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CASE REPORT

Aggressive pituitary adenomas occurring in young patients in a large Polynesian kindred with a germline R271W mutation in the *AIP* gene

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Abstract

Objective: Mutations in the aryl hydrocarbon receptor-interacting protein (*AIP*) were recently shown to confer a pituitary adenoma predisposition in patients with familial isolated pituitary adenomas (FIPA). We report a large Samoan FIPA kindred from Australia/New Zealand with an R271W mutation that was associated with aggressive pituitary tumors.
Design and methods: Case series with germline screening of *AIP* and haplotype analyses among R271W families.
Results: This previously unreported kindred consisted of three affected individuals that either presented with or had first symptoms of a pituitary macroadenoma in late childhood or adolescence. The index case, a 15-year-old male with incipient gigantism and his maternal aunt, had somatotropinomas, and the maternal uncle of the index case had a prolactinoma. All tumors were large (15, 40, and 60 mm maximum diameter) and two required transcranial surgery and radiotherapy. All three affected subjects and ten other unaffected relatives were found to be positive for a germline R271W *AIP* mutation. Comparison of the single nucleotide polymorphism patterns among this family and two previously reported European FIPA families with the same R271W mutation demonstrated no common ancestry.
Conclusions: This kindred exemplifies the aggressive features of pituitary adenomas associated with *AIP* mutations, while genetic analyses among three R271W FIPA families indicate that R271W represents a mutational hotspot that should be studied further in functional studies.

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Introduction

Pituitary adenomas occur frequently in the general population, with clinically diagnosed tumors having a prevalence of one case per 1064 individuals (1, 2). In general, pituitary adenomas occur most frequently in adults, with pituitary adenomas in the pediatric or adolescent setting being quite uncommon (3, 4). However, early onset of pituitary adenomas in children and adolescents can be associated with aggressive disease and more dramatic phenotypic features, such as gigantism (3).

Although many molecular genetic abnormalities have been reported in pituitary tumors, most are somatic in nature and are not associated with a defined clinical phenotype (4, 5). Very few germline genetic mutations are associated with pituitary adenomas in a sporadic or familial context. Well-characterized syndromes include multiple endocrine neoplasia type 1 (MEN1) or more rarely Carney complex (CNC) (6, 7). Pituitary adenomas can occur in kindreds in the absence of MEN1/CNC, a clinical condition known as familial isolated pituitary adenomas (FIPA) (7). Recently, Vierimaa *et al.* discovered that mutations in the aryl hydrocarbon receptor (AhR)-interacting protein gene (*AIP*) on chromosome 11q13 were associated with a pituitary adenoma predisposition (PAP) among kindreds in Finland and Italy with acromegaly and prolactinomas (8). *AIP* mutations were subsequently shown to account for about 15% of FIPA kindreds (5, 9); nonsecreting adenomas can also be associated with *AIP* mutations (5). International genetic screening studies have identified other *AIP* mutations among familial and sporadic pituitary adenoma populations (9–15). These series, albeit involving limited numbers of affected patients, suggest that tumors in patients with *AIP* mutations are larger and occur at a younger age than sporadic cases (16).

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Some *AIP* mutations (e.g. R304X) have been reported in multiple unrelated kindreds and appear to represent hotspots. One missense *AIP* mutation, R271W, has been reported in two European FIPA kindreds with acromegaly. We report a large Polynesian kindred with the R271W *AIP* mutation with three affected members, each of whom demonstrated distinct phenotypic features of highly aggressive pituitary adenomas.

Case reports

The genealogy of the family is shown in Fig. 1 and includes three patients with pituitary adenomas (II-1, II-5, and III-6).

Case 1 (patient III-6)

Patient III-6 presented with headaches and visual disturbances at the age of 15.5 years. His weight was 104 kg and height was 193 cm, both in excess of the 97th centile (+2.5 S.D). His height was excessive in comparison with his calculated mid-parental height of 185 cm (90th centile). The characteristic overgrowth of the extremities and typical facial appearance of acromegaly were absent. He was euthyroid and appropriately advanced in puberty with 15 ml testicular volume and normal secondary sexual characteristics. No visual field defect was apparent on clinical examination. Initial investigation revealed an insulin-like growth factor 1 (IGF1) of 658 μg/l, normal for the patient's age and sex. No other hormonal abnormalities were present. On magnetic resonance imaging (MRI), the patient had a pituitary macroadenoma of 15 mm in maximum diameter without invasion of surrounding structures and with posterior displacement of the pituitary stalk (Fig. 2). Over the following 14 months, the patient remained under close review and no change in the pituitary adenoma characteristics was noted. Despite an adult bone age, absent distinctive acromegalic features, and normal age/sex-matched IGF1 levels, the patient gained a further 2.8 cm in height over this period. GH hypersecretion was confirmed on oral glucose tolerance test (OGTT), with an elevated basal GH (7.3 μg/l), which failed to suppress (nadir GH 4.2 μg/l). The patient is currently awaiting transsphenoidal excision of the tumor.

Following discussions with the patient's family, it came to light that his maternal uncle (patient II-1) and aunt (patient II-5) both had a past history of pituitary adenomas that had been treated in New Zealand.

Case 2 (patient II-1)

This patient is the 32-year-old maternal uncle of patient III-6. He presented in 1988 at 12 years of age with a history of severe headaches and reduced visual acuity in his right eye. Pallor of the right optic disc and a bitemporal hemianopia were present on examination. Hormonal analysis revealed an elevated prolactin (PRL) level of 247 000 mU/l (normal up to 450 mU/l), and a CT scan of the brain demonstrated a giant (40 mm diameter) pituitary adenoma with suprasellar extension. Owing to his visual impairment and the size of the tumor, a craniotomy with partial decompression was performed in December 1988. Histology showed a pleomorphic chromophobe adenoma with a moderately high mitotic rate; immunochemistry was strongly positive for PRL and negative for GH and ACTH. He was treated with bromocriptine,

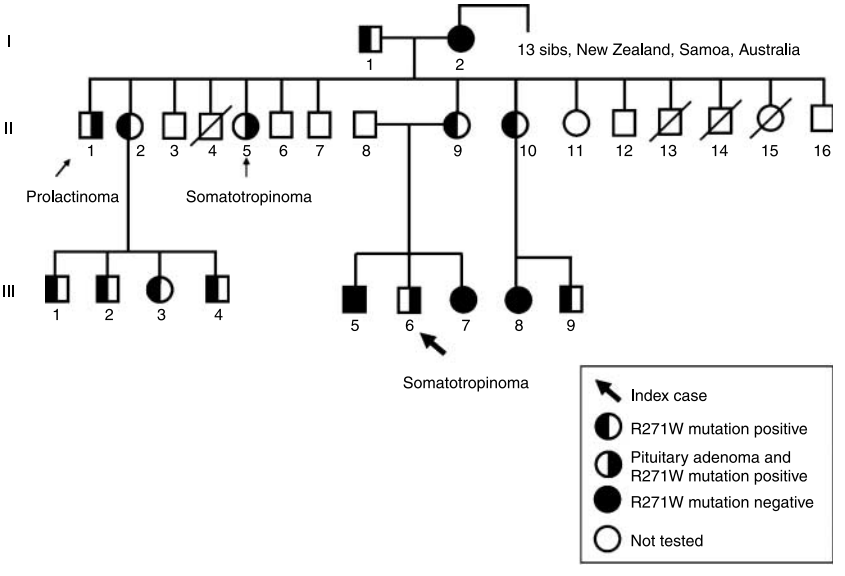

Figure 1 Genealogical tree of three generations of a Samoan FIPA kindred with an R271W AIP mutation.

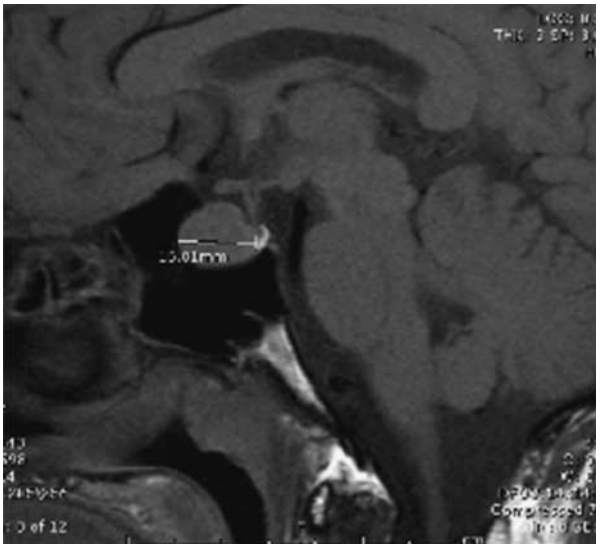

Figure 2 Sagittal MRI scan of patient III-6 demonstrating a large noninvasive pituitary macroadenoma.

and external beam pituitary radiotherapy was given in February–April 1989. No tumor regrowth occurred but panhypopituitarism subsequently developed. With hormonal replacement (including GH therapy), the patient reached a final height of 169 cm.

