Article

Loss of Heterozygosity in Chromosome 11q13 Covering *MEN1* and *AIP* Associates with Aggressive Features in Pituitary Tumors

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Abstract: Around 10% of pituitary tumors are estimated to be aggressive and associated with poor prognosis. Loss of heterozygosity (LOH) in chromosome 11q13 has been observed in aggressive pituitary tumors (APTs). Both *MEN1* and *AIP*, located on 11q13 with an interval of 2.7 Mb, have been discovered as genetic markers of APTs. We aimed to investigate whether 11q13 LOH covering *MEN1* and *AIP* in pituitary tumors associate with aggressiveness and the possible interactive mechanism of the two genes. A systematic case review was conducted to search for pituitary tumors with 11q13 LOH covering *MEN1* and *AIP*. Individual clinical data were extracted from articles meeting the selection criteria, including demographic information, genetic variations, tumor size, tumor type, aggressive features, therapy and prognoses. Bioinformatics analysis was applied to explore underlying pathogenic mechanisms. 11q13 LOH covering *MEN1* and *AIP* was reported in 16 pituitary tumor cases. Patients were aged 30 ± 10 years old with 10 males and 6 females. 75.00% had macroadenomas. There were 56.25% GH-, 12.50% ACTH-, and 31.25% GH-PRL-secreting tumors. 68.75% had features suggesting aggressiveness, including clinical invasiveness, post-operative persistence, recurrence, and metastasis. Concurrent dysfunction of *MEN1* and *AIP* possibly induced the tumorigenesis by strengthening the same pathogenesis pathway. 11q13 LOH covering *MEN1* and *AIP* in pituitary tumors relates to features suggestive of aggressiveness and poor outcome. Dual dysfunction of these two tumorigenesis genes could interact to exert pathogenic mechanisms. We were the first to propose that this concomitant mutation in pituitary tumors might be a unique genetic subtype.

Keywords: pituitary tumor; 11q13; loss of heterozygosity; *MEN1*; *AIP*; aggressive

1. Introduction

Pituitary neuroendocrine tumors are usually considered as benign (however sometimes malignant) adenomas originating from the pituitary anterior lobe [1]. It accounts for 15% of intracranial tumors [2]. However, around 10% surgical pituitary adenomas (PAs) are estimated to be aggressive [3] and related to poor prognosis. According to the European Society of Endocrinology (ESE) Clinical Practice Guidelines [4], the aggressive pituitary tumor (APT) is generally characterized by radiologically invasive, or rapid growth rate, or clinically recurrence after standard therapies. Unlike other malignancies, genetic detection has not been suggested as common practice in the evaluation of APT and pituitary carcinoma yet. Nevertheless, the proposal of subtype classified by genetic features was neither mentioned in 2022 World Health Organization Classification [5] nor supported by profound evidence [6]. As genetics has rapidly promoted the therapeutic intervention of neoplastic diseases in recent years, it is urgent to characterize pituitary tumor patients carrying specific genomic alterations, especially in APTs and carcinomas.

Among genes already known for pituitary tumorigenesis, *MEN1* and *AIP* have been found associated with aggressiveness [4]. Both genes are tumor suppressor genes of dominant inheritance. Interestingly, these two genes are closely located on chromosome 11q13, with an interval of about 2.7 mega-bases (Mb). Since pathogenic variations involving a fraction of chromosome is common in pituitary tumors [7], it is possible that *MEN1* and *AIP* mutate simultaneously due to the same chromosomal variation. Given that the loss of heterozygosity (LOH) in 11q13 has been observed in radiologically invasive PAs [8], it is likely that *MEN1* and *AIP* were both covered in 11q13 LOH and characterized with specific prognosis. Similar phenomenon has been reported in the hematology disease myelodysplastic syndrome (MDS) with isolated del(5q). This disease is normally caused by a 1.5-Mb deletion of chromosome 5 [9]. In this region, *RPS14* and *MIR145*/*MIR146A* alterations have been recognized as pathogenic element of erythropoiesis and megakaryocyte abnormalities [10]. These two genes are closely located on the chromosome and both causative to the dysfunctional or poorly formed blood cells in MDS.

Therefore, in this research, we aimed to explore for the first time whether 11q13 LOH covering *MEN1* and *AIP* in pituitary tumors associates features suggestive of aggressiveness. In conditions where experimental or observational studies are lacking [11–13], systematic case review could be performed to describe manifestations, novel genotype, diagnostic and therapeutic approaches, and outcomes. Since pituitary tumor cohorts with sequencing data were limited, we aimed to establish a case series of 11q13 LOH covering *MEN1* and *AIP* in pituitary tumors and investigate the underlying pathogenic mechanism by bioinformatics analysis. As the concomitant occurrence of key mutations were relatively common in tumors, we believe this study would be of significance in discovering the relationship of simultaneous genetic mutations and clinical outcomes, also improving precision medicine of pituitary tumors and other neoplasms with similar characteristics.

