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# Secondary Findings in Turkish Pituitary Neuroendocrine Patients

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**ABSTRACT**

**Objective:** A secondary finding (SF) is characterized as a genetic variant that could have medical significance but is not connected to the primary purpose of the testing. SFs were published in various communities with diverse ethnic backgrounds, however, there is limited data for patient groups with specific clinical conditions.

**Methods:** A total of 46 PitNETs patients were included in this study. The 81 genes recommended by the latest ACMG SF guideline (v3.2) were screened in 46 Turkish pituitary neuroendocrine tumor (PitNET) patients.

**Results:** For the NGS study, ''The TrueSight One Expanded'' sequencing kit containing 6.704 genes (including all ACMG SF v3.2 genes) was used, and sequencing was performed using the Illumina Nextseq 550 platform. In the 81 genes included in ACMG v3.2, a total of 9.430 variants were detected in 46 patients. After filtration steps, in 3 (6.5%) patients, a total of 4 different pathogenic variants were detected in *LMNA, APOB, RYR2*, and *TTN* genes. The heterozygous c.5464del (p.Ile1822Serfs*8) variant in the *RYR2* gene was novel. Additionally, in 11 patients (23.9%), a total of 13 heterozygous known variants were detected in 5 different genes (*BTD, HFE, GAA, MUTYH*, and *ATP7B*) associated with autosomal recessive diseases.

**Conclusion:** The limited knowledge about the genetic etiology of PitNETs makes it inevitable that studies conducted in this field will contribute to shedding light on the etiology. This study, being the first investigation of SFs in PitNET patients, will make a valuable contribution to the literature..

**Keywords:** Pituitary neuroendocrine tumors, secondary finding, next-generation sequencing, american college of medical genetics and genomics

## 1. INTRODUCTION

Pituitary neuroendocrine tumors (PitNETs, previously known as pituitary adenomas), are tumors that result from abnormal cell growth in the pituitary gland (1). These tumors can affect the function of the pituitary gland and can lead to various hormonal disorders. While most PitNETs are sporadic and not associated with a known genetic cause, there are certain genetic syndromes and familial cases where genetic factors are implicated. In the literature, the most commonly detected variants in cases of PitNETs are found in the *AIP* and *MEN1* genes. Besides these genes, *CDKN1B*, *PRKAR1A*, *DICER1*, *TSC1*, *TSC2*, and *SDHx* genes also play a role in the etiology of PitNETs, although the genetic etiology can be elucidated in only about 5% of cases (2).

With the widespread use of next-generation sequencing (NGS) technologies, it has become possible to sequence many genes simultaneously. This provides a significant advantage, particularly in cases with genetic heterogeneity, by offering speed and convenience in elucidating the molecular etiology. With NGS, pathogenic variants in genes that may not be directly related to the patient's clinical presentation can be detected. This can create an ethical dilemma regarding whether or not to report these variants to the patient. American College of Medical Genetics and Genomics (ACMG) published recommendations in 2013 on these incidental findings (3). These recommendations focused on reporting pathogenic variants in 56 specific genes, irrespective of the patient's clinical presentation. After several versions and the decision to refer to these findings as secondary findings (SFs), the final version (v3.2) was published in 2023, including




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the addition of *CALM1*, *CALM2*, and *CALM3* genes, bringing the total number of genes to 81 (4).

SFs had been studied in many ethnic groups (5, 6, 7, 8, 9, 10). However, investigating SFs in specific medical conditions where the genetic etiology is not fully understood, such as PitNETs, can indeed provide valuable insights into the genetic mechanisms underlying these conditions. Additionally, it could help identify patients who may be at risk for other diseases or conditions, allowing for early intervention and treatment.

Aim of the study is to analyze SFs in Turkish PitNET patients. This is the first report that investigates SFs in patients diagnosed with PitNET.

## 2. METHODS

### *2.1. Study participants*

Written informed consent was obtained from all patients. For pediatric patients, consent was obtained from their parents. The study was approved by the Ethics Committee of Marmara University (Approval number:09.2022.113).

A total of 46 patients were included in this study. The ages of the cases ranged from 13 to 72, with a mean age of 40 years. Four patients were diagnosed under the age of 18. Of the 46 patients included in this study, 25 were male (54.4%), and 21 were female (45.6%). Only one patient had a positive family history for PitNET. All patients had macroadenoma. The demographic characteristics of the patients are summarized in the Table 1.

