The goals of this study were to:

- Identify a genetic basis for the co-existence of acromegaly
- Novel association with endocrine tumors might be involved.
- Exclusion of MEN-1 mutations
- Falsely negative
- Extensive DNA testing
- MEN1 genetic screening (GeneDX)
- Identification of new genes associated with acromegaly
- Evaluation of the MEN1 clinical syndrome
- Correlation in acromegaly in patient number six.
- Whole exome sequencing
- Identification of the gene
- Multiple endocrine neoplasms (MEN1) analysis of 1336 mutations reported in the decade following identification of the gene. Hum Mutat. 2008;29:22–32.

STUDY OBJECTIVES

- Identify a genetic basis for the co-existence of acromegaly
- Complete genetic and clinical findings in this population

MATERIALS AND METHODS

- Paired samples from 15 patients with acromegaly and primary hyperparathyroidism were identified from a large acromegaly database. Ten of these patients, including 7 in whom MEN1 genetic screening (GeneDX) was requested, provided a blood sample for informed consent for genetic testing.
- DNA sequence analysis was performed for genes including MEN1, CDC73, CDKN1A, CDKN2B, and AIP. In addition, multiplex ligation-dependent probe amplification was used to search for deletions or duplications in MEN1, CDC73, CDKN1B, and AIP genes.

CONCLUSIONS

1. In patients with acromegaly plus primary HPT, DNA sequencing of MEN1, CDKN1A, CDKN1B, CDKN2B, CDKN2C, and AIP genes was unrevealing.
2. New mutations may explain the co-occurrence of parathyroid and pituitary adenomas.
3. A mutation in CDC73, whose mutations usually cause the primary HPT jaw-tumor (HPT-JT) syndrome with higher association of parathyroid cancer (3), was identified in a patient with HPT, acromegaly and NET.
4. This finding expands the spectrum of CDC73-related disorders, establishing a novel association of parathyroid NET and somatotropinoma with CDC73.

Table 1: Pathology

<table>
<thead>
<tr>
<th>Pituitary adenoma</th>
<th>Hyperparathyroidism</th>
<th>NET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth Hormone</td>
<td>PRL Staining</td>
<td></td>
</tr>
<tr>
<td>Adenoma</td>
<td>Hyperplasia</td>
<td>Unknown Low Grade PT2N0</td>
</tr>
</tbody>
</table>
| 100 % -40 %       | 50%                 | 20% | 30% | 100%

N=10 patients with acromegaly plus HPT

Therapy:
- 1 had pituitary surgery
- 7 had parathyroid surgery
- 1 had resection of pancreatic NET
- 3 received pituitary radiation (patient 4,6,8)

Other Endocrine Lesions:
- 2 had adrenal adenomas (patient 2.5)
- 1 had thyroid nodules (patient 1.9)

Phenotype of patient 6 with germline CDC73 heterozygous nonsense mutation Leu380Phe:
- Acromegaly, mild primary HPT, pancreatic NET
- No known family history of endocrine tumors
- Acromegaly was diagnosed at age 22 years
- Required surgery, radiation, & medical therapy
- Pancreatic tumor pathology: well differentiated NET, low grade, PT2N0, 1 mitosis per HPF

Figure 1: DNA Analysis

A germline CDC73 mutation:
- (A) DNA sequence analysis showing a heterozygous C>T transversion identified in exon 11, nucleotide position c.1138 of CDC73. (B) The C>T transversion was predicted to lead to a substitution of a leucine to phenylalanine at codon 380.

LIMITATIONS AND FUTURE DIRECTIONS

- It is possible that 1) patients with GH secreting tumors have parathyroid tumors indirectly as a result of GH excess, rather than due to a genetic cause and 2) that a CDC73 mutation was responsible for the hyperparathyroidism but not a cause of the hyperparathyroidism at acromegaly in patient number six.
- We plan to perform whole exome sequencing to identify new genes associated with acromegaly in the setting of the MEN1 clinical syndrome and to evaluate paraffinum expression in the pancreatic tumor of patient 6 who had a CDC73 mutation.

Table 2: Clinical Characteristics and DNA Analysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Number</th>
<th>Gender</th>
<th>Age of HPT Diagnosis (years)</th>
<th>Age of Acromegaly Diagnosis (years)</th>
<th>NET</th>
<th>Parathyroid Pathology</th>
<th>Other Neoplasms</th>
<th>Family History of MEN1</th>
<th>Mutation</th>
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<tr>
<td>1</td>
<td>49</td>
<td>54</td>
<td>-</td>
<td>-</td>
<td>adenoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>CDKN2C</td>
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<tr>
<td>2</td>
<td>F</td>
<td>78</td>
<td>59</td>
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<td>N=10 patients with acromegaly plus HPT</td>
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<td>+ CDC73</td>
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<tr>
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<td>sister with pancreatic NET &amp; MEN1</td>
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</tr>
<tr>
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<td>F</td>
<td>52</td>
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Table 2: Pathology

<table>
<thead>
<tr>
<th>Number</th>
<th>Treatment</th>
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<th>HPT</th>
<th>Diagnosed</th>
<th>Age (years)</th>
<th>Therapy</th>
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<tbody>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>54</td>
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</tr>
<tr>
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<td>+</td>
<td>50%</td>
<td>20%</td>
<td>30%</td>
<td>54</td>
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</tr>
<tr>
<td>3</td>
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<td>40%</td>
<td>50%</td>
<td>20%</td>
<td>54</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Abbreviations: HPT=hyperparathyroidism; NET=neuroendocrine tumor; IPMN=intraductal papillary mucinous neoplasm; RCC=renal cell carcinoma; PTC= papillary thyroid cancer; CA=cancer.

REFERENCES


Genetic abnormalities were not detected in 9/10 patients.