Mutations summary

Adrenal disease's part 1:

1) Adrenal **adenoma** – mutation of **PRKAR1A ~** cAMP-dependent protein kinase ~ excessive cAMP release.

2) Adrenal **carcinoma** – mutation of:
   * Activation of beta-catenin (**CTNNB1**)
   * Inactivation of **TP53**
   * **MEN1**
   * **PRKAR1A**

3) **Macro**nodular adrenal hyperplasia, 3 forms of disease, each with different mutations:
   a) Familial type: inherited mutation of a tumor suppressor gene (**ARMC5**) ~ Armadillo repeat containing 5.

   b) Sporadic cases:
   * 50% of cases show **ARNC5** mutation.
   * Others show **ectopic production of G-protein coupled hormone receptors** that are similar to ACTH (lead to proliferation without ACTH).

   c) Syndromic cases: McCune Albright syndrome, germline activating mutation in **GNAS** ~ excessive cAMP release.

4) **Micro**nodular adrenal hyperplasia, 2 variants of disease, both with the same mutation in **PRKAR1A** gene.

Adrenal disease's part 2:

Primary hyperaldosteronism

1) Bilateral idiopathic hyperaldosteronism – germline mutation in **KCNJ5.**

2) Conn syndrome (Adrenal adenoma)
   * 50% have **KCNJ5** mutation, this gene encodes for potassium channel in zona granulosa (GIRK4 protein), the mutant protein allows influx of sodium and activation of aldosterone synthase enzyme.
   * Similar mutations affect: **CACNA1H** + **ATP1A1**

3) Familial hyperaldosteronism
   FH-1 is the most common subtype aka (glucocorticoid-remediable aldosteronism), mutation in **CYP11B2** (this gene encodes aldosterone synthase enzyme); the gland is now sensitive to ACTH

Congenital adrenal hyperplasia

21-hydroxylase deficiency, the most common deficiency, mutation in **CYP21A1** gene, variable degree of deficiency resulting in:
* Salt wasting syndrome, associated with deficiency in aldosterone, cortisol and catecholamines synthesis (hyponatremia, hypokalemia, hypotension, CV collapse, virilization in females).
* Simple virilization, with no salt wasting.
* Late-onset adrenal virilism, common, partial deficiency, hirsutism, acne, irregular menses.

PHEOCHROMOCYTOMA – chromaffin cells

Genetic mutations in growth-factor receptor pathway genes **(RET, NF1)** OR increased activity of hypoxia-induced transcription factors **(HIF-1α, HIF-2α)**

Type 1 diabetes

Associated with (**HLA-DR3), (HLA-DR4), (HLA-DQ8)**
Also, polymorphism in **CTLA4** and **PTPN22** genes (similar to Hashimoto)
These genetic factors are related to inflammation and function of the immune system (T1D is autoimmune).
Environmental factors are important

Type 2 diabetes

Genetic factors are important here, 90% concordance rate in identical twins, 10x risk in first degree relative, Genes related are:
* Adipose-tissue distribution
* B-cell function
* Obesity

Monogenic diabetes – mutations in a *single* gene, (T1D+T2D are genetically caused by *multiple* genes)

Results from germline (*loss of function*) mutation in **Glucokinase (GCK) genes**, affects glucose metabolism and insulin secretion.

*Rarely: Mutation is insulin-receptor synthesis, binding, or activity.

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