2. Methods

2.1. Searching Strategy

We searched for cases of pituitary tumor with 11q13 LOH covering *MEN1* and *AIP* in PubMed and Embase from inception to 15 July 2025. The searching strategy was pituitary AND ((11q13 OR 11q) OR (AIP AND MEN1)), in the title, abstract, keywords, or full text. An additional search of the Web of Science Core Collection, covering publications from 1 June 2024 to 15 July 2025, using the topic search: pituitary* AND ((11q13 OR 11q) OR (AIP AND MEN1)). The full text of all literature in the searching result was accessed. If the full text was not reachable in any electronic source, the title and abstract were carefully inspected. Review articles were also read through to extract cases summarized. No restriction was set on language.

2.2. Selection Criteria

All articles were screened for eligible cases based on the predefined inclusion and exclusion criteria as follows. Inclusion criteria: (a) the patient was diagnosed with pituitary tumor, including isolated PA or clinical syndrome involving pituitary; (b) the case had complete reports of diagnosis, therapy, outcome and prognosis; (c) the molecular genetic analysis of resected pituitary tumor suggested 11q13 LOH covering both *MEN1* and *AIP*; (d) the pituitary tumor might carry other mutations of *MEN1* or *AIP*, including single nucleotide variations (SNVs), insertion/deletions (indels), copy number variations (CNVs), etc. Exclusion criteria: (a) the clinical records were not clearly reported; (b) the variant form was not explicitly described or was likely benign; (c) the patient carried mutations of other gene that possibly lead to aggressive pituitary, including *GNAS*, *USP8*, *IDH1*, *PI3KCA*, *HMGA2*, *TP53*, *CDKN1B*, *CDKN1A*, *CDKN2B*, and *CDKN2C* [1,4,5,14,15].

2.3. Data Extraction and Quality Assessment

For each included case, a standard data extraction form was used to extract patient information as follows: age, sex, race, diagnosis, pituitary hormone excretion, pituitary imaging (tumor size, Knosp Grading, aggressive signs), pathology (tissue type, immunohistochemistry, proliferation markers), gene sequencing result (11q13 region, *MEN1*, *AIP*), therapy (drug, radiotherapy, surgery), and outcome (remission, post-operative persistence, recurrence, metastasis, death). According to the ESE Clinical Practice Guidelines of APT [4], cases with features suggestive of aggressiveness were defined as those had radiologically invasive pituitary tumors, post-operative persistence, recurrence, and metastasis; cases with features suggestive of non-aggressiveness were defined as those had non-invasive and non-proliferative pituitary tumors and clinical remission. As shown in Table S1, quality assessment was performed with the Joanna Briggs Institute (JBI) critical appraisal tool for case series [12].

Literature search, review, data extraction, and risk assessment were performed by SC and JQ independently. Uncertainties were resolved by consulting a third investigator (HZ) for arbitration.

2.4. Data Synthesis and Statistical Analysis

Individual clinical data were collected in a spread sheet and unified in a standard format. Mean age was calculated and reported as mean ± standard deviation. Number of patients in each subcategory were counted and calculated for proportion in the total. Microsoft Excel and R studio (version 4.0.0) software were used in statistical analysis.

To evaluate whether the proportion of APTs in this cohort was elevated compared to other reported pituitary tumor populations, we conducted pairwise comparisons using Fisher's exact test. Publicly available cohorts including *MEN1*-mutated tumors [16], non-*MEN1*-mutated tumors [16], *AIP*-mutated pituitary tumors [17], and non-*AIP*-mutated tumors [17] were used as comparators. The *MEN*1-mutated and *AIP*-mutated reference cohorts were derived from two independent published studies. For each comparison, a 2 × 2 contingency table was constructed to compare the proportion of APTs and non-APTs between this cohort of cases with 11q13 LOH encompassing both *MEN1* and *AIP* and each reference group. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the magnitude of association. $P < 0.05$ was considered statistically significant. All analyses were performed in R (version 4.3.1).

