

Carney Complex: A Comprehensive Review of Clinical Presentation, Genetics, and Therapeutic Advances

Rodrigo García González¹, Aridna Melissa Alonso Padilla², Jennifer Aída Ortega Romero³, Melissa Anahí Chan Verdugo⁴

^{1,2,3,4} Hospital General Regional #1. Instituto Mexicano del Seguro Social. Tijuana, Baja California, México.

ABSTRACT

Carney Complex (CNC) is a rare, complex, and multisystem disorder with variable clinical manifestations, characterized by the development of benign tumors and hyperplastic lesions in several organ systems. This article provides a comprehensive overview of CNC, encompassing its clinical features, genetic underpinnings, and current therapeutic interventions. With an emphasis on the diverse clinical presentations and challenges associated with this condition, the aim of this review is to enhance our understanding of CNC, shed light on the latest research findings, and explore potential directions for future studies. A thorough exploration of the pathophysiology of CNC is essential to guide early diagnosis, management, and improved patient outcomes.

KEYWORDS: Carney, complex, rare, genetic

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INTRODUCTION

Carney Complex (CNC), a rare and enigmatic genetic disorder, was first described by J. Aidan Carney in 1985. It belongs to a group of conditions collectively known as "familial lentiginosis syndromes," and its intricate clinical features encompass a wide range of benign tumors and hyperplastic lesions affecting multiple organ systems, including the heart, skin, endocrine glands, and nervous system. With a prevalence estimated to be around 1 in 200,000 individuals, CNC is considered an orphan disease, and its complexity has posed substantial diagnostic and therapeutic challenges.^{1,2}

The underlying genetic basis of CNC is closely linked to mutations in genes responsible for the regulation of protein kinase A (PKA) activity, with the most commonly implicated genes being *PRKAR1A* and *PDE11A*. Dysregulated PKA signaling underlies the development of various manifestations of CNC, including cardiac myxomas, cutaneous lentiginosis, primary pigmented nodular adrenocortical disease (PPNAD), and other neoplastic and non-neoplastic lesions. The vast phenotypic diversity observed in CNC patients has necessitated a multidisciplinary approach to diagnosis and management.^{2,3}

This article aims to provide an in-depth exploration of CNC, delving into its clinical presentation, pathophysiology, genetics, and current therapeutic strategies. Understanding the

complexity of CNC is critical for early diagnosis and intervention, which can ultimately improve the quality of life for affected individuals. By elucidating the intricacies of CNC, this review contributes to the ongoing effort to expand our knowledge of rare genetic disorders, leading to more effective management and treatment options.^{2,3}

Epidemiology

Epidemiology, a fundamental branch of medical science, plays a pivotal role in comprehending the prevalence, incidence, distribution, and determinants of diseases within populations. In this context, we delve into the epidemiology of Carney Complex (CNC), a rare genetic disorder of multifaceted clinical manifestations. To fully appreciate the impact of CNC, it is imperative to elucidate its epidemiological characteristics, contributing to a deeper understanding of its global burden and potential factors influencing its occurrence.^{2,3}

CNC is considered an orphan disease, with an estimated prevalence of approximately 1 in 200,000 individuals. While the exact prevalence and incidence figures may vary across different populations and regions, CNC's rarity is a defining feature. The condition often poses diagnostic challenges due to its variable and diverse clinical presentations. As a result, CNC may be underdiagnosed or misdiagnosed, leading to underreporting in epidemiological studies. Improving

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awareness and knowledge among healthcare professionals and the general public is crucial to accurately assess CNC's true epidemiological landscape.^{2,3}

This condition exhibits an autosomal dominant pattern of inheritance, primarily due to mutations in the *PRKAR1A* and *PDE11A* genes, which are integral components of the cAMP-protein kinase A (PKA) signaling pathway. These genetic mutations drive the development of benign tumors and hyperplastic lesions in multiple organ systems, thereby contributing to the diverse clinical spectrum of CNC. Therefore, a family history of CNC and genetic testing in affected individuals and their relatives are pivotal for diagnosing and understanding the epidemiological aspects of this

condition.^{3,4}

The wide-ranging clinical manifestations associated with CNC encompass cardiac myxomas, cutaneous lentiginos, endocrine abnormalities (such as primary pigmented nodular adrenocortical disease - PPNAD), schwannomas, and other neoplastic and non-neoplastic lesions. The variable expression of these features further complicates CNC's epidemiological analysis, as the condition may manifest differently from one individual to another. This clinical diversity necessitates a multidisciplinary approach, involving specialists from cardiology, dermatology, endocrinology, and genetics, for accurate diagnosis and management.^{3,4}

To date, the limited number of documented cases and the rarity of CNC have hindered the comprehensive study of its epidemiology. Collaborative efforts among healthcare providers, researchers, and advocacy groups are essential to assemble larger datasets, allowing for more robust epidemiological investigations. Establishing CNC registries and conducting international studies can provide a broader perspective on its global distribution and prevalence. It is also crucial to explore potential geographical and ethnic variations in CNC incidence, which may provide valuable insights into genetic predisposition and environmental factors contributing to the condition.^{3,4}

In summary, the epidemiology of Carney Complex is marked by its rarity, genetic underpinnings, and highly variable clinical presentations. The development of a more accurate and comprehensive epidemiological profile for CNC necessitates increased awareness, collaborative efforts, and the establishment of robust data collection mechanisms. By gaining a deeper understanding of the epidemiological aspects of CNC, we can take significant strides towards improving early diagnosis, appropriate management, and better outcomes for affected individuals.^{4,5}

Clinical Manifestations

Carney Complex (CNC) is a rare, autosomal dominant genetic disorder characterized by a diverse array of clinical manifestations, affecting multiple organ systems. This condition is known for its complexity, given its potential to manifest as benign tumors and hyperplastic lesions in various tissues. To gain a comprehensive understanding of

CNC, it is essential to delve into its intricate clinical presentations, each of which contributes to the clinical heterogeneity observed in affected individuals.^{5,6}

Cardiac Involvement:

- Cardiac myxomas, particularly atrial myxomas, are a hallmark feature of CNC. These tumors may lead to a range of cardiac symptoms, including arrhythmias, heart murmurs, and congestive heart failure.^{5,6}
- Embolic events, often due to myxoma fragments, can result in strokes or peripheral embolization.^{5,6}

Dermatological Manifestations:

- Multiple cutaneous lentiginos, also known as freckle-like skin pigmentation, are a common feature of CNC.^{5,6}
 - Blue nevi, which are benign pigmented skin lesions, may also be observed.^{5,6}

Endocrine Abnormalities:

- Primary pigmented nodular adrenocortical disease (PPNAD) is a key endocrine manifestation in CNC, characterized by the development of adrenal gland nodules and cortisol overproduction, leading to Cushing's syndrome.^{5,6}
- Growth hormone-secreting pituitary adenomas may cause acromegaly in some CNC patients.^{5,6}

Gastrointestinal Involvement:

- Gastrointestinal stromal tumors (GISTs) may develop in the gastrointestinal tract, with potential complications such as bleeding or obstruction.^{5,6}

Nervous System Lesions:

- Schwannomas, benign nerve sheath tumors, can affect various peripheral nerves, leading to symptoms such as numbness, weakness, or pain.^{5,6}

Ovarian Involvement (in females):

- Ovarian cysts and, less commonly, ovarian tumors can occur in women with CNC. Other Clinical Features:

- Thyroid nodules or goiter may be present.^{5,6}
- Testicular tumors have been reported in a subset of male CNC patients.
- Affected individuals may experience pituitary gland anomalies and thyroid cancer, although these are less common.^{5,6}

The clinical manifestations of CNC are often highly variable between affected individuals, even within the same family. This variability is attributed to the specific genetic mutations that underlie the condition, with *PRKAR1A* and *PDE11A* gene mutations being the most frequently identified culprits. Dysregulation of the cAMP-protein kinase A (PKA) signaling pathway, as a consequence of these mutations, is central to the pathogenesis of CNC.^{5,6}

Diagnosing CNC typically requires a comprehensive evaluation by a team of specialists, including cardiologists, endocrinologists, dermatologists, and geneticists, among others. Genetic testing and molecular analysis play a critical role in confirming the diagnosis, especially in the presence of a family history of CNC.^{7,8}

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Understanding the broad spectrum of clinical manifestations associated with Carney Complex is essential for early diagnosis, effective management, and improved patient outcomes. Further research into the genetic and molecular basis of CNC is needed to uncover potential therapeutic targets and interventions, ultimately enhancing the quality of life for individuals affected by this rare and complex disorder.^{7,8}

Diagnosis

Diagnosing Carney Complex (CNC), a rare genetic disorder characterized by multifaceted clinical manifestations, presents a unique set of challenges due to its clinical heterogeneity and the diversity of organ systems it affects. A comprehensive diagnostic approach is essential to accurately identify and confirm CNC in affected individuals, allowing for timely intervention and management.^{9,10}

Clinical Assessment: The diagnostic journey typically begins with a thorough clinical assessment. Clinicians carefully evaluate the patient's medical history and present symptoms. The varied clinical manifestations of CNC may involve multiple organ systems, including the heart, skin, endocrine glands, and nervous system. It is critical for healthcare providers to maintain a high index of suspicion, especially when encountering patients with a family history of CNC or individuals displaying characteristic clinical features.^{9,10}

Cardiac Evaluation:

- Cardiac myxomas, particularly atrial myxomas, are a cardinal feature of CNC.

Echocardiography, specifically transesophageal echocardiography (TEE), is a key diagnostic modality for detecting these cardiac tumors.^{11,12}

- Cardiac magnetic resonance imaging (MRI) may also be employed to provide detailed information on the location, size, and characteristics of myxomas.^{11,12}

Dermatological Assessment:

- The presence of multiple cutaneous lentiginos, blue nevi, and other skin pigmentation abnormalities is a strong clinical indicator. Dermatological examination plays a crucial role in CNC diagnosis.^{11,12}

Endocrine and Hormonal Investigations:

- For patients suspected of having primary pigmented nodular adrenocortical disease (PPNAD), hormonal studies, including cortisol, aldosterone, and adrenocorticotropic hormone (ACTH) levels, are performed to assess adrenal gland function.^{11,12}

- Imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI) help visualize adrenal nodules.^{11,12}

Genetic Testing:

- Genetic testing is pivotal for confirming CNC diagnosis, especially when the clinical presentation is consistent with the disorder. Mutations in genes such as PRKARIA and PDE11A, which are integral to the cAMP-protein kinase A (PKA) signaling pathway, are commonly associated with CNC.^{11,12}
- Molecular genetic analysis of these genes, either by

Sanger sequencing or next-generation sequencing, can identify pathogenic mutations.^{11,12}

Ophthalmological Examination:

- Patients may undergo eye examinations to assess for abnormalities such as myopia or pigmentary abnormalities in the retina, which can be associated with CNC.^{11,12}

Radiological Imaging:

- Depending on the clinical context and symptoms, additional radiological studies may be performed to evaluate the presence of tumors or other structural abnormalities in the nervous system, gastrointestinal tract, thyroid, or other affected areas.^{11,12}

Family Screening:

- Due to the autosomal dominant inheritance pattern of CNC, it is crucial to screen family members for potential gene mutations and clinical manifestations, even in the absence of symptoms. This allows for early detection and intervention.^{11,12}

The diagnosis of CNC is often a multidisciplinary effort, involving specialists in cardiology, dermatology, endocrinology, genetics, and other relevant fields. Collaboration among these experts is essential to ensure a holistic assessment of the patient and facilitate timely intervention.^{11,12}

In conclusion, the diagnosis of Carney Complex necessitates a comprehensive and integrated approach that combines clinical evaluation, genetic testing, and specialized investigations. Early and accurate diagnosis is paramount in guiding appropriate management and improving the quality of life for individuals affected by this rare and complex genetic disorder. Moreover, ongoing research efforts in the genetics and pathophysiology of CNC hold promise for enhanced diagnostic precision and therapeutic options in the future.^{11,12}

Treatment

Carney Complex (CNC), a rare and complex genetic disorder characterized by a broad spectrum of clinical manifestations, demands a multifaceted and individualized treatment approach. Given the heterogeneity of CNC and the diversity of affected organ systems, management strategies must be tailored to address specific clinical features while maintaining a comprehensive, patient-centered perspective. This article explores the various therapeutic interventions and their evolving landscape in the context of CNC.^{13,14}

Surgical Intervention:

- Cardiac myxomas, which are frequently encountered in CNC, typically require surgical excision to alleviate symptoms and reduce the risk of embolic events. A thorough assessment of the tumor's size, location, and involvement of cardiac structures guides the surgical approach.^{13,14}
- Dermatological interventions may involve laser therapy or excision for cutaneous lesions, including lentiginos and

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blue nevi, to improve cosmetic outcomes.^{13,14}

Endocrine Management:

- For individuals with primary pigmented nodular adrenocortical disease (PPNAD) and resultant Cushing's syndrome, medical management with steroidogenesis inhibitors may be considered. Adrenal-sparing surgery, if applicable, is another option.^{13,14}

- Regular endocrine follow-up and cortisol level monitoring are essential for those with PPNAD.^{13,14}

Cardiac Surveillance:

- After surgical removal of cardiac myxomas, lifelong cardiac surveillance, including regular echocardiography and cardiology consultations, is necessary to monitor for recurrence or the development of new tumors.^{13,14}

Genetic Counseling:

- Genetic counseling plays a pivotal role in CNC management. Affected individuals and their families benefit from understanding the genetic basis of CNC, which aids in risk assessment, family planning, and early detection.^{13,14}

Surveillance for Associated Tumors:

- Regular screening for associated tumors, such as gastrointestinal stromal tumors (GISTs), schwannomas, and testicular tumors, is essential. Imaging modalities like CT scans, MRIs, and ultrasound are employed to detect these neoplasms.

- Ovarian monitoring for cysts or tumors is recommended in females with CNC.^{13,14}

Hormonal Management:

- For individuals with hormone-secreting pituitary adenomas, endocrinologists may consider medical therapy, radiation, or surgical intervention to manage hormone excess and tumor size.^{13,14}

- In cases of acromegaly due to growth hormone-secreting pituitary adenomas, somatostatin analogs or growth hormone receptor antagonists may be utilized.^{13,14}
- Ophthalmological Care:

- Regular eye examinations are necessary to monitor for myopia and retinal pigmentary abnormalities, both of which are potential ophthalmological manifestations of CNC.^{13,14}

Research and Emerging Therapies:

- Due to the limited understanding of CNC and its genetic basis, ongoing research is critical to elucidate the underlying molecular pathways and develop targeted therapies.^{13,14}

- Emerging treatment modalities, including potential therapies targeting the dysregulated cAMP-protein kinase A (PKA) signaling pathway, are under investigation.^{13,14}

Supportive Care:

- CNC patients often benefit from psychological and emotional support to cope with the challenges associated with the condition. Support groups and counseling services can offer valuable assistance.^{13,14}
- Long-Term

Follow-Up:

- Lifelong follow-up, coordinated by a team of specialists, is crucial for managing CNC, as the condition's clinical manifestations may evolve over time.^{13,14}

The management of Carney Complex is complex, necessitating a multidisciplinary approach, close patient monitoring, and a proactive stance in addressing the varied clinical manifestations.

Additionally, it is vital for healthcare providers to stay informed about emerging therapies and research developments, which may hold promise for more targeted treatments in the future. In the context of this rare genetic disorder, personalized care is paramount to optimize the quality of life and outcomes for those living with CNC.^{13,14}

CONCLUSION

In the realm of rare genetic disorders, Carney Complex (CNC) stands as a unique and intricate puzzle, challenging both patients and healthcare professionals with its multifaceted clinical manifestations. This article has explored CNC in-depth, shedding light on its clