responses[53]. Additionally,

Extrasellar extension
Growth of a pituitary adenoma outside of the borders of the sella turcica.

Table 1 | **Clinical characteristics of patients with pituitary gigantism and acromegaly**

Features	Pituitary gigantism[a]	Acromegaly[b]
Sex	78% men	54.5% women
Age at diagnosis (median; years)	21.0	45.2
Age at first symptoms (median; years)	14.0	33.5
Delay in diagnosis (median; years)	5.3	9.0
Maximum tumour diameter (median; mm)	22.0	15.0
Macroadenoma (%)	84.3	71.8
Invasion at diagnosis (%)	54.5	47.6
Prolactin co-secretion (%)	34	10

[a]$n = 208$ (REF.[25]). [b]$n = 3{,}173$ (REF.[43]).

AIP has a number of important interactions that might contribute to its tumorigenic role in the pituitary, including with chaperones, phosphodiesterases, G protein subunit-α_i and zinc-finger protein ZAC1 (also known as PLAGL1)[54–61]. Genetic disruption of *AIP* has revealed a number of important regions in the molecule, particularly the carboxyl terminus and tetratricopeptide repeat domain[62–64]. These regions can modulate the interaction of AIP with partner proteins such as heat shock protein 90, phosphodiesterases and AHR[53–64]. AIP is a complex molecule, and mutation or disruption of the amino terminus has also been plausibly linked to dysfunctional cell models such as rat pituitary GH3 cells[65].

Given the role of AHR in detoxifying organic compounds and other toxins, it has been shown that the prevalence of acromegaly is higher in highly polluted regions than less polluted ones and that acromegaly patients with genetic variants of *AHR* and *AIP* might have increased acromegaly disease severity[66–68]. Homozygous knockout of *Aip* in mice leads to embryonic lethality due, in large part, to vascular defects[69]. By contrast, as compared with wild-type animals, mice that are heterozygous for *Aip* mutations ($Aip^{+/-}$) have an increased tendency to develop pituitary adenomas, usually somatotropinomas[70,71]; this tumorigenesis might be preceded by hyperplasia[72], which is also occasionally reported in humans[73].

In 2006, germline *AIP* mutations were first discovered to be involved in the pathogenesis of patients with FIPA and sporadic pituitary adenoma from Finland and Italy[74]. In the tumours of these patients, loss of heterozygosity at the *AIP* locus indicated that the germline mutation was followed by a 'second hit', thereby removing the normal *AIP* allele. The affected patients developed early-onset, large pituitary adenomas, which were most frequently somatotropinomas. Since then, hundreds of patients have been found to carry germline *AIP* mutations and a clear clinical phenotype has emerged[46,51,75–86]. These patients usually present with FIPA, and ~75% have somatotropinomas[46,47,52]. The emergence of these tumours begins at a much earlier age than the emergence of sporadic acromegaly (20 years), and tumours are generally large and invasive at presentation, which makes surgical cure difficult[51]. The management of patients with *AIP* mutations is further complicated by the fact that loss of AIP in the tumour leads to decreased responses to medical therapy with somatostatin analogues[51]. Even in patients with acromegaly without *AIP* mutations, low levels of AIP immunohistochemical staining of tumour specimens is a strong predictor of poor response to somatostatin analogue therapy[87–90]. In patients with germline *AIP* mutations, tumoural immunohistochemical staining for AIP can be variable. Patients with early truncating mutations (and a somatic loss of the normal allele) might have tumours that are devoid of or have very low levels of AIP staining, whereas in those with pathogenic missense *AIP* mutations, AIP immunostaining might be retained[87,91]. Double pituitary adenomas are rare in patients with *AIP* mutations[52].

The median age at disease onset or emergence of the first symptoms in patients with *AIP* mutation-related somatotropinomas is 17.5 years, and cases have been reported with symptoms beginning in those as young as 4 years[51]. As noted previously, this early disease onset in childhood or adolescence development leads to a relatively high rate of gigantism among patients with acromegaly with *AIP* mutations (~30%) as compared with acromegaly patients with normal *AIP* genetic sequences[51]. Patients with *AIP* mutation-related gigantism are mostly male (95%), and a sizeable proportion (42%) come from families with FIPA. Additionally, patients with *AIP* mutation-related gigantism can also present as simplex cases, accompanied by asymptomatic mutation carriers with no pituitary disease in the kindred. *AIP* mutations have a low penetrance (15–25%); therefore, distant relatives with pituitary adenomas might be unknown to patients when discussing family history. Indeed, increasing evidence suggests that ancient founder *AIP* mutations dating back thousands of years could lead to large and extensive kindreds with members affected in the present day[82,92].

The higher prevalence of *AIP* mutation carriers in or from a discrete geographic region could lead to recurrent cases of pituitary adenomas, including those causing gigantism. This effect is well illustrated by the high prevalence of the Arg304X *AIP* mutation among patients with acromegaly or gigantism and unaffected carriers in the Mid-Ulster region of Northern Ireland compared with contiguous and neighbouring regions; this risk was originally identified following genetic studies of the skeleton of the famous 18th century Irish Giant, Charles Byrne[82,93,94]. Such mutations can also be traced in line with emigration overseas in the case of both the Mid-Ulster haploblock and another common *AIP* mutation (Phe269–His275 duplication) in the UK, USA and France[92,93]. Follow-up of well-defined kindreds with FIPA and *AIP* mutations has led to the identification of multiple mutation carriers with pituitary adenomas, some with accompanying signs and hormonal abnormalities and others in a clinically asymptomatic state[93]. As incidental small pituitary microadenomas are very frequent in the general population, it is difficult to determine whether small asymptomatic tumours, present in *AIP* mutation carriers, are likely to develop into larger adenomas[95,96]. Further follow-up of these cohorts might allow the identification and resection of early-stage *AIP*-related pituitary

Haploblock
Also known as haplotype block. A set of neighbouring genetic alleles or markers that tend to be inherited together over generations.

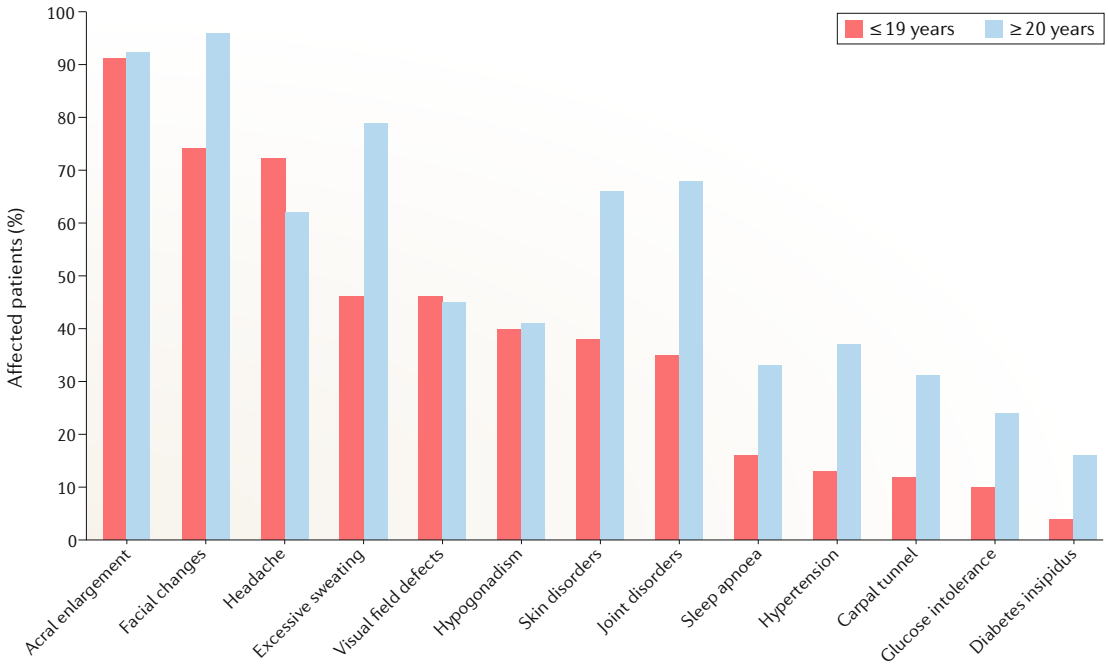

Fig. 2 | **Signs and symptoms in pituitary gigantism at diagnosis.** The 208 patients with pituitary gigantism were separated into younger (≤19 years) and older (≥20 years) cohorts for comparison purposes. The study demonstrated that older age at diagnosis (and greater disease exposure) is associated with an increased prevalence of many pathological signs and symptoms, particularly those related to longer-term exposure to elevated levels of growth hormone and insulin-like growth factor 1 (joint disease, facial changes, skin changes and diabetes mellitus)[25].

adenomas while they are still microadenomas, potentially preventing the onset of clinical syndromes, such as acromegaly and gigantism.

Compared with patients who have genetically negative pituitary gigantism, patients with *AIP* mutations differ significantly in terms of greater male predominance and a younger age of disease onset or diagnosis. One of the important consequences of *AIP* mutation-related somatotropinomas is the difficulty in achieving clinical control as patients commonly need multimodal therapy, including repeat surgery. The biology of *AIP*-related somatotropinomas is also relevant, as these tumours have a statistically significantly lower response rate to somatostatin analogues in terms of hormonal control and tumour shrinkage than the tumours of patients with non-*AIP* mutated acromegaly[51].

X-linked acrogigantism syndrome. X-LAG syndrome is a recently described disorder associated with pituitary gigantism that has a very consistent pattern of clinical presentation in young children[44,45]. X-LAG syndrome is very rare, with ~30 individual cases described to date worldwide[44,45,97–103]. Historical information suggests that X-LAG syndrome is the cause of many of the tallest humans in history; these individuals had the characteristics of a remarkably young age at disease onset and profound overgrowth that typifies X-LAG syndrome[44,104,105]. For example, a genetic diagnosis of X-LAG syndrome was established in the case of Julius Koch (Giant Constantin; FIG. 1), a well-studied man with pituitary gigantism from the early 20th century, who measured up to 259 cm in height[104].

X-LAG syndrome is associated with duplications on chromosome Xq26.3 that involve *GPR101*, an orphan G protein-coupled receptor[45,106]. These duplications are readily identified in most cases using array comparative genome hybridization protocols; other techniques such as high-definition arrays or digital droplet PCR can be used to assist diagnostic efforts and when complex duplications are present.

Patients with X-LAG syndrome are usually born following uncomplicated pregnancies and in most cases have normal growth patterns in the initial postnatal period; cases of X-LAG syndrome below the 3rd percentile and above the 97th percentile of the normal distribution at birth have been described[44,100,102]. During early childhood, often within the first year of life, these patients begin to demonstrate increases in height and weight that inexorably increase over time until the child is well in excess of the 97th percentile. Height and weight increases are not always synchronized at the outset, and one might precede the other by some months. Apart from increased growth and gigantism, patients with X-LAG syndrome also have acromegalic features, despite their young age. At presentation, patients usually have large hands and feet, facial coarsening with a broad nasal bridge and a prominent mandible, and some patients have increased interdental spaces. Acanthosis nigricans (dry, dark patches of skin that are usually found in the armpits, neck or groin) has been reported in some individuals, which is usually indicative of underlying insulin resistance[44]. In at least one-third of cases, the overgrowth is accompanied by increased appetite and hunger, which might be episodic in nature. The aetiology of increased

appetite is unknown but appears to be specific to X-LAG syndrome as it is not typically reported in acrogigantism due to other causes.

