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Genetics of adrenocortical carcinoma: A review

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Abstract

Adrenocortical carcinoma (ACC) is a aggressive endocrine cancer and rare in nature. It develops in the outer layer (cortex) of the adrenal gland. These glands are located on the top of each kidney, responsible for producing steroid hormones that help regulate blood pressure, salt levels and the body's response to stress. Adrenocortical carcinoma (ACC) shares both sporadic and familial forms, with genetic mutations playing a key role in its development. Current understanding of genetics of ACC is debated and studies are conducted to understand. Developments in genetic analysis in the form of next-generation sequencing, aided by bioinformatics, have enabled high-throughput molecular characterisation of these tumours. Most of the reports indicates the involvement of P53 gene mutations along with other mutations. Though some reports revealed the involvement of genes related to wnt signalling pathaway, sonic hedgehog pathway and many more for the development of ACC. This review will shed light on the genetic aspect of ACC pathogenesis.

Keyword: Adrenocortical Carcinoma; Genetics; Cancer; Adrenal Gland; Pathogenesis

1. Introduction

Adrenocortical carcinoma (ACC) is a rare kind of tumor of the adrenal cortex. Data from the United States and the Netherlands show that the incidence of ACC is 1-2 case per 1 million person- years in the general population and 0.21 cases per 1 million person- years in children and young adults. It was also reported that in the United States, the age-standardized general cancer incidence is 4,500 cases per 1 million person- years in adults and 150 cases per 1 million person- years in children (1). The incidence of ACC follows a bimodal age distribution, with a peak in child hood and a plateau occurring between 40 and 50 years of age. The incidence is more frequent in women (sex ratio 1.5) (2). Adreno Cortical Carcinoma shares about 8-11% of adrenal tumors in clinical and surgical series. On the other way, about 80% of adrenal tumors are adrenocortical adenomas, 7-10% are pheochromocytomas derived from the adrenal medulla and 5-7% are adrenal metastases from other type of cancer. The circumstances of discovery are: (1) hormonal hypersecretion (40-74% of cases), (2) tumor syndrome (40-60% of cases), (3) an "adrenal incidentaloma" (10- 20% of cases), (4) more rarely a paraneoplastic syndrome (fever, poor general condition, hypoglycemia) (3). ACC is almost always sporadic, except when congenital (Beckwith- Wiedemann) and/or hereditary (Li-Fraumeni syndrome, MEN1, Gardner syndrome, Lynch syndrome)(4, 5).

Several multicenter studies on the ACC pathogenesis have been performed in the recent years and the result of 'multi-omic' studies showed that only a minority of ACC cases have pathogenic genetic driver mutations. Two large consortia have characterized the landscape of molecular alterations in ACC. They included deregulated cell-cycle and apoptosis pathways (p53 and RB), impaired chromatin and DNA maintenance (mismatch and double stranded DNA repair as well as TERT overexpression or alternative lengthening of telomeres), altered adrenocortical differentiation, signaling pathway activation (most commonly WNT–β-catenin signaling but also cAMP and the mitogen- activated protein kinase pathways). Yin et. al. in 2023 reported that microarray results showed 72 up-regulated and 134 down regulated genes

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in three datasets. They also reported that function enrichment analyses of differentially expressed genes by DAVID online database and the results revealed that the differentially expressed genes (DEGs) were mainly enriched in cell cycle, cell cycle process, mitotic cell cycle, response to oxygen-containing compound, progesterone-mediated oocyte maturation, p53 signaling pathway (6). This compact review will shed light on genetic aspect of ACC which will greatly contribute to the understanding of the underlying mechanisms and candidate targeted therapy options for ACC.

2. ACC and molecular genetics

Adrenocortical carcinoma (ACC) is a rare endocrine cancer with limited prognosis. The origin of the disease is from the adrenal gland cortex and lacks effective treatment. To elucidate the pathogenesis of ACC many efforts have been made, but the molecular mechanisms remain unclear. Yin et al. in 2023 tried to identify the key genes underlying ACC pathogenesis. The expression profiles of GSE143383 ,GSE12368 and GSE90713 were downloaded from the Gene Expression Omnibus (GEO) database (6) to identify the key genes and the pathways in ACC. A total of 16 normal tissues and 127 ACCs were obtained from the three GEO datasets. The GEO database served the gene expression profiles of ACC (https://www.ncbi.nlm.nih.gov/geo/). The screening criteria were as follows: i) adrenocortical carcinoma, ii) samples containing tumor and normal adrenal gland tissues, iii) expression profiling by array and iiii) Homo sapiens. The detail methodologies can be found from the reference (6).

As per Yin et al., 2023 function enrichment analyses of DEGs were performed by DAVID online database and the results revealed that the DEGs were mainly enriched in cell cycle, cell cycle process, mitotic cell cycle, response to oxygen-containing compound, progesterone-mediated oocyte maturation, p53 signaling pathway. The STRING database was used to construct the protein protein interaction (PPI) network, and modules analysis was performed using Cytoscape. Finally eight hub genes were filtered out, including CDK1, CCNA2, CCNB1, TOP2A, MAD2L1, BIRC5, BUB1 and AURKA. Biological process analysis showed that these hub genes were significantly enriched in nuclear division, mitosis, M phase of mitotic cell cycle and cell cycle process. Violin plot, Kaplan Meier curve and stage plot of these hub genes confirmed the reliability of the results (7).