Case 3 (patient II-5)

The third patient, the maternal aunt of patient III-6 and sister of patient II-1, presented (in 1990) at 22 years of age with a 3-year history of amenorrhea, galactorrhea, and headaches. At the presentation, she had acromegalic features and a diagnosis of acromegaly was made based on an elevated IGF1 level of 240 μg/l (normal range on in-house RIA: 17–66 μg/l) and a plasma GH of 11 μg/l, which rose to >30 μg/l following an OGTT. In addition, she had an elevated PRL level of 981 mU/l (normal <600 mU/l) and multiple anterior pituitary hormonal deficiencies including ACTH deficiency, hypogonadotrophic hypogonadism, and secondary hypothyroidism. A 60 mm pituitary macroadenoma extending 50 mm above the pituitary fossa with frontal lobe distortion was found on CT imaging of the brain. She underwent craniotomy and partial tumor decompression in 1990, followed by external beam pituitary irradiation and medical therapy with bromocriptine for 2 years. She developed panhypopituitarism and required thyroxine, hydrocortisone, and estrogen replacement. At last follow-up aged 39 years, she had normal GH, IGF1, and PRL levels, indicating tumor remission.

Genetic analyses

Given the family occurrence of pituitary adenomas in this kindred, genetic screening was undertaken. MEN1 and CNC were outruled by clinical and genetic criteria. Sequencing of the *AIP* gene was then performed. The DNA was extracted from peripheral lymphocytes and analyzed for AIP mutations by direct sequencing, as previously described by Vierimaa *et al.* (8). The structure of the *AIP* gene was based on Ensembl sequences ENST00000279146 and ENSG00000110711.

DNA analysis in patient III-6 revealed a previously described R271W (c.811 C>T) *AIP* mutation. Based on this finding, a kindred analysis was undertaken. Following the provision of informed consent, 16 family members from three successive generations submitted blood for germline *AIP* analysis. The R271W mutation was also detected in affected patients II-1 and II-6. As expected, the mother of patient III-6, an obligate carrier, proved to be mutation positive. In addition, eight other family members were carriers of the R271W mutation. All carriers were entirely asymptomatic, and on further study with MRI of the pituitary gland in these subjects, no pituitary adenomas were identified. The R271W *AIP* mutation had been reported by Daly *et al.* previously in two European FIPA families (9). As there was no genealogical evidence of a known common ancestor among the Samoan and European kindreds, we undertook single nucleotide polymorphism (SNP) analysis of the members of identified FIPA R271W kindreds. SNP analysis excluded a common ancestry amongst the Polynesian and European kindreds. At rs2276020, a T/T genotype is not observed in Caucasian individuals. The members of the Samoan Australian/New Zealand kindred demonstrated this T/T genotype, while all members of the European kindreds had the C/C genotype.

Discussion

Pituitary adenomas occur infrequently in the pediatric/adolescent age group. Familial pituitary adenomas are also rare, accounting for only 3% of pituitary adenomas (6). Mutations in the *AIP* gene are associated with PAP and account for about 15% of FIPA kindreds (8, 9). Pituitary adenomas described to date in the setting of *AIP* mutations are most often somatotropinomas and prolactinomas; nonsecreting adenomas are increasingly reported, in addition to one case of Cushing's disease (8, 9, 12, 17). From individual studies and case reports, it appears that patients with *AIP* mutations tend to have larger tumors that occur at a younger age than is usual (16).

The cases described in the current report typify many aspects of the clinical phenotype in FIPA kindreds with *AIP* mutations. Patient III-6 and II-1 presented with pituitary adenomas at an early age with symptoms first occurring in early to mid adolescence, and in both cases, these tumors were macroadenomas. Despite the identical R271W mutation, the three patients in this kindred demonstrated phenotypic variability (somatotropinomas and a prolactinoma). Although both

patients III-6 and II-5 had somatotropinomas, in the former patient, the tumor was associated with incipient gigantism but no other hormonal abnormalities and typical acromegalic features were absent. In patient II-5, the tumor was very large and was associated with clinical acromegaly in addition to hyperprolactinemia and multiple pituitary hormonal deficits at baseline. These features serve to underline the variable phenotypes that can be associated with the same *AIP* mutation even within the same family.