At the pituitary level, patients with X-LAG syndrome present with pituitary macroadenomas or infrequently with pituitary hyperplasia alone[44,45]. Histologically, there might be a presentation of adenoma, hyperplasia or both together; multiple cases have shown a pattern of multiple microadenomatous foci within a background of hyperplasia[44,45]. This pattern suggests that the condition could begin as hyperplasia and then progress to microadenoma formation; subsequently, one of the microadenomas could then grow to become a macroadenoma. Left untreated for considerable periods, adenoma progression in X-LAG syndrome is aggressive[98]. Tumour and hyperplasia in X-LAG syndrome generally show strong GH and prolactin positivity. Whether the disease process in X-LAG syndrome occurs via a pituitary-specific pathway or the pituitary pathology is driven by other factors is unknown. Among the genes in the duplicated chromosome Xq26.3 region, only *GPR101* mRNA is highly upregulated in the pituitary adenomas of patients with X-LAG syndrome. However, in multiple cases of X-LAG syndrome, elevated levels of growth hormone-releasing hormone (GHRH) have been measured at diagnosis, indicating that hypothalamic dysregulation might be a causative feature[100]. Supporting these data, both GH and prolactin secretion from tumour cells in X-LAG syndrome are sensitive to both GHRH and a GHRH antagonist in vitro[100].

Genetically, X-LAG syndrome can occur in patients with a germline duplication of *GPR101* on chromosome Xq26.3 or in men who have a somatic mosaicism for the duplication in which only a proportion of their cells (as low as 16%) are affected by the duplication[97,99,102]. As noted in one case, there is the potential for not identifying a duplication in a patient with X-LAG syndrome using DNA derived from peripheral blood leukocytes owing to mosaicism; in such cases, testing of other tissues such as skin or pituitary gland could be used for diagnostic testing[97]. Importantly for patient management, X-LAG syndrome can be inherited, and three families with FIPA and paediatric-onset somatotropinomas and gigantism have been reported to date. Genetic variants in *GPR101*, although having some effect on cell function in vitro, do not appear to be a frequent cause of sporadic acromegaly or other forms of pituitary disease[102,107–111].

X-LAG syndrome differs from most other forms of pituitary gigantism owing to its very young age at diagnosis or onset, although MAS manifests in the first few years of life, but very rarely with pituitary tumoural overgrowth. As noted previously in the Review, patients with X-LAG syndrome usually have rapid growth between 12 and 24 months of age, and most are diagnosed by the age of 3–5 years. The tumour or hyperplasia is accompanied by very elevated levels of GH that are not suppressed on an oral glucose tolerance test, and prolactin hypersecretion is usually also present.

Multiple endocrine neoplasia type 1. MEN1 is a multiorgan syndrome of endocrine and non-endocrine pathologies that is clinically diagnosed by the presence of tumours in at least two of the following characteristically affected glands or structures: parathyroid, anterior pituitary and pancreatic islets[112]. Pituitary adenomas are one of the principal tumour types in MEN1 and affect up to 40% of patients with MEN1 in their lifetimes[113–115]. Furthermore, the most predominant pituitary tumours in MEN1 are prolactinomas, whereas somatotropinomas make up about one-quarter of pituitary adenomas that occur in the setting of MEN1 (REFS[113–115]). The frequency of pituitary adenomas that secrete multiple hormones (known as plurihormonal) in MEN1 is increased as compared with non-MEN1 pituitary tumours, and cases of double pituitary adenomas, in which separate secretory types develop independently, have been reported[116–118]. Pituitary adenomas occurring in the setting of MEN1 are more likely to be macroadenomas than sporadic non-MEN1-related cases and have a tendency to be more invasive at diagnosis than non-MEN1-related pituitary adenoma[119,120]. *MEN1* mutations are rarely associated with acromegaly[80,81]. Furthermore, pituitary gigantism is exceptional in MEN1, making up only 1% of genetically studied cases in the largest series[25]; excessive levels of GH in MEN1 could also be caused by GHRH hypersecretion from a neuroendocrine tumour. Despite this rarity, the early presentation of a GH and prolactin-secreting

Table 2 | **Genetic causes of pituitary gigantism[25]**

Syndrome or genetic cause	Genetic abnormalities	Presentation	Percentage of cases
AIP gene	*AIP* mutations; exon and whole-gene deletions	Isolated pituitary adenomas; sporadic, familial gigantism and FIPA	29
X-Linked acrogigantism syndrome	Duplications on chromosome Xq26.3 including *GPR101*; somatic mosaicism	Isolated pituitary adenomas; sporadic, familial gigantism and FIPA	10
McCune–Albright syndrome	*GNAS* mosaicism	Syndromic multiorgan disease; sporadic	5
Multiple endocrine neoplasia type 1	*MEN1* gene mutations, deletions; possibility of pituitary hyperplasia due to GHRH hypersecretion from neuroendocrine tumour	Syndromic multiorgan disease; sporadic and familial	1
Carney complex	*PRKAR1A* mutations and deletions	Syndromic multiorgan disease; sporadic and familial	1
Unknown genetic cause	As yet unidentified	Isolated or syndromic; sporadic and familial	54

AIP, aryl hydrocarbon receptor-interacting protein; FIPA, familial isolated pituitary adenomas; GHRH, growth hormone-releasing hormone; *GNAS*, GNAS complex locus; *GPR101*, G protein-coupled receptor 101; *MEN1*, multiple endocrine neoplasia type 1; *PRKAR1A*, protein kinase cAMP-dependent type 1 regulatory subunit-α.

mammosomatotrope pituitary tumour in a 5-year-old patient from a family with MEN1 means that screening for pituitary disease in MEN1 carriers is recommended from the age of 5 years[113,121]. In this patient, the tumour onset was associated with overgrowth beyond the 95th percentile and associated acromegalic features.

As an inherited condition with agreed screening guidelines, MRI screening of pituitary glands of asymptomatic carriers of an *MEN1* mutation could lead to the identification of many patients with small pituitary adenomas that are not associated with clinical symptoms[122]. In the absence of accompanying biochemical or hormonal abnormalities, it could be challenging to determine whether these tumours are related to MEN1 disease or whether they are incidentalomas, which are known to occur in one-fifth of the general population[96,123]. Hence, when a pituitary adenoma is identified during screening, careful follow-up of carriers of *MEN1* mutations with clinical and hormonal testing is important.