2.5. Bioinformatics Analysis

Genes located in 11q13 region other than *MEN1* and *AIP* were screened for associations with pituitary aggressiveness. Protein-protein interaction (PPI) network was acquired from the STRING (v11.5) database (http://string-db.org, based on the database release available at the time of analysis) [18]. The minimum required interaction score was set at medium confidence (0.400). Biological associations with experimental evidence were searched in literature reports collected by PubMed. Gene expression in human normal tissues was performed with the web server GTExPortal (http://gtexportal.org/home/, accessed on 27 August 2026). The gene ontology (GO) enrichment analysis was conducted with the R studio (version 4.0.0) and R package clusterProfiler [19] to reveal pathways involved in pituitary tumorigenesis. Homo sapiens was selected as the species in all the analyses. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Searching Result

In the electronic literature research, 458 publications were retrieved after deduplication and replenishment. After screening the full texts (or title & abstract if the full text was not accessible), 13 publications [20–32] involving 16 cases were included according to the predefined criteria (Figure 1). Individual clinical data of the 16 patients was extracted as shown Table 1. Clinical features and prognoses were summarized as shown in Table 2.

3.2. Pituitary Tumors with 11q13 LOH Covering MEN1 and AIP

In the series, 56.25% (9/16) of patients carried additional mutations of *MEN1* and *AIP*, including missense mutation, nonsense mutation, deletion, and frameshift mutation. The age of these patients was 30 ± 10 years old on average. There were 10 males and 6 females. The ethnicities included Italian, British, Japanese, Chinese, Korean, Mexican, Brazilian, etc. The diagnoses were sporadic pituitary adenoma (SPA), familial isolated pituitary adenoma (FIPA), and *MEN1*. 75.00% (12/16) cases had macroadenoma and 6.25% (1/16) microadenomas. In addition to 9 somatotropinomas and 2 adrenocorticotropinomas, 5 patients had mixed growth hormone (GH)-prolactin (PRL)-secreting tumors.

68.75% (11/16) of patients had features suggestive of aggressiveness, including 6 (37.50%) with radiological invasive tumors, 2 (12.50%) with post-operative persistence, 2 (12.50%) with recurrence, and 1 (6.25%) with metastases. All these patients underwent surgery, including transsphenoidal surgery (TSS), hypophysectomy, and craniotomy resection. Radiotherapy and expanded surgery were applied for perioperative persistence or recurrence tumors. 31.25% (5/16) patients had non-aggressive features, including 3 (18.75%) had non-invasive and non-proliferative tumors and 2 (12.50%) recovered with no relapse. Among these patients, 4 were operated with TSS, and the other patient's treatment was unknown.

As shown in Table 3, the proportion of APTs in our cohort was 68.75% (11/16), higher than that observed in all reference cohorts. Compared to *MEN1*-mutated pituitary tumors, our cohort exhibited a significantly increased frequency of APTs (OR = 4.84, 95% CI: 1.33–17.67, $p = 0.0291$). A similar trend was observed in comparison with *AIP*-mutated tumors (OR = 2.14, 95% CI: 0.68–6.76), although the difference did not reach statistical significance ($p = 0.2700$). Notably, the APT rate in our cohort was substantially higher than in non-*MEN1*-mutated tumors (OR = 13.42, 95% CI: 4.36–41.35, $p < 0.0010$) and non-*AIP*-mutated pituitary tumors (OR = 3.47, 95% CI: 1.17–10.32, $p = 0.0322$). These findings suggest a potential enrichment of aggressive clinical behavior associated with 11q13 loss.

Table 1. Case Review of Pituitary Tumors with 11q13 LOH covering *MEN1* and *AIP*.

Source	Age [a]	Sex	Ethnicity	Diagnosis	*MEN1* [b]	*AIP* [b]	Tumor Size	Tumor Type [c]	Invasion	Proliferation	Therapy	Outcome	Prognosis
1, Iwata, 2014 [20]	16	F	Japanese	FIPA	LOH	Nonsense (Q315X), LOH	Macro	Two tumors: GH, mixed PRL/GH	Suprasellar extension	Ki-67: 1.5%/3.5%	TSS	Remission	Satisfactory
2, Cai, 2013 [21]	35	M	Chinese	SPA	LOH	Missense (D262N), LOH	Macro	GH	Non-invasive	Ki-67: 2%	NM	NM	Satisfactory
3, Cai, 2013 [21]	30	M	Chinese	SPA	LOH	Missense (G326R), LOH	Macro	GH, PRL	Suprasellar cisterna and cavernous sinus invasion	Ki-67: 4%, p53 overexpression (IHC-positive)	Octreotide, surgery	Recurrence	Adverse
4, Guaraldi, 2012 [22]	46	F	Caucasian	FIPA	LOH	Nonsense (R81X), LOH	Macro	GH	NM	NM	TSS → repeat expanded TSS	Recurrence	Adverse
5, Occhi, 2010 [23]	32	M	Italian	FIPA	LOH *	Nonsense (R304X), LOH *	Macro	GH, PRL	NM	NM	Octreotide, cabergoline → TSS → pegvisomant	Post-operative persistence	Adverse
6, Iwata, 2007 and Yamada, 1997 [24,30]	26	M	Japanese	FIPA	LOH	Frameshift (Val96fs), LOH	Macro	GH	Cavernous sinus invasion	NM	TSS	NM	Adverse
7, Iwata, 2007 and Yamada, 1997 [24,30]	22	M	Japanese	FIPA	c.1682delA, LOH	Frameshift (Val96fs), LOH	Micro (two)	Two tumors: GH, mixed PRL/GH	NM	NM	TSS	NM	Satisfactory
8, Nam, 2001 [25]	43	F	Korean	SPA	LOH *	LOH *	Macro	ACTH	Hardy Class: Grade 4, Stage E (cavernous sinus invasion)	p53 wild type (no mutation detected)	Surgery	NM	Adverse
9, Gadelha, 1999 [26]	23	M	Mexican	FIPA	LOH *	LOH *	Macro	GH	Suprasellar extension	NM	Craniotomy resection, TSS	NM	Adverse
10, Gadelha, 1999 [26]	21	M	Mexican	FIPA	LOH *	LOH *	Macro	GH	Suprasellar extension	NM	TSS, pituitary irradiation	NM	Adverse
11, Gadelha, 1999 [26]	29	M	Brazilian	FIPA	LOH *	LOH *	NM	GH	NM	NM	Frontal craniotomies, radiotherapy	Post-operative persistence	Adverse

Table 1. *Cont.*

Source	Age [a]	Sex	Ethnicity	Diagnosis	*MEN1* [b]	*AIP* [b]	Tumor Size	Tumor Type [c]	Invasion	Proliferation	Therapy	Outcome	Prognosis
12, Gadelha, 1999 [26]	24	F	Brazilian	FIPA	LOH *	LOH *	Macro	GH	Infra- and suprasellar extensions	NM	TSS, radiotherapy	NM	Adverse
13, Gadelha, 1999 [26]	15	F	Brazilian	FIPA	LOH *	LOH *	Macro	GH	Suprasellar expansion	NM	TSS, radiotherapy	NM	Adverse
14, Tanaka, 1998 and Shintani, 1995 [27,31]	43	M	Japanese	*MEN1*	Frameshift, LOH *	LOH *	NM	Two tumors: GH, null cell adenoma	Remarkable enlargement with heterogeneous intensity	NM	TSS	Satisfactory	Satisfactory
15, Tanaka, 1998 and Yoshimoto, 1997 [28,29]	45	F	Japanese	SPA	Nonsense, LOH *	LOH *	NM	GH, PRL	Hardy's classification I-0	NM	TSS	NM	Satisfactory
16, Bates, 1995 [32]	30	M	British	SPA	LOH *	LOH *	Macro	Nonfunctional → ACTH	Metastasis	p53 overexpression (IHC-positive)	Hypophysectomy, radiotherapy	Metastasis, death	Adverse

Abbreviations: NM = not mentioned; F, female; M, male; SPA, sporadic pituitary adenoma; FIPA, familial isolated pituitary adenoma; MEN1, multiple endocrine neoplasia 1 syndrome 1; LOH, loss of heterozygosity; micro, microadenoma; macro, macroadenoma; PRL, prolactin; GH, growth hormone; ACTH, adrenocorticotrophic hormone; TSS, transsphenoidal surgery; IHC, immunohistochemistry. Note: [a] Age (years) at reported; [b] *MEN1* and *AIP* mutation of the case. [c] Confirmed by clinical endocrine tests or immunohistochemistry. "/" indicates double tumor with different compositions. "→" indicates secreting function change in recurrence. * Putative from LOH marker spanning the genomic region of *MEN1* and *AIP* on Chr11. Descriptions in the "Invasion" column are reported as originally described in the source publications.