The *AIP* gene is located on chromosome 11q13 (8) and encodes a protein of 330 amino acids. AIP is a ligand activated co-chaperone protein that forms a complex with the AhR in addition to two hsp90 molecules (18). AIP contains a number of conserved regions including three tetratricopeptide repeat sequences (TPR), the third of which is crucial for AhR signal transduction (19). Mutations within the third TPR domain abolish binding of AIP to hsp90 and reduce AhR binding by up to 80% (20). AhR, also known as the dioxin receptor, is widely accepted to mediate carcinogenic and toxic effects in animals and humans (21). By means of ligand activation, the AhR complex modulates gene transcription and is involved in cell programing, cell-cycle regulation through growth factor signaling and programed cell death (22). The precise role of *AIP* in pituitary tumorigenesis remains obscure at this time, and it is still uncertain whether tumorigenesis involves AhR-related pathways or other elements such as phosphodiesterase activity or newly reported interactions with RET–survivin (23, 24).

In 2006, Vierimaa *et al.* first identified a Q14X *AIP* mutation in the northern Finnish population, in which a founder effect for this mutation is clearly present (8). In the last 3 years, many more *AIP* mutations have been reported, some of which lead to protein truncation. Other missense mutations appear to target amino acid residues that are vital for correct protein function. The mutation detected in the current study, R271W, occurs within the sequence coding for the critically important third TPR domain. This mutation has been previously described in two European FIPA kindreds. The previously reported families were of a father and son, both with acromegaly (but not gigantism) and the other, a mother with a somatolactotrope tumor and a son with a GH-secreting tumor (9). Ancestral linkage between these European families and this family was excluded through *AIP* SNP haplotype analysis, highlighting the recurrent nature of the mutation and the likely functional importance of R271W as a mutational hotspot.

AIP mutations are found in 15% of FIPA kindreds (8, 9, 14), but as is the case with *MEN1* and *PRKAR1A* (a gene for CNC), *AIP* mutations play a minor role in the pathogenesis of unselected sporadic pituitary adenoma cases (10, 11, 13, 25, 26). However, few specific screening studies have been performed among the potentially at risk young population. Studies to date strongly suggest that somatotropinomas in the young (aged <25–30 years) are quite frequently associated with germline *AIP* mutations (27, 28). Larger studies in young populations with various pituitary tumor phenotypes are required to define precisely the more general association of young age at diagnosis and *AIP* mutation status.

AIP mutations are thought to confer a moderate to low penetrance disease. In our three-generational family, 12 members harbored a pathological *AIP* mutation and three of these had pituitary adenomas. It is common practice to define penetrance among adults, but seven carriers in our kindred remain under the age of 18. The penetrance of this pathological mutation is 37.5% if only those aged >18 years are considered; currently, 25% of all mutation carriers in this kindred have pituitary adenomas. This is similar to reported penetrance figures in other extensively studied kindreds (8, 14). For this reason, longitudinal data are needed on previously reported families with known *AIP* mutations in order to determine lifetime risks of developing pituitary adenomas. These data are a necessary element for accurate counseling of asymptomatic carriers in these families. In particular, children identified as carriers may have a lifelong increased risk of developing pituitary adenomas. The frequency and type of follow-up required have not been determined; however, current suggestions are for pituitary imaging at identification of carrier status and, thereafter, once yearly hormonal studies involving at least PRL and IGF1 (16). In the absence of symptoms or signs suggestive of hormonal or clinical abnormalities, very frequent pituitary MRI screening is probably not warranted. As for all familial screening for disease, the aim in the case of *AIP* mutation carriers is early diagnosis to lessen morbidity and facilitate early definitive treatment. Given the preponderance of somatotropinomas in pituitary adenoma patients with *AIP* mutations, the acknowledged increase in mortality associated with exposure to elevated GH and IGF1 levels means that close follow-up of mutation carriers could facilitate early diagnosis and curative treatment before major systemic pathological effects of acromegaly have manifested themselves (29).

In conclusion, this family highlights the importance of exploring the family history in young patients with pituitary adenomas and underlies the utility of considering *AIP* mutation status and screening in such young patients and their relatives.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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