McCune–Albright syndrome. MAS is probably the longest established clinical syndrome involving pituitary gigantism. MAS was first clinically described in the late 1930s as a classic triad of precocious puberty, fibrous dysplasia and café-au-lait macules (coffee-coloured patches on the skin)[124,125]. MAS is caused by a post-zygotic gain-of-function mutation in *GNAS* that appears in a mosaic state[126,127]. Most cases of MAS are due to missense mutations at the Arg201 residue that lead to constitutive activation of $G\alpha_s$, which increases levels of cAMP, driving cellular dysregulation[128]. Multiple cell types (endocrine gland, skin and bone) can be affected by this *GNAS* mosaicism, and MAS is now recognized as being clinically heterogeneous and more complex than the classic triad. This heterogeneity is largely due to the varied effects of the disease in the endocrine system, although dysregulation of cells in the gastrointestinal tract and liver are becoming better recognized[129–132].

Among the endocrinopathies associated with MAS, one of the most severe forms involves pituitary somatotrope dysregulation, hyperplasia and tumorigenesis, leading to acrogigantism[133–135]. In MAS, ~10–15% of patients have excessive levels of GH causing acromegaly, and MAS accounts for 5% of patients with pituitary gigantism, including some well-known historical cases[25,136–141]. The complex clinical presentation of MAS in patients with acromegaly–gigantism is due to the interplay of the pituitary and bone pathologies[133,134,142,143]. Patients with MAS-related GH excess can have severe craniofacial fibrous dysplasia including the skull base, which has a number of important sequelae (such as skull and facial bone deformation and cranial nerve impingement, including serious risks of vision and hearing loss)[143–146]. The pituitary gland in these patients can present with diffuse hyperplasia or tumour, but the surrounding bony thickening and deformation can make surgical access and resection complicated. In addition, the fibrous dysplasia makes concomitant conventional radiotherapy contraindicated owing to the risk of transformation of affected bone into a sarcoma. In these patients, the inhibition of GH hypersecretion is clinically important to control overgrowth and to ameliorate its negative effects on craniofacial fibrous dysplasia.

In MAS, there is an additional complication in that precocious puberty has a variable onset and its occurrence can lead to epiphyseal closure, thereby halting growth. This potential interplay between endocrine manifestations of MAS should be recognized and the possibility of excessive levels of GH occurring in young patients with fused epiphyses suggests that the presence of acromegalic signs and symptoms should be monitored. Treatment of MAS-related acrogigantism is challenging because of the difficulty of surgical access and the presence of diffuse hyperplasia. Somatostatin analogues are usually only partially effective, and given the importance of GH or IGF1 control, the GH receptor antagonist pegvisomant should be considered, as it has been proved effective in a number of cases and small series[147,148].

Other genetic causes. A number of other genetic causes of pituitary adenomas occurring in a syndromic setting have been identified. Carney complex is a multiorgan disorder caused, in most cases, by loss-of-function mutations in protein kinase cAMP-dependent type 1 regulatory subunit-α (*PRKAR1A*). This *PRKAR1A* inactivation leads to characteristic patterns of skin lesions (including freckles, lentigines and café-au-lait macules), myxomas (cardiac and skin) and primary pigmented nodular adrenal cortical disease in affected patients[149,150]. Other tumours affecting the testes, thyroid and the pituitary are found to a variable extent. In the pituitary, Carney complex can lead to frequent biochemical increases in circulating levels of GH and prolactin (up to 75%), although acromegaly occurs in ~10% of cases[151–154]. Pituitary somatomammotropin hyperplasia can accompany or even precede pituitary adenoma formation in Carney complex[155]. Despite fairly frequent biochemical disorders of GH secretion in Carney complex, pituitary gigantism is very rare, accounting for only 1% of cases in our international series[25].

Mutations in *CDKN1B*, which codes for cyclin-dependent kinase inhibitor 1B, cause MEN4 (REF.[156]). This rare condition leads to pituitary adenomas in some affected patients, but somatotropinomas are infrequent[156–162]. Only one case of pituitary gigantism with a *CDKN1B* mutation has been reported to our knowledge[163]. Animal models of *CDKN1B* inactivation, whether spontaneous in the case of rats (MENX) or generated experimentally in mice, are associated with both pituitary adenomas and overgrowth[164–166]. The adenomas arise from the intermediate lobe of the pituitary gland in these animals and do not involve the somatotrope lineage. The gigantism observed in *Cdkn1b*-knockout rodents is not due to excessive levels of GH; rather, it appears to be caused by generalized multiorgan dysregulation of cell proliferation.

Mutations or intragenic deletions in genes (for example, succinate dehydrogenase complex flavoprotein (*SDHx*) and MYC-associated factor X (*MAX*)) that are classically associated with phaeochromocytomas and paragangliomas have also been associated with pituitary tumours in a syndrome termed

3PA (pituitary adenoma, phaeochromocytoma and paraganglioma association)[167–170]. Although these genes have been associated with cases of syndromic acromegaly, pituitary gigantism has yet to be reported in that setting[171,172].

Hypothalamic–pituitary disorders, including precocious puberty and excessive levels of GH, can occur in patients with neurofibromatosis type 1 (NF1)[173]. In NF1, gliomas can affect the optic pathway and most commonly present in childhood, occurring in up to one-fifth of paediatric patients[173–179]. In patients with NF1 with increased growth velocity, the cause is usually due to precocious puberty, in which it is self-limiting, and short stature is the more probable result. In rare cases, overgrowth in NF1 is due to excessive levels of GH. The aetiology of this excess has been long debated, as a specific hypothalamic cause has not been demonstrated, and a disturbance of somatostatinergic tone by tumour invasion has been posited[180]. Owing to its rarity, few large series of acromegaly and gigantism related to NF1 exist. A study published in 2017 reported a group of 7 patients who had a height velocity >2 s.d. for age among 64 children (10.7%), with NF1-related optic pathway gliomas[173]. In all seven patients with excessive levels of GH, the optic tract glioma had reached the optic chiasm, in contrast to 24.5% of those with normal GH secretion. The excessive levels of GH led to increased circulating IGF1 levels in all patients, and treatment with a somatostatin analogue in three patients led to hormonal control. GH hypersecretion in this setting can be responsive to either somatostatin analogues or pegvisomant. Interestingly, spontaneous resolution of excessive levels of GH is also known to occur in patients with NF1 with optic tract gliomas; therefore, close follow-up is required so that unnecessarily aggressive interventions are avoided if possible[173,179,181].