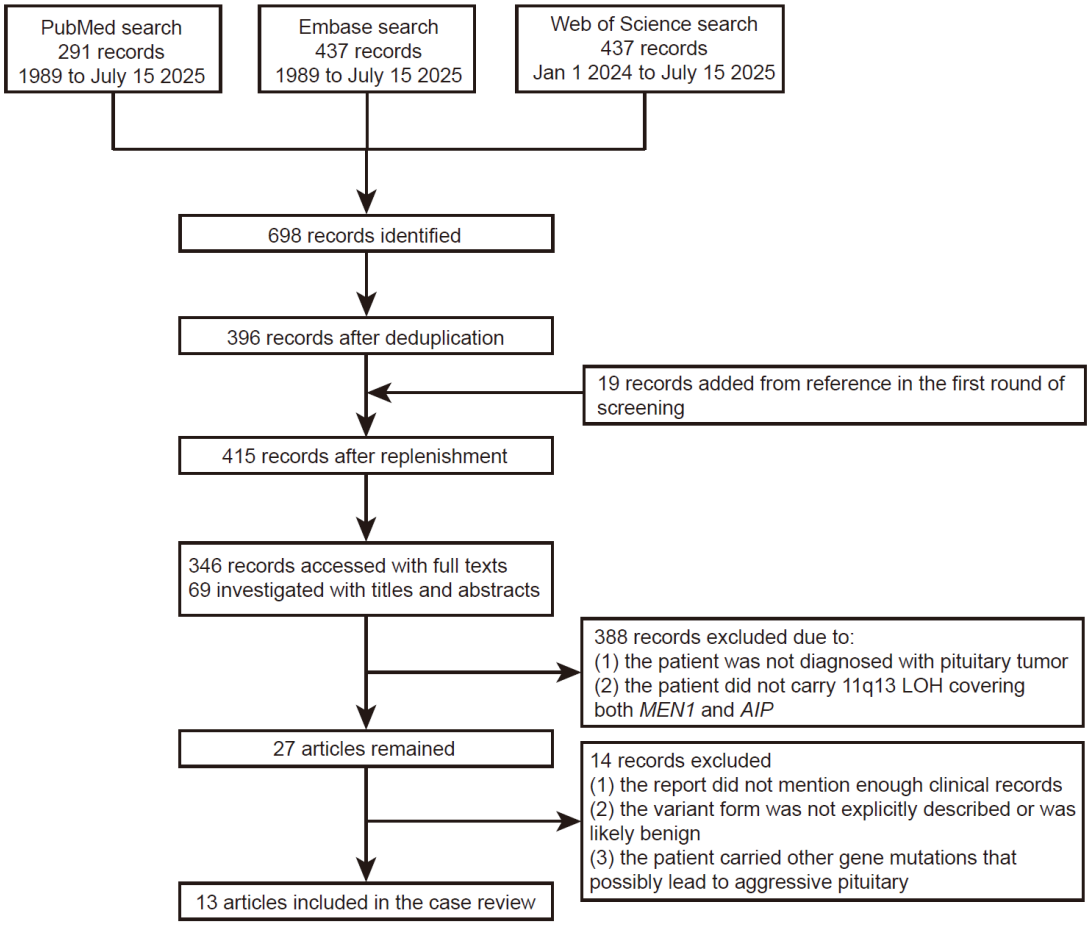

Figure 1. Flowchart of literature research.

Table 2. Clinical Features and Prognoses of the Pituitary Tumor Patients with 11q13 LOH Covering *MEN1* and *AIP*.

	Number of Patients	Percentage (%)
Age (years), mean ± standard deviation	30 ± 10	NA
Sex		
Male	10	62.50
Female	6	37.50
Diagnosis		
Sporadic pituitary adenoma	5	31.25
Familial isolated pituitary adenoma	10	62.50
MEN1 syndrome	1	6.25
Tumor Size		
Macroadenoma	12	75.00
Microadenoma	1	6.25
Not mentioned	3	18.75
Tumor Type		
GH	9	56.25
ACTH	2	12.50
GH-PRL	5	31.25
Aggressive Feature		
Aggressive		
Radiologically invasive	6	37.50
Post-operative persistence	2	12.50
Recurrence	2	12.50
Metastasis	1	6.25
Not Aggressive		
Non-invasive and non-proliferative	3	18.75
Clinical remission	2	12.50

Abbreviations: LOH, loss of heterozygosity; GH, growth hormone; ACTH, adrenocorticotropic hormone; PRL, prolactin. Note: Each patient was counted once according to the primary aggressive clinical feature.

Table 3. Comparison of our cohort to the reference group.

Cohort	Total	APT	Non-APT	Ratio (%)	OR (95% CI)	*p*-Value
11q13 LOH cohort	16	11	5	68.75	NA	NA
MEN1-mutated	32	10	22	31.3	0.0291	4.84 [1.33, 17.67]
Non-*MEN1*-mutated	213	30	183	14.0	<0.0010	13.42 [4.36, 41.35]
AIP-mutated	75	38	37	50.7	0.2700	2.14 [0.68, 6.76]
Non-*AIP*-mutated	232	90	142	38.8	0.0322	3.47 [1.17, 10.32]

3.3. Underlying Biological Interaction of MEN1 and AIP

None of the other genes located in 11q13 region were associated with pituitary aggressiveness. The PPI network of menin (encoded by *MEN1*) and aryl hydrocarbon receptor-interacting protein (*AIP*) (encoded by *AIP*) was revealed (Supplementary Figure S1). Among proteins that interact with menin or *AIP* alone, few was reported to associate with *MEN1* and *AIP* simultaneously. Then we searched PubMed for more evidence in literature. It turned out that LOH of *MEN1* and *AIP* could induce hibernoma by firstly interacting with peroxisome proliferator-activated receptor (PPAR)-α (encoded by *PPARA*) and PPAR-γ (encoded by *PPARG*). Then the latter two proteins function, probably by interacting with PPAR-γ coactivator 1-α (encoded by *PPARGC1A*), to promote the expression of uncoupling protein 1 (UCP1), which is pivotal to the development of hibernoma [33] (Figure 2a).

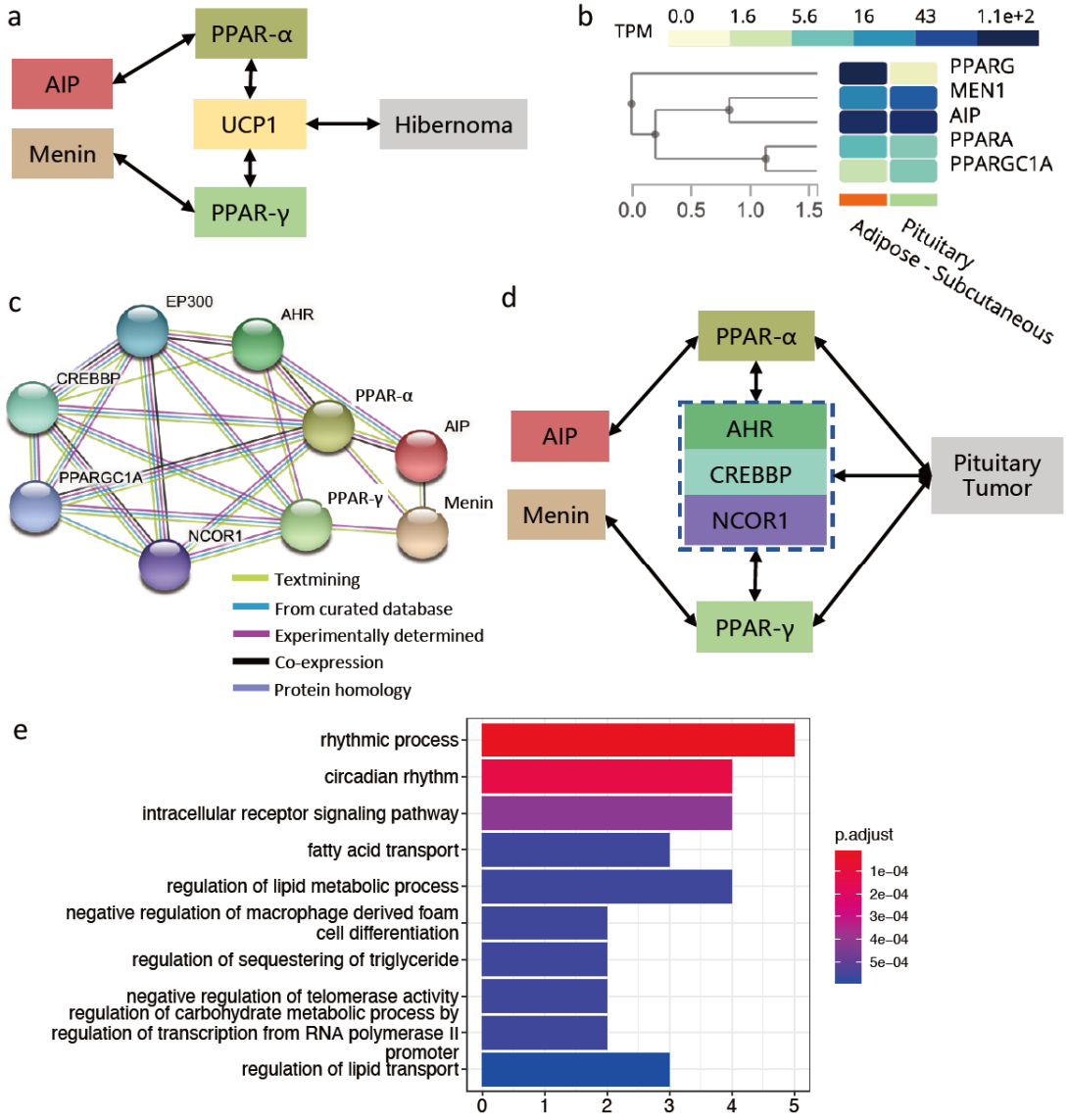

Figure 2. Underlying biological interaction of *MEN1* and *AIP*. (**a**). Tumorigenesis mechanism of *MEN1* and *AIP* in hibernoma. (**b**). Expression of *MEN1*, *AIP*, *PPARA*, *PPARG*, and *PPARGC1A* in normal subcutaneous adipose tissue and pituitary. (**c**). Protein-protein interaction of menin, *AIP*, PPAR-α, PPAR-γ. (**d**). Putative tumorigenesis mechanism of *MEN1* and *AIP* in the pituitary tumor. (**e**). Gene ontology enrichment of involved proteins.

In the pituitary, the expression pattern of *MEN1*, *AIP*, *PPARA*, *PPARG* and *PPARGC1A* were similar to that of adipose tissue (Figure 2b). In the PPI network of menin, *AIP*, PPAR-α, and PPAR-γ, proteins encoded by *AHR*, *EP300*, *CREBBP*, *PPARGC1A*, and *NCOR1* are simultaneously linked to PPAR-α and PPAR-γ (Figure 2c). Among these, AHR, CREBBP, and NCOR1 have been previously reported to play roles in PAs, suggesting they may act as functional mediators within a shared signaling axis, analogous to the role of UCP1 in hibernoma.

Based on these findings, we propose a putative model in which *MEN1* and *AIP* converge functionally through the PPAR signaling network (Figure 2d). Dysregulation of PPAR signaling may represent a converging mechanism by which *MEN1* and *AIP* mutations contribute to pituitary tumorigenesis, characterized by menin loss–induced PPAR-γ activation and *AIP* deficiency–associated PPAR-α suppression. Enrichment analysis revealed that several molecular pathways are commonly associated with *MEN1*, *AIP*, *PPARA*, *PPARG*, *AHR*, *CREBBP*, and *NCOR1* (Figure 2e), supporting the existence of a complex, fine-tuned regulatory network potentially contributing to pituitary tumorigenesis.

4. Discussion

In this research, we generated main findings as follows: (a) 11q13 LOH covering closely located genes *MEN1* and *AIP* in pituitary tumors had features suggestive of aggressiveness and adverse prognoses; (b) Since other genes in 11q13 were found unassociated with pituitary aggressiveness, a putative mechanism was raised that *MEN1* and *AIP* might be key mutations in 11q13 LOH to induce pituitary tumorigenesis in an interactive network.

The systematic case review was composed of 16 patients carrying pituitary tumors with 11q13 LOH covering *MEN1* and *AIP*. Though these two tumor suppressor genes have been elucidated associated with pituitary aggressiveness respectively before [4], this was the first time the joint variation has been discussed. LOH in the region of tumor suppressor genes has been frequently observed and contribute to uncontrollable cell divisions in a variety of cancer types. The closely located *MEN1* and *AIP* enable 11q13 LOH causing dual dysfunction to prevent abnormal divisions in pituitary cells, making it a specific genetic variation.

In the case series, the genetic background may account for the distinctive clinical profiles observed. Contrasting with the reported mean age of pituitary adenomas (~51 years) [34], patients harboring the concomitant genetic marker tended to be younger around 30 years old. This discrepancy may be explained by the high proportion of tumors associated with FIPA or *MEN1*, both hereditary conditions that typically present earlier. Differing from the known epidemiology in which prolactinomas are approximately four times more common than somatotropinomash [35], few prolactinomas were identified in this cohort. Compared with typical pituitary adenomas, the proportion of aggressive tumors appeared higher, exceeding what has been reported for *MEN1*-related tumors or adenomas carrying only an *AIP* mutation. These contrasts highlight that tumors harboring simultaneous *MEN1* and *AIP* mutations may represent a distinct genetic subgroup with unique clinical behavior.

From a mechanistic perspective, both *MEN1* and *AIP* participate in multiple biological pathways [36,37], but their respective contributions to pituitary tumorigenesis remain unclear. Evidence from hibernoma suggests that concomitant loss of *MEN1* and *AIP* may act synergistically [33]: menin normally coactivates PPAR-γ–mediated transcription [38], while AIP represses PPAR-α [39]. When both are absent, PPAR-α and PPAR-γ signaling is enhanced, leading to upregulation of UCP1 and promoting tumor development [33,40]. A similar mechanism may also occur in the pituitary gland. Both PPAR-α and PPAR-γ have been implicated in pituitary tumor biology. PPAR-α is involved in regulating somatotropinomas and is enriched in prolactinomas and NFPAs [41], while PPAR-γ shows altered expression across several adenoma subtypes compared with normal pituitary tissue [42,43]. These factors may further interact with proteins such as AHR [44], CREBBP [45], and NCOR1 [46], which are linked to tumorigenesis or malignant progression.

Given that *MEN1* and *AIP* are located close together on chromosome 11q13, loss of heterozygosity in this region could simultaneously affect both genes, potentially explaining the aggressive features and adverse prognosis observed in patients carrying these variations. Based on these findings, we propose a novel subtype, termed ‘UNION’, referring to pituitary tumors with 11q13 LOH encompassing both *MEN1* and *AIP*. Identifying such a subtype may improve risk stratification and guide therapeutic decision-making. As seen in other cancers—such as gliomas with 1p/19q deletion that benefit from combined chemotherapy and radiotherapy —molecular subtyping can inform tailored treatment [47]. For UNION tumors, multidisciplinary strategies including repeat surgery, radiotherapy, antisecretory agents, temozolomide, peptide receptor radionuclide therapy, and molecularly targeted approaches may be considered to optimize outcomes [1].

Though in this research we proposed several practical insights, there are some limitations to mention. First, though we reached all accessible resources to perform a systematic case review using proposed critical appraisal, there might still be unreported or missed cases. Second, we excluded cases with incomplete reports and ambiguous

description. Eligible cases might have been excluded, but on the other hand we ensure the quality of every case included into this review. Third, our study is limited by the small sample size and retrospective design. Ideally, a case-control study with matched genetic and clinical data would be preferable; however, such comprehensive pituitary tumor cohorts, especially for aggressive cases, are currently lacking. Existing pituitary tumor database is insufficient to support large-scale genetics analyses and accurate evaluation of aggressiveness. Despite these limitations, comparison with larger published cohorts shows that the APT rate in our cohort is substantially higher than in *MEN1*-mutated, *AIP*-mutated, and non-*MEN1*/non-*AIP* controls. Because comprehensive screening for both genes was not available in the original cohort, complete mutual exclusivity between the two reference cohorts could not be confirmed. Nevertheless, this suggests that the observed enrichment of aggressive behavior related to 11q13 loss is likely a true biological signal rather than a sampling bias. This study lays background and foundation for clinical trials in the future to identify the clinical characteristics and observe the prognosis of patients with 11q13 LOH covering *MEN1* and *AIP*.

5. Conclusions

In summary, since APTs are accompanied by invasion, rapid growth and recurrence, there is a need of precise subtyping diagnosis for personalized treatment to achieve better prognosis. We were the first to propose that 11q13 LOH covering the closely located *MEN1* and *AIP* could be a possible genetic subtype of pituitary tumor carrying features suggestive of aggressiveness and poor outcome. Dual dysfunction of these two tumor suppressor genes with an interval of 2.7 Mb might interact to exert pathogenic mechanisms. We believe our study will be helpful in expanding the knowledge of pituitary tumorigenesis, and providing practical benefits for patients with such genetic markers in terms of more active therapy.

Supplementary Materials: The following supporting information can be downloaded at: https://media.sciltp.com/files/content/11q13-SupplementaryMaterial1.docx. Figure S1: Protein–protein interaction network of MEN1 and AIP; Table S1: Quality Assessment using the Joanna Briggs Institute (JBI) Critical Appraisal Tool.

Author Contributions: J.Q., S.C., H.P. and H.Z. conceived and designed the study. J.Q. and S.C. collected and analyzed the data of case review. J.Q. performed the bioinformatics analysis. S.C., L.L., Y.Y., H.D., L.D. and S.J. interpreted clinical relevance. J.Q., S.C., H.P. and H.Z. drafted the manuscript. All authors revised and approved the final version of the manuscript. All authors had full access to all the data in the study. H.P. and H.Z. accessed and verified the underlying data and had final responsibility for the decision to submit for publication. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: An ethics statement is not applicable because this study is based exclusively on published literature.

Informed Consent Statement: Patient consent was waived because the data were retrieved from a review of publicly available literature.

Data Availability Statement: All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies: No AI tools were utilized for this paper.

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