

most genes are regulated by combinations of enhancers. We previously found that neighboring estrogen-responsive enhancers exhibit cooperative/synergistic contributions to an estrogenic transcriptional response¹. However, when the same combinations of enhancers are targeted with synthetic activators in the absence of estrogens, then the regulatory regions exhibit independent effects on gene expression². Taken together, these findings indicate that estrogen receptor alpha (ER) bound enhancers cooperate with each other in *cis* but influence target gene promoters independently. To determine the molecular underpinnings of enhancer cooperativity, we generated genetic deletions of individual ER bound enhancers. We discovered “regulatory sharing” between enhancers in which loci containing full estrogen response elements (EREs) contribute ER binding to neighboring sites, while enhancers with pre-existing histone acetylation/accessibility contribute this permissible chromatin environment to the neighboring enhancers upon estrogen induction. Genome engineering revealed that a cluster of two half ERE enhancers could not compensate for a full ERE site loss within the cluster. However, two full ERE enhancers produced a transcriptional response greater than the wild-type locus, suggesting that combinations of enhancers are not necessarily configured for a maximal response. By swapping genomic sequences, we found that the genomic location in which a full ERE resides strongly influences enhancer activity. Our results lead to a model in which a full ERE is critical for ER recruitment, but the presence of pre-existing histone acetylation and accessibility within an enhancer cluster is also needed in order for estrogen-induced gene regulation to occur.

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Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS I

Aggressive De Novo MEN1 Variant in a Child with Metastatic Pancreatic Acth and Crh Co-Secreting Neuroendocrine Tumor: Diagnosis and 10-Year Follow Up

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Background:

In Multiple Endocrine Neoplasia type 1 (MEN1) only about 2% of pituitary adenomas are ACTH-secreting. Cushing Syndrome due to ectopic ACTH or CRH secretion from neuroendocrine tumors (NETs), carcinoid tumors, or pheochromocytomas is very rare, though patients with MEN1 are at increased risk for these three types of

tumors, as well as autonomous adrenal secretion of cortisol. The 10-year follow up of a previously-reported case of a child with MEN1 and metastatic pancreatic ACTH/CRH-secreting NET is presented.

Clinical Case:

A previously-reported (J Clin Endocrinol Metab, 2015) now 21 yo female presented to the National Institutes of Health (NIH) at 11 yo with persistent hypercortisolemia despite transsphenoidal surgery for suspected Cushing Disease. However, the resected tissue revealed pituitary hyperplasia, and she remained hypercortisolemic. A CRH test was consistent with an ectopic source, and abdominal CT, PET scan, and Octreotide scan revealed a mass in the pancreatic tail. The patient underwent partial pancreatectomy at 11 yo with the resected tissue staining positive for ACTH and CRH. However, she remained hypercortisolemic, so bilateral adrenalectomy was performed. At 12 yo metastases were found, so Octreotide therapy was initiated. She continued to have elevated ACTH levels > 1000 pg/mL (5-46). Additionally, a pituitary adenoma was noted at 12 yo, which has since increased in size. The patient also developed mild primary hyperparathyroidism, first noted at 19 yo. Sequencing of *MEN1* for the patient and her parents revealed a de novo heterozygous c.1546dupC variant, consistent with sporadic MEN1. The patient also had a chromosome 8p23.2 duplication that was present in unaffected relatives.

Conclusion:

While 2% of patients with MEN1 may develop Cushing Syndrome due to an ACTH-secreting pituitary adenoma, it is also important to consider ectopic secretion of ACTH/CRH from MEN1-associated NETs, carcinoid tumors, or pheochromocytomas, as well as autonomous adrenal secretion of cortisol. Given the early age and severe presentation of MEN1 features in this patient, the c.1546dupC heterozygous variant of *MEN1*, which has been previously reported in multiple other cases of MEN1, may represent a higher-risk causative variant of MEN1. Alternatively, expression of this variant may have been affected by the concurrent presence of an otherwise apparently benign chromosomal variant.

References:

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Cardiovascular Endocrinology

PATHOPHYSIOLOGY OF CARDIOMETABOLIC DISEASE

Cardiac Phenotype in Familial Partial Lipodystrophy

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Background Pathogenic variants in Lamin A/C (*LMNA*) gene are the most common monogenic etiology in Familial Partial Lipodystrophy (FPLD) causing FPLD2. *LMNA* pathogenic variants have been previously associated with cardiomyopathy, familial arrhythmias or conduction system abnormalities independent of lipodystrophy. We aimed to assess cardiac impacts of FPLD, and to explore the extent of overlap between cardiomyopathies and FPLD. **Methods** We conducted a retrospective review of an established cohort of 122 patients (age range: 13-77, M/F 21/101) with FPLD from Michigan (n = 83) and Turkey (n = 39) with an accessible cardiac evaluation. Also, functional syncytia of mature human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from a FPLD2 patient was studied for assessment of autonomous rhythm and action potential duration with optical mapping using a voltage sensitive dye. **Results** In the whole study cohort, 95 (78%) patients had cardiac alterations (25% ischemic heart disease, 36% arrhythmia, 16% conduction abnormality, 20% prolonged QT interval, 11% cardiomyopathy, and 15% congestive heart failure). The likelihood of having an arrhythmia (OR; 3.95, 95% CI: 1.49-10.49) and conduction disease (OR: 3.324, 95% CI: 1.33-8.31) was significantly higher in patients with *LMNA* pathogenic variants. Patients with *LMNA* pathogenic variants were at high risk for atrial fibrillation/flutter (OR: 6.77, 95% CI: 1.27- 39.18). The time to first arrhythmia was significantly shorter in the *LMNA* group with a higher hazard rate of 3.04 (95% CI: 1.29-7.17, p = 0.032). Non-482 *LMNA* pathogenic variants were more likely to be associated with cardiac events (vs. 482 *LMNA*: OR: 4.74, 95% CI: 1.41-15.98 for arrhythmia; OR: 17.67, 95% CI: 2.44- 127.68 for atrial fibrillation/flutter; OR: 5.71, 95% CI: 1.37- 23.76 for conduction disease. hiPSC-CMs from a FPLD2 patient had higher frequency of autonomous activity, and shorter Fridericia corrected action potential duration at 80% repolarization compared to control cardiomyocytes. Furthermore, FPLD2 functional syncytia of mature hiPSC-CMs presented several rhythm alterations such as early after-depolarizations, spontaneous quiescence and spontaneous tachyarrhythmia; none of those were observed in the control cell lines. Finally, FPLD2 hiPSC-CMs presented significantly slower recovery in chronotropic changes induced by isoproterenol exposure; which indicates disrupted beta-adrenergic response. **Conclusion** Our results suggest the need for vigilant cardiac monitoring in FPLD, especially in patients with FPLD2 who have an increased risk to develop cardiac arrhythmias and conduction system diseases. In addition, study of human induced pluripotent stem cell-derived cardiomyocytes may prove useful to understand the mechanism of cardiac disease and arrhythmias and to create precision therapy opportunities in the future.

Thyroid

THYROID CANCER CASE REPORTS II

Detection of Thyroid Cancer Recurrence in Patients with Positive Thyroglobulin Antibody Receiving Immunoglobulin Therapy.

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Introduction: Differentiated thyroid cancers such as papillary and follicular thyroid cancer make up more than 90% of all thyroid cancers. The presence of thyroglobulin autoantibodies makes interpretation of the thyroglobulin level unreliable, as it could be falsely low or falsely high. Studies have shown that rising thyroglobulin antibody levels, could be used to monitor for disease recurrence in patients with negative thyroglobulin and imaging studies. However, there are challenges in detecting recurrence in patients with normal thyroglobulin level and thyroid imaging studies, who are on lifelong immunoglobulin therapy and who have increasing thyroglobulin antibody levels.

Clinical case: A 63 yr old female was found to have an incidental left thyroid nodule at age 48yrs from a carotid ultrasound. She underwent US guided FNA of the thyroid nodule and was found to have papillary thyroid cancer. She had total thyroidectomy a month later, with removal of a 1.4cm primary, with no evidence of extrathyroidal extension, clear margins and no evidence of lymphovascular invasion – Stage T1bN0M0. There was left level 6 neck dissection with no carcinoma identified in the 2 lymph nodes removed. She received 105.3 mCi radioactive iodine (RAI) and whole body thyroid scan done 7 days later revealed, increased uptake involving the thyroid bed likely residual thyroid tissue. Activity was noted inferolateral to the right thyroid bed which most likely represents a lymph node. There was no evidence of distant metastasis.

She was commenced on levothyroxine post operatively. Her other past medical history is significant for idiopathic urticaria and angioedema, immune deficiency disorder with low IgG and IgM and asthma. She was commenced on monthly IV immunoglobulins 5yrs post RAI therapy, due to recurrent sinusitis, rhinitis and chronic diarrhea. She was later transitioned to weekly SQ immune globulin – Hizentra which she is on till date.

Over the past 15 years, serial neck ultrasounds post radioiodine ablation have been negative for recurrence. Her TSH ranged 14.91 to 0.04 (ref 0.27-4.2 uIU/ml) and thyroglobulin (Tg) titer remains <0.1 (ref <0.1). Her thyroglobulin antibody titers have trended up from <0.2 (ref <2.0) 5yrs post RAI therapy to 49 (ref <4 IU/ml) on her most recent test this year. She is currently undergoing further work up to rule out recurrence of her cancer. In our review of the literature we found one report that showed use of Liquid Chromatography–Mass Spectrometry (LC-MS) was able to differentiate thyroid cancer recurrence in an individual with positive antithyroglobulin antibody receiving immunoglobulin therapy.

Conclusion: In patients with negative Tg levels, but elevated thyroglobulin antibody while receiving immune globulin therapy, thyroglobulin antibody levels may not be a reliable indicator of thyroid cancer recurrence. Measurement of Tg levels using a LC-MS may provide some clarity.