### *2.2. Molecular studies*

Whole blood samples were collected from the patients. For DNA isolation, the "Lab-Aid 824 DNA Isolation Kit" (Xiamen Zeesan Biotech Co., Ltd., P.R. China) and the "Lab-Aid 824s Nucleic Acid Isolation Device" (Xiamen Zeesan Biotech Co., Ltd., P.R. China) were used. The purity and concentrations of DNA samples were measured using the Qubit 3.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA). DNA samples that met the purity criteria and had an initial concentration of at least 100 ng in 15 µL were included in the study.

For the NGS study, ''The TrueSight One Expanded'' sequencing kit (Illumina, San Diego, CA, USA) containing 6.704 genes (including ACMG SF v3.2 genes) was used, and sequencing was performed using the Illumina Nextseq 550 platform (San Diego, CA, USA). The analysis of variants was performed using the Sophia DDM® v4 platform (Sophia Genetics, SA, Switzerland). Variants were aligned to the human reference genome, hg19. All variants reported as pathogenic and/or likely pathogenic in ClinVar, as well as variants not reported in ClinVar with a minor allele frequency of <0.1% and classified as pathogenic and/or likely pathogenic according to ACMG criteria (11), were documented. The Varsome (12) and Franklin (Genoox Ltd, Tel Aviv, Israel) were used to assess the pathogenicity of novel variants according to ACMG criteria.

## 3. RESULTS

In the 81 genes included in ACMG v3.2, a total of 9.430 variants were detected in all 46 patients. Four of these variants were pathogenic/likely pathogenic variants associated with autosomal dominant inherited disease that the ACMG SF guideline recommends reporting. The rate of identifying SFs in the patients was 6.5% (3/46). Two patients were male and one patient was female. No SF was detected in the pediatric age group of 4 patients. In total, pathogenic variants were detected in *APOB*, *RYR2*, *LMNA*, and *TTN* genes (Table 2). Pathogenic variants were detected in two different genes (*RYR2* and *APOB*) in one patient. All detected variants were in the heterozygous state. Out of the 4 variants, 3 had been previously described variants, while one was a novel variant (c.5464del, p.Ile1822Serfs*8 variant in the *RYR2* gene). There were no common pathogenic variants identified among different patients. Of the identified pathogenic variants, 50% were missense variants, and the remaining 50% were truncating variants. The variant identified in the *LMNA* gene (c.1633C>T, p.Arg545Cys) was submitted to ClinVar once as a pathogenic variant and ten times as a variant of unknown clinical significance (VUS). The variant was evaluated as likely pathogenic based on the comprehensive study by Kandert et al., in 2009 (13) and the pathogenicity classifications in Varsome and Franklin. In one patient, heterozygous known c.1102_1104del (p.Glu368del) pathogenic variant in the *MEN1* gene was detected. Even though the *MEN1* gene is included in ACMG SF v3.2, it was considered a primary finding because it explained the patient's clinical presentation.

In 11 patients (23.9%), 13 heterozygous variants were detected in genes associated with autosomal recessive diseases. In one patient, heterozygous variants were detected in both the *MUTYH* and *BTD* genes, while in another patient, heterozygous variants were found in both the *ATP7B* and *BTD* genes. The variants were detected in the following genes; *BTD* (7/13, 53.8%), *MUTYH* (2/13, 15.3%), *ATP7B* (2/13, 15.3%) *HFE* (1/13, 7.6%), and *GAA* (1/13, 7.6%) (Table 3). Apart from the c.1330G>C variant detected in four different patients and the c.1595C>T variant found in three different patients in the *BTD* gene (NM_000060), no other common variants were observed in the patients. Overall, 8 different variants were detected in genes associated with autosomal recessive diseases. Two truncating variants were detected in the *MUTYH* and *ATP7B* genes, one inframe insertion was found in the *MUTYH* gene, and five missense variants were identified in the *BTD*, *GAA*, *ATP7B*, and *HFE* genes. All variants were known as pathogenic and/or likely pathogenic. None of the 3 patients who had pathogenic variants in genes associated with autosomal dominant diseases were carriers of autosomal recessive diseases.

***Table 1.*** *The demographic characteristics of the patients and detected variants in the patients*

| Patient no. | Age | Gender | Age at Diagnosis | Family history of pituitary adenoma | PitNET subtype | Variant detected in the patient |
|---|---|---|---|---|---|---|
| 1 | 17 | Male | 11 | - | Somatotroph | - |
| 2 | 44 | Male | 42 | - | Somatotroph | - |
| 3 | 54 | Male | 32 | + | Somatotroph | - |
| 4 | 43 | Female | 41 | - | Gonadotroph | - |
| 5 | 50 | Female | 49 | - | Somatotroph | *TTN* heterozygous c.69415C>T p.Arg23139* |
| 6 | 57 | Female | 55 | - | Gonadotroph | 1-*MUTYH* heterozygous c.411_416dup p.Trp138_Met139insIleTrp<br>2 – *BTD* heterozygous c.1330G>C p.Asp444His |
| 7 | 63 | Male | 60 | - | Corticotroph | - |
| 8 | 49 | Female | 47 | - | Gonadotroph | 1-*ATP7B* heterozygous c.3583G>A p.Ala1195Thr 2-*BTD* heterozygous c.1330G>C p.Asp444His |
| 9 | 29 | Male | 27 | - | Prolactinoma | - |
| 10 | 30 | Male | 29 | - | Prolactinoma | *LMNA* heterozygous c.1633C>T p.Arg545Cys |
| 11 | 66 | Female | 65 | - | Corticotroph | - |
| 12 | 36 | Female | 35 | - | Gonadotroph | - |
| 13 | 41 | Female | 37 | - | Corticotroph | - |
| 14 | 38 | Female | 36 | - | Somatotroph | - |
| 15 | 36 | Male | 35 | - | Somatotroph | - |
| 16 | 52 | Male | 48 | - | Gonadotroph | - |
| 17 | 26 | Male | 22 | - | Somatotroph | - |
| 18 | 32 | Female | 31 | - | Somatotroph | *MEN1* heterozygous c.1102_1104del p.Glu368del (not a secondary finding) |
| 19 | 17 | Male | 8 | - | Thyrotroph | *BTD* heterozygous c.1595C>T p.Thr532Met |
| 20 | 42 | Female | 36 | - | Corticotroph | - |
| 21 | 49 | Male | 47 | - | Gonadotroph | - |
| 22 | 53 | Female | 48 | - | Corticotroph | *BTD* heterozygous c.1595C>T p.Thr532Met |
| 23 | 72 | Male | 67 | - | Gonadotroph | *ATP7B* heterozygous c.19_20del p.Gln7Aspfs*14 |
| 24 | 25 | Female | 20 | - | Somatotroph | *GAA* heterozygous c.896T>C p.Leu299Pro |
| 25 | 56 | Male | 51 | - | Null-cell | - |
| 26 | 48 | Male | 47 | - | Gonadotroph | - |
| 27 | 20 | Female | 15 | - | Prolactinoma | - |
| 28 | 44 | Female | 41 | - | Corticotroph | *BTD* heterozygous c.1330G>C p.Asp444His |
| 29 | 31 | Male | 29 | - | Prolactinoma | *MUTYH* heterozygous c.817del p.Ala273Profs*32 |
| 30 | 65 | Male | 50 | - | Somatotroph | - |
| 31 | 51 | Male | 43 | - | Somatotroph | - |
| 32 | 49 | Female | 38 | - | Somatotroph | - |
| 33 | 44 | Female | 33 | - | Somatotroph | *RYR2* heterozygous c.5464del p.Ile1822Serfs*8<br>*APOB* heterozygous c.13151T>C p.Leu4384Pro |
| 34 | 33 | Male | 22 | - | Somatotroph | - |
| 35 | 36 | Male | 33 | - | Somatotroph | - |
| 36 | 49 | Male | 46 | - | Prolactinoma | - |
| 37 | 65 | Female | 62 | - | Corticotroph | *BTD* heterozygous c.1595C>T p.Thr532Met |
| 38 | 36 | Male | 35 | - | Prolactinoma | *BTD* heterozygous c.1330G>C p.Asp444His |
| 39 | 26 | Female | 23 | - | Corticotroph | - |
| 40 | 38 | Male | 23 | - | Somatotroph | - |
| 41 | 25 | Female | 24 | - | Somatotroph | - |
| 42 | 43 | Female | 38 | - | Plurihormonal | - |
| 43 | 28 | Female | 18 | - | Plurihormonal | - |
| 44 | 49 | Male | 47 | - | Somatotroph | - |
| 45 | 46 | Male | 45 | - | Prolactinoma | *HFE* heterozygous c.845G>A p.Cys282Tyr |
| 46 | 36 | Male | 35 | - | Prolactinoma | - |

***Table 2.*** *Pathogenic variants detected in 81 ACMG recommended genes*

| Gene | Refseq mRNA | Zygosity | Nucleotide change | Amino acid change | Clinvar | Varsome | Franklin | Turkish variome | Disease |
|---|---|---|---|---|---|---|---|---|---|
| *TTN* | NM_001256850 | het. | c.69415C>T | p.R23139* | P,LP | P | P | N/A | DCM |
| *LMNA* | NM_005572 | het. | c.1633C>T | p.R545C | P,VUS | LP | LP | N/A | DCM |
| *RYR2* | NM_001035 | het. | c.5464del | p.I1822Sfs*8 | - | LP | LP | N/A | CPVT |
| *APOB* | NM_000384.3 | het. | c.13151T>C | p.L4384P | P | LP | LP | 0.0354% | FH |

*het: heterozygous; P: Pathogenic, LP: Likely pathogenic, VUS: Variant of unknown clinical significance, N/A: not available, DCM: Dilated cardiomyopathy, CPVT: Catecholaminergic polymorphic ventricular tachycardia, FH: Familial hypercholesterolemia*

***Table 3.*** *Variants detected in genes associated with autosomal recessive diseases*

| Gene | Refseq mRNA | Zygosity | Nucleotide change | Amino acid change | Clinvar | Disease | No. of cases | Turkish variome |
|---|---|---|---|---|---|---|---|---|
| *BTD* | NM_000060 | het.<br>het. | c.1595C>T<br>c.1330G>C | p.T532M<br>p.D444H | P<br>P,LP,VUS | Biotinidase deficiency | 3<br>4 | 0.19%<br>N/A |
| *MUTYH* | NM_001048171 | het.<br>het. | c.817del<br>c.411_416dup | p.A273Pfs*32<br>p.W138_M139insIW | P,LP<br>P | MUTYH-associated polyposis | 1<br>1 | N/A<br>N/A |
| *ATP7B* | NM_000053 | het.<br>het. | c.3583G>A<br>c.19_20del | p.A1195T<br>p.Q7Dfs*14 | LP,VUS<br>P,LP,VUS | Wilson disease | 1<br>1 | 0.13%<br>0.06% |
| *HFE* | NM_000410 | het. | c.845G>A | p.C282Y | P | Hereditary hemochromatosis | 1 | 0.3275% |
| *GAA* | NM_000152.5 | het. | c.896T>C | p.L299P | P | Pompe disease | 1 | N/A |

*het: heterozygous, N/A: not available; P: Pathogenic, LP: Likely pathogenic, VUS: Variant of unknown clinical significance*

## 4. DISCUSSION

The aim of this study was to investigate variants in the 81 genes from the ACMG SF v3.2 in Turkish PitNET patients. Four different pathogenic variants were detected in 3 out of the 46 patients (6.5%). Pathogenic variants were detected in *APOB*, *RYR2*, *LMNA*, and *TTN* genes. In a study conducted with 622 cases in the Turkish population, no pathogenic variants were detected in the *TTN* and *LMNA* genes in any of the patients (7). However, variants were found in the *RYR2* and *APOB* genes in one case each (7). But different variants were detected compared to the variants identified in this study. Hence, it is not yet possible to discuss founder variants in these genes within the Turkish population. The variants identified in the *LMNA*, *TTN*, and *RYR2* genes were not found in the 3.362 Turkish exome/genome data (14). The variant identified in the *APOB* gene was found at a frequency of 0.0354% in the Turkish variome data (14). This indicates that it is a very rare variant in the Turkish population. In this study, the frequency of the variant identified in the *APOB* gene was 0.02%, and there was no significant difference compared to the Turkish variome.

Functional studies had previously been conducted on the effect of the c.1633C>T (p.Arg545Cys) variant in the *LMNA* gene (15). This variant had been shown to cause nuclear morphological changes such as a continuous double membrane with lobulation. Additionally, an abnormal distribution of transcriptionally active RNA polimerase II had been demonstrated in the myoblasts of patients with this variant. This variant had also been shown to cause impaired distribution and function of proteasomes. In summary, both clinically and functionally, the pathogenicity of the variant had been demonstrated.

It had been shown that tissues with the p.Glu368del variant in the *MEN1* gene exhibit reduced expression of menin (16). Additionally, it has been shown that the intracellular stability of the produced menin protein is affected (16).

Functional studies for the identified *TTN* (c.69415C>T; p.R23139*) and *RYR2* (c.5464del; p.I1822Sfs*8) variants have not been found in the literature. Therefore, detailed molecular studies are needed for these variants to understand their implications.