Clinical management

Clinical guidelines on different aspects of the diagnosis and management of acromegaly are available[42,182–184]. As pituitary gigantism and acromegaly form a continuum of chronic somatotrope axis excess, the general aims of treatment are largely the same. These include the need to safely control GH and IGF1 hypersecretion, control pituitary tumour growth, ameliorate the effects of the tumour on local structures and reduce the pathological effects of hormonal hypersecretion on end-organ function. Pituitary gigantism differs from acromegaly in some important ways that have an effect on management. Patients with pituitary gigantism are often diagnosed when young (children and adolescents), and drug doses and intervals that are labelled for adults might not be directly applicable. Indeed, most medications used in acromegaly treatment have not been formally studied in paediatric populations and are not indicated for use in children, which can raise important hurdles to obtaining prescriptions for effective therapies. As control of excessive levels of hormones at an earlier age is associated with significantly lower final height, a key feature of pituitary gigantism management is the implementation of effective therapy to normalize GH and IGF1 secretion as soon as possible[25].

Combination therapy. For pituitary gigantism management, combination therapy is frequently used owing to the aggressiveness of the underlying pituitary disease, with a mean maximal tumour diameter of 22 mm, >75% of patients having extrasellar extension and ~55% of tumours being already invasive at the time of diagnosis in an international cohort[25]. Primary control rates using medical therapy are, therefore, very low (4%), whereas the first surgery controls the disease in only 26% of operated patients. Reoperation and adjuvant medical therapy are frequent, and nearly one-third of patients require three or more interventions or modalities (including reoperation). Despite this heavy treatment burden, disease control (including tumoural stability or shrinkage, symptom control, levels of IGF1 under the upper limit of normal levels and levels of GH <1 ng/ml) was achieved in only 39% of patients during long-term follow-up (>12 months)[25]. This resistance to treatment also led to the frequent use of radiotherapy in this international cohort, and after a median of 168 months of follow-up, 26 of 61 (43%) patients who received radiotherapy achieved disease control. As a consequence of the multiple surgeries and radiotherapy, hypopituitarism during long-term follow-up was common in pituitary gigantism (64%). Although treatment to control GH or IGF1 hypersecretion and tumour mass is clearly important, there is a substantial and ongoing symptom burden in pituitary gigantism, such that improvements in certain symptoms are balanced out by new-onset problems or disease exacerbation at last follow-up (for example, joint disease and carbohydrate metabolism problems; FIG. 3).

Controlling stature in children. Another exacerbating factor particular to pituitary gigantism is the additive effect of pubertal delay or hypogonadism on final height, as patients with hypogonadism with pituitary gigantism have a greater excessive height than patients with gigantism with normal gonadal function[25]. Large pituitary adenomas can damage or impair the function of normal pituitary gonadotropes, whereas substantial hyperprolactinaemia (common in cases related to mutations in *AIP* and X-LAG syndrome) further worsens the functional hypogonadal state. Surgery and radiotherapy both carry substantial risks of hypopituitarism, including dysfunction of the gonadal axis. A lack of or deficiency in sex steroids in growing patients with excessive levels of GH suggests that the epiphyseal growth plates remain open for longer than in unaffected individuals. In severe cases, evidence suggests epiphyses might never close[36]; the overall effect is to produce a longer period of long bone growth in pituitary gigantism, leading to more severe GH and IGF1-driven excess height.

Controlling stature in children with tumoural GH hypersecretion in order to avoid reaching the start of puberty at a height excessively >+2 s.d. is beneficial. The somatotrope axis and gonadal axis each contribute about half of the increase in pubertal height. When patients with GH-induced childhood gigantism enter puberty or when tumoural GH excess begins during puberty, the combined effect of elevated levels of GH and IGF1 and normal gonadal steroids can exacerbate the elevated final height. The height gain during puberty is

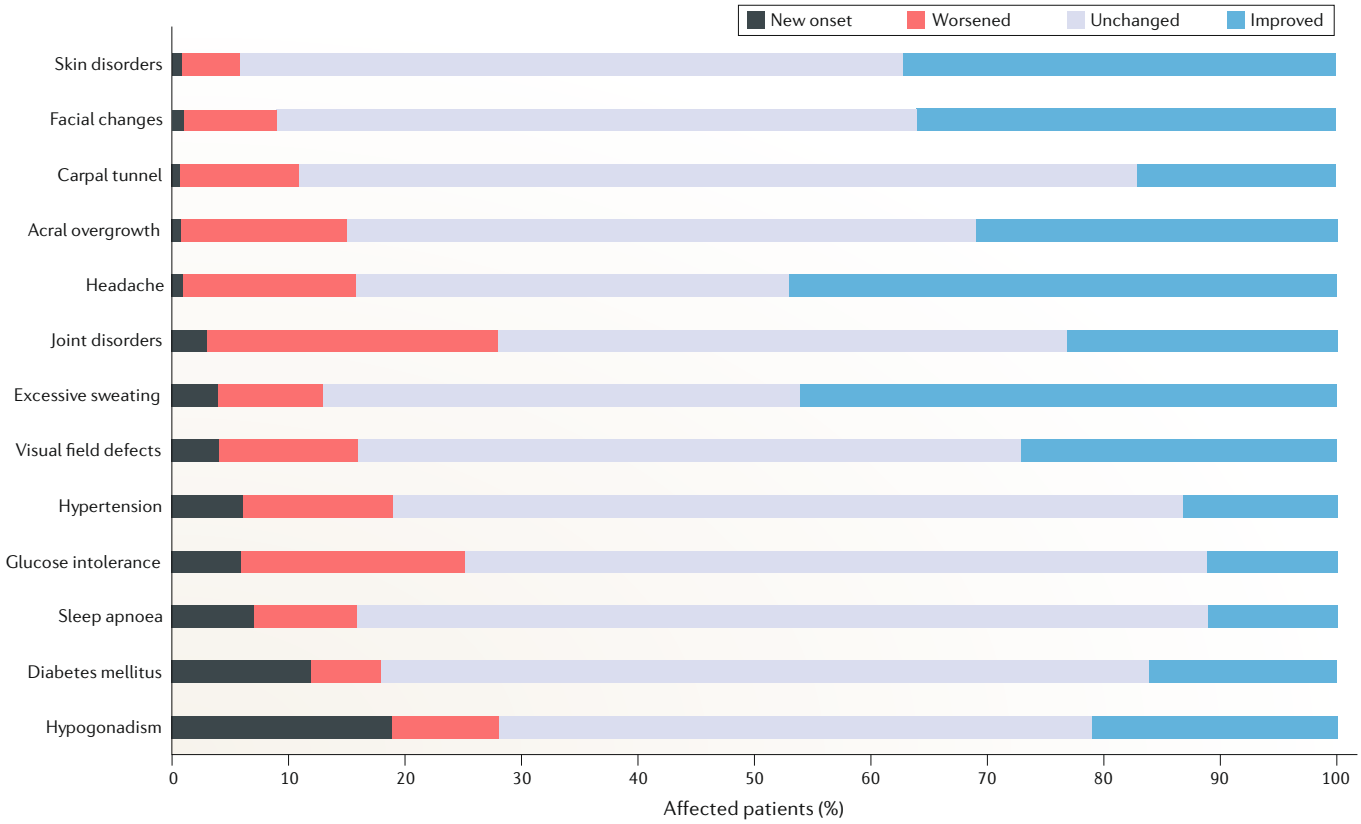

Fig. 3 | **Evolution of the severity of signs and symptoms of pituitary gigantism before and after treatment.** The severity of signs and symptoms in 208 patients with pituitary gigantism at diagnosis compared with disease severity after treatment at last follow-up. Each sign and symptom is classified as new onset at last follow-up (black), worsened since diagnosis (red), unchanged (grey) or improved (blue)[25]. It is instructive to note that despite multimodal therapy, the majority of signs and symptoms are unchanged or worsened at last follow-up, whereas new-onset endocrine and metabolic disorders such as hypogonadism and diabetes mellitus rise.

overall fairly stable; therefore, the predicted final height can be estimated. For this reason, therapeutic efforts before the onset of puberty in pituitary gigantism should focus on keeping excessive growth to a minimum via control of levels of GH and IGF1.

Treatment during puberty. Once puberty has begun, effective limitation of pubertal height gain in pituitary gigantism can be complicated. Somatostatin analogues have a fairly minor effect on final height in those with constitutional tall stature and are not a highly effective option[185,186]. In pituitary gigantism, by contrast, somatostatin analogue treatment can reduce excessive levels of GH and IGF1, but owing to the aggressive nature of the tumour, hormonal control is not guaranteed with this pharmacotherapy alone[25]. As previously noted, the most frequent genetic forms of pituitary gigantism (*AIP* mutations and X-LAG syndrome) are characterized by a poor hormonal and tumoural response to first-generation somatostatin analogues[44,51]. The utility of the new-generation somatostatin receptor ligand pasireotide in pituitary gigantism has not been established. The GH receptor antagonist pegvisomant is effective for IGF1 control in pituitary gigantism on the basis of individual cases and small series, where somatostatin analogues or other treatment modalities have failed[187–192]. In cases of somatostatin analogue-resistant pituitary gigantism with X-LAG syndrome or *AIP* mutations, pegvisomant can reduce levels of IGF1 into the normal range and reduce growth[44,193]. For instance, a study reported successful symptomatic, hormonal and height control with pegvisomant in three children with pituitary gigantism who had uncontrolled disease following surgery and somatostatin analogue therapy[187]. Pegvisomant can be used as monotherapy and in combination with somatostatin analogues; however, in most jurisdictions, it is not labelled for use in paediatric populations[194–197]. One limitation with pegvisomant is its potential for tumour enlargement during therapy, although this is a rare occurrence. However, such tumour expansion can occur in patients with pituitary gigantism and can lead to treatment withdrawal[187,198].

Surgery. Surgical resection of the pituitary adenoma by an expert pituitary neurosurgeon is a recommended first-line therapy for acromegaly[42]. In pituitary gigantism, neurosurgery is also a valid first-line option, although in children access to the pituitary might be more complicated[185,186]. Lack of pneumatization of the sphenoid sinus can make transsphenoidal access difficult whereas incomplete pneumatization can produce sellar floor asymmetry. The small facial size in

Pneumatization
Development of an air space within a sinus, such as the sphenoid sinus, that gradually takes place over childhood and has an influence on the neurosurgical access to the anterior pituitary gland.

Transsphenoidal
Neurosurgical approach to access the pituitary gland in the sella turcica via the sphenoid sinus.

Sellar floor
The base of the sella turcica in which the pituitary gland lies.

Transfrontal approach
A neurosurgical approach to the pituitary gland via the frontal bone of the skull.

Tumour debulking
Removal of tumour tissue to reduce overall tumour size and related symptoms when full tumour resection cannot be performed.

children can make instrument access and visualization via the nostrils difficult. Very large macroadenomas might also be difficult to access via the transsphenoidal route in the paediatric setting; a transfrontal approach could represent an alternative.