There are many other reports excluding these genes, to mention another set of genes, cellular pathways, chromosomal changes and many more, which are thought to be causal factors for ACC pathogenesis. A group of ACC cases in the study were found to have heavy genomic instability, including genomic loss and whole-genome doubling and many more. While whole-genome doubling is common across a range of cancers, an association with patient outcomes has only been demonstrated in ovarian cancer. Verhaak, Hammer, Giordano and co-workers have shown that whole-genome doubling is associated with an aggressive clinical course in ACC, which suggests that it could be a marker of ACC progression. However, Hammer cautions that much is still unknown about why whole-genome doubling occurred in this particular subset of ACCs, the mechanisms underlying the process and the implications for cancer initiation, maintenance and progression is still debated (1).

These analyses helped the researchers to specify several new genes associated with ACC — PRKAR1A, TERF2, RPL22, CCNE1 and NF1. Interestingly, the loss-of-function mutation in PRKAR1A is known to be associated with benign adrenocortical cancers, which suggests that there could be pathophysiological links between benign and malignant adrenocortical tumours. Amplification of TERF2 and telomerase was found in several samples, which suggests that telomere maintenance could be involved in the development of ACCs. The researchers found that 16% of the samples had a homozygous deletion of ZNRF3 (a gene involved in the Wnt signalling pathway), with an overall 19.3% having some kind of alteration in this gene (8).

Another report by Sun-Zhang et al, 2024 showed that among 3903 significantly differentially expressed genes, the mRNA expression levels of 461/3903 genes significantly impacted survival in ACC. Subsequent analysis revealed 45 of these genes to be mutated in patients with significantly worse survival. The relationship was significant even after adjusting for stage and age. Protein-protein interaction showed previously unexplored interactions among many of the 45 proteins, including the cancer-related proteins DNA polymerase delta 1 (POLD1), aurora kinase A (AURKA), and kinesin family member 23 (KIF23). Furthermore 14 of the proteins had significantinteractions with TP53 which is the most frequently mutated gene in the germline of patients with ACC (8).

Another report by Grisanti et al in 2025 showed the multigenetic involvement of ACC (Table 1) (9) (10). The reports says that ACC is polygenic in nature with complex behavior. The review discussed the different genetical aspects of ACC pathogenesis:

- Germline DNA mutations and hereditary components
- Aneuploidy

- Somatic mutation
- Epigenetic changes

Table 1 List of genes found in ACC cases and the probable downstream effects of mutations (11)

Name of Gene	Gene Symbol	Downstream effects
Tumor suppressor genes	TP53	Cell cycle arrest and repair damage; places cell to induce apoptosis
	PRKAR1A	DNA damage response and proapoptotic signals induction.
	MEN1	Epigenetic gene regulation and histone modification through several pathways; control cellular proliferation.
Oncogenes	IGF-II	Transcription factors downregulation.
Growth factors	VEGFR EGFR/ TGF-α/TGF β1/FGF-2/ interleukins	Tyrosine-kinase-coupled receptor- mediated cellular proliferation, survival, angiogenesis, apoptosis resistance and metastasis.
DNA methylation and epigenetics Signaling molecules	Many genes	Silencing of tumor suppressor genes and/or activation of oncogenes
	Wnt/B-catenin pathway	Activation of genes of pro-growth and pro-proliferation genes

On the basis of different reports, it can be understood that there are multigenic involvement in the ACC and the survival (8, 9, 12-14). To summarize, the key genetic factors and drivers are as follows:

- IGF2 Overexpression: Nearly ubiquitous, driving excessive cell proliferation and growth.
- Wnt/β-catenin Pathway: Frequent activating mutations in CTNNB1 and inactivating mutations/deletions in ZNRF3 drive development and correlate with poor survival.
- p53 Pathway: TP53 mutations are common, especially in aggressive tumors.
- 11q13 Loss of Heterozygosity (LOH): Observed in up to 90% of cases, often indicating loss of tumor suppressor genes.
- Steroidogenic Factor-1 (SF-1/NR5A1): Constitutive expression is a hallmark of adult ACC, supporting proliferation and differentiation.

Epigenetic and chromosomal abnormalities are reported from various cases. A strong CpG island methylator phenotype (CIMP-high), significant loss of genomic material, overexpression of *miR-483-5p* and downregulation of *miR-195* are common in ACC severity (1, 15-17). Some hereditary syndromes are also likely to increase the chance of ACC occurrence i.e. Li-Fraumeni Syndrome (P53 mutation), Beckwith-Wiedemann Syndrome, Lynch syndrome, MEN1, and familial adenomatous polyposis etc are also linked to increased risk (8).

It is evident from different reports that somatic mutations take part the main role in the ACC pathogenesis when genetical aspect is considered. Though epigenetic background is very less understood (18). Few reports are there to discuss the epigenetic modification in ACC but these reports do not confirm the direct link with ACC pathogenesis. A report by Dipika R Mohan et al. in 2023 showed the involvement of EZH2 and SF1 with beta catenin in ACC metastasis in-vivo and in-vitro.

3. Conclusion

ACC are rare and aggressive malignancies with limited treatment options in the advanced settings. Surgery can serve the only potentially curative treatment option. The most common limitation of the previous reports is the small cohort as the disease is very rare. Though based on the present reports it can be said that no proper genetic marker has yet been identified. Though next-generation sequencing, m-RNA profiling can help to facilitate the early molecular diagnosis and further treatment for all patients and the persons at high risk of developing this rare and aggressive cancer.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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