Since 2013, studies aiming to determine the frequency of SFs have been published in various communities with diverse ethnic backgrounds (5, 6, 7, 8, 9, 10, 17, 18). In these publications, the frequency of SFs varies between 1.2% (16) and 12% (18), while in Turkish literature (7), the frequency was 2.1%. It is important to emphasize that the difference in frequencies is not solely attributable to different ethnic groups. The significant disparity in the findings of the two studies conducted within Qatar can likely be attributed, at least in part, to the differences in the sequencing techniques (19, 20). Furthermore, differences in variant classification criteria and the inclusion of more recent evidence at the time of publication may have contributed to these disparities.

There is limited data available for patient groups with specific clinical conditions. To the best of our knowledge, there are two publications in the literature that have studied populations with specific clinical conditions (21, 22). In one of the studies, a total of 85 medically actionable genes, including the 59 genes from ACMG SF v2.0, were analyzed in 836 non-obstructive azoospermia patients (21). The rate of detecting SFs was determined to be 3.6% in the 85 genes and 3.3% in the ACMG v2.0 genes. SFs were detected most frequently in genes associated with cardiac

diseases and cancer. In the other study, ACMG SF v3.0 genes and an additional four genes (*HBB*, *HSD32B*, *G6PD*, and *ACADM*) were investigated in 130 trios from African families with non-syndromic orofacial clefts (22). In a total of 390 patients, pathogenic/likely pathogenic variants in the ACMG SF v3.0 genes were detected in 9 individuals (2.3%). Pathogenic variants were identified in *PALB2*, *RYR1*, *LDLR*, and *PRKAG2* genes. Additionally, pathogenic variants of *HBB* were identified in 45 individuals, which accounts for 11.5% of the cases. The frequency of SF detected in this study (6.5%) is higher than that in the two previous studies. When genes were selected based on ACMG SF v3.0 and v2.0, the SF detection frequencies in this study were 6.5% and 4.3%, respectively, which are also higher than those in previous studies. Therefore, the high frequency cannot be solely attributed to the greater number of genes in ACMG SF v3.2. In addition to differences in ethnic background, sequencing methods, and variant analysis, this study has also demonstrated that the selected patient group can influence SF detection rate. When examining the relationship between the clinical characteristics of the patients and the detection rates of SFs, no significant relationship was found with either the type of PitNETs or the age at diagnosis.

It is not recommended to report heterozygous variants in the *BTD*, *ATP7B*, *MUTYH*, *HFE*, and *GAA* genes. Furthermore, as highlighted in previous literature, informing the patient about carrier status in countries with a high rate of consanguineous marriages is important for enabling the planning of prenatal and preimplantation genetic tests for future generations (7, 10). Moreover, there is broad consensus that individuals with the monoallelic *MUTYH* allele have an increased risk of colorectal cancer (23). So, it is important to follow-up these patients to provide early diagnosis. Two different heterozygous pathogenic variants have been identified in the *MUTYH* gene in two different patients. One of the variants was a truncating variant, while the other was an in-frame duplication. The carrier frequency identified in this study (4.3%) is significantly higher than the previously reported frequency of 1.2% (7). There are studies that demonstrate a relationship between *MUTYH* and pancreatic neuroendocrine tumors (24, 25), however no relationship between *MUTYH* and PitNET has been reported to date. Considering the common genetic characteristics of neuroendocrine tumors and high expression of MUTYH in the pituitary gland , it can be hypothesized that there might be a potential relationship between *MUTYH* and PitNET. The higher frequency of *MUTYH* variants detected in our study could be related to this potential association with PitNET pathogenesis; however, further research is needed on this topic.

While there have been publications reporting an increased frequency of PitNET in association with pathogenic variants in Lynch syndrome related genes (26), in our study, no pathogenic variants were found in cancer susceptibility genes, including Lynch syndrome related genes. This result suggests that there could be a different process involved in the development of PitNET, distinct from known cancer-related genes/pathways. Nevertheless, the limited number of patients in the study should be considered.

## 5. CONCLUSION

Overall, investigating secondary findings in diseases with unknown or complex genetic etiologies can significantly advance our knowledge of these conditions, improve clinical management, and potentially lead to novel therapeutic strategies. It underscores the importance of ongoing genetic research and the integration of genetics into clinical practice. Therefore, this study, by investigating secondary findings in PitNET cases for the first time, will make a significant contribution to the literature.

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***Author Contributions:***

*Research idea: CA, AİG*
*Design of the study: CA, AİG*
*Acquisition of data for the study: AB, BA, FBÇ, FB, ZSA*
*Analysis of data for the study: AB, BA, FBÇ, FB, ZSA*
*Interpretation of data for the study: CA, AİG*
*Drafting the manuscript: CA*
*Revising it critically for important intellectual content: AİG*
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