In X-LAG syndrome, tumours are not frequently invasive, but treatment is complex and cure is often achieved only after radical surgery or multiple therapies[25,44,45,102]. If the anterior pituitary is heavily affected by hyperplasia, in some patients radical resection of the entire anterior pituitary has been performed. Partial resection of the tumour in X-LAG syndrome is not associated with control of levels of GH as quite small remnants of tumour appear to be capable of producing elevated levels of GH for decades postoperatively[199]. In patients in whom surgery is ineffective or refused, the use of the GH receptor antagonist pegvisomant is effective in controlling levels of IGF1 in X-LAG syndrome and other resistant forms of pituitary gigantism[44]. Prolactin hypersecretion, unlike that of GH and IGF1, is readily amenable to medical therapy with dopamine agonists, such as cabergoline.

The choice of surgery or medical therapy and their later outcomes have not been widely reported in pituitary gigantism. In a review of 68 published cases of paediatric somatotropinomas, two-thirds of cases had primary surgery whereas one-third had primary medical therapy[198]. Disease control appeared better (85%) in those who received pharmacotherapy as their first treatment (usually before surgery) versus about half of those that had surgery first. We highlighted that therapy in patients with pituitary gigantism is usually multimodal and that few are cured by primary neurosurgery[25]. Overall, the hormonal control rate was only 39%. Primary surgery and reoperation might not frequently control levels of GH or IGF1, and pituitary tumour debulking can improve the control rate with medical therapy in pituitary gigantism, as has been well established in acromegaly[42,200].

With more aggressive tumour resection, the rate of pituitary axis deficits rises accordingly, but in pituitary gigantism there is a relatively high rate of hypopituitarism at baseline (25%)[25]. Nearly two-thirds of patients with pituitary gigantism have hypopituitarism at last follow-up. The main factor predicting hypopituitarism at last follow-up is large tumour size at diagnosis — tumours that, in turn, require considerably more treatment modalities to control[25]. Younger patients with pituitary gigantism undergoing surgery appear to be at greater risk of hypopituitarism at follow-up, which is similar to results focused on postoperative posterior pituitary deficits in patients with paediatric pituitary adenoma[201].

Radiotherapy. Pituitary radiotherapy is an option for long-term hormonal and tumoural control, but as it takes many years to show onset of effects, it does not have a substantial role in rapidly controlling gain in height due to excessive levels of GH or IGF1 in pituitary gigantism. As part of the multimodal strategy that is usually employed to combat the large and invasive pituitary tumours in patients with pituitary gigantism, radiotherapy is generally considered only after the failure of both primary medical and surgical therapies. At long-term follow-up (5–20 years), hormonal control of levels of GH or IGF1 was seen in 43% of patients with pituitary gigantism who received secondary radiotherapy[25]. Radiotherapy is not considered a good option in patients with MAS owing to the danger of malignant transformation of craniofacial fibrous dysplasia. Additionally, radiotherapy contributes to the high rate of hypopituitarism seen in patients with pituitary gigantism at long-term follow-up.

Sex hormone replacement. Large somatotropinomas that commonly occur in patients with pituitary gigantism lead to hypopituitarism at diagnosis in one-quarter of patients; the most frequent axis affected is the gonadal axis. In the setting of increased statural growth stimulated by excessive levels of GH or IGF1, a lack of sex hormones can lead to delayed closing of the epiphyses and increased final height. The fact that somatotropinomas in pituitary gigantism often co-secrete prolactin (34% of cases) can also potentially exacerbate hypogonadism[25]. Whether sex hormone replacement has a role in limiting final height in post-pubertal patients with pituitary gigantism with hypogonadism is unknown; however, epiphyseal closure could be facilitated in this way. In pre-pubertal patients with pituitary gigantism with excessive levels of GH or IGF1, the role of sex steroid treatment in reducing final height is unclear. Long-term follow-up of girls with constitutional tall stature treated with oestrogen suggests potential impairment of fertility, whereas testosterone treatment of boys with constitutional tall stature is complicated by adverse effects, such as acne and aggression. Together, these findings underline that in cases of pituitary gigantism, the main initial focus of treatment to control height gain should be focused on controlling somatotrope hyperfunction and inhibiting GH and IGF1 excess.

Orthopaedic intervention. In patients with constitutional tall stature that do not have an identifiable hormonal or other growth-related pathology, orthopaedic surgical intervention to destroy the growth plates at the level of the distal femur and the proximal tibia or fibula (epiphysiodesis) has been used to limit height gain. Epiphysiodesis is considered potentially useful among those patients with constitutional tall stature in whom puberty has already begun, as hormonal means of limiting pubertal growth spurts have low efficacy[14,22,202,203]. Clinical trials of epiphysiodesis suggest that final height can be reduced by up to 7 cm in boys and 5.9 cm in girls[204–206]. In experienced centres, the adverse effect rate is low. Little published experience in large series regarding epiphysiodesis in those patients with a history of excessive levels of GH and IGF1 exists, and there is a risk that excessive hormones could cause unwanted outcomes such as axis deformity owing to unequal leg growth. Hence, in pituitary gigantism, therapeutic efforts to reduce final height should be concentrated primarily on controlling excessive levels of GH and IGF1.

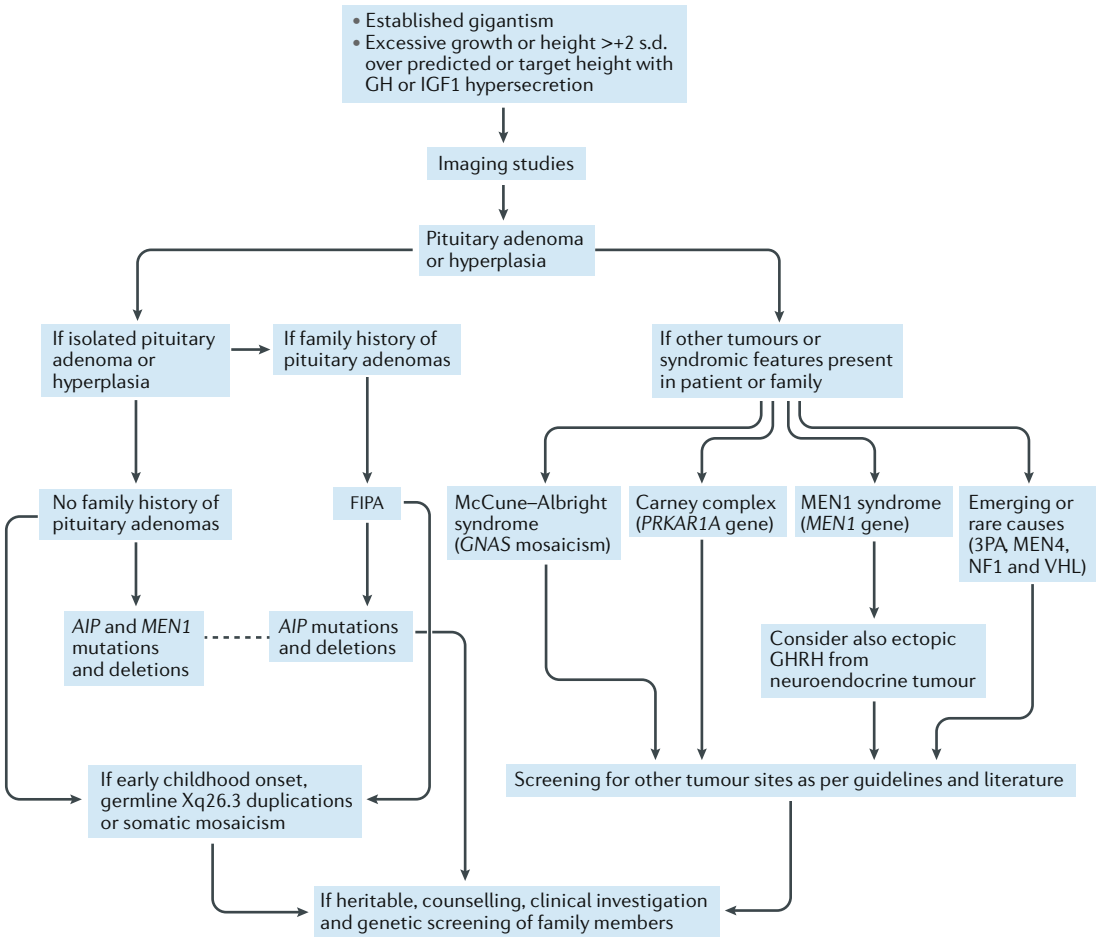

Fig. 4 | **Schematic for performing genetic investigations in patients with pituitary gigantism.** A variety of genetic changes can lead to pituitary tumorigenesis, including mutations (such as point, insertion–deletions, frameshift and truncation mutations) and copy number variations (including intragenic, whole-gene, multigene deletions or duplications) and mosaicism for such variants. Comprehensive testing of pituitary tumour risk genes by next-generation sequencing panels and array comparative genome hybridization are used in clinical genetic practice and can be augmented by whole-exome sequencing or research-based tools, such as digital droplet PCR and long-range PCR, to improve diagnostic certainty[99,131]. A high degree of clinical suspicion and thorough surveillance for syndromic features in non-pituitary tissues can help to guide correct testing. The presence of isolated pituitary disease is more characteristic of conditions such as *AIP* mutations; age at pituitary tumour onset is another helpful feature as very early childhood onset (12–60 months) is more suggestive of McCune–Albright syndrome and X-linked acrogigantism (X-LAG) syndrome than other genetic causes. 3PA, pituitary adenoma, phaeochromocytoma and paraganglioma association; FIPA, familial isolated pituitary adenoma; GH, growth hormone; GHRH, growth hormone-releasing hormone; IGF1, insulin-like growth hormone 1; MEN1, multiple endocrine neoplasia type 1; NF1, neurofibromatosis type 1; VHL, Von Hippel–Lindau syndrome.

Conclusion

Pituitary gigantism is a rare but important form of overgrowth caused by excessive levels of GH or IGF1. If identified early, pituitary gigantism can be treated using multimodal therapeutic approaches to limit the pathological effects on height and reduce the substantial disease burden attributable to chronic excessive levels of GH. Research advances in the past decade have converted pituitary gigantism from an obscure and poorly understood entity into one in which multiple genetic aetiologies have been identified and ~50% of cases have a known genetic cause. Given this high percentage of identifiable genetic causes, it would seem reasonable to suggest that patients with pituitary gigantism be referred for genetic counselling and testing for causative genetic abnormalities. An orderly process to identify genetic causes is helpful for the effective investigation and diagnosis of patients with pituitary gigantism (see FIG. 4).

Some genetic causes, such as *AIP* mutations and X-LAG syndrome, are conditions specific to the pituitary that require a high degree of clinical suspicion in order to diagnose the underlying pituitary adenoma. Large international series were absent until 2015, and data from our group and others demonstrate the aggressive clinical profile of pituitary gigantism, with large pituitary macroadenomas being almost universally present, in addition to displaying a strong male predominance, which contrasts markedly with the adult form of the disease, acromegaly.

Pituitary gigantism is challenging to treat and control, with some genetic causes (*AIP* mutations and *GPR101* duplications) leading to somatotrope tumours

that can be resistant to widely available medical therapies such as somatostatin analogues. Despite the severe phenotypes associated with pituitary gigantism related to *AIP* mutations and X-LAG syndrome (including some of the tallest patients with gigantism in history), it is sobering to note that as a group, cases of pituitary gigantism with an as-yet unknown genetic cause have a substantially poorer prognosis in terms of higher levels of GH and IGF1, a longer delay in diagnosis (5 years longer), more requirement for multimodal therapy and a greater age at the time of disease control (10 years older than the *AIP* mutation group)[25]. Although large strides have been made in understanding pituitary gigantism, it is probable that other important molecular genetic pathways remain to be identified in this rare and classic endocrine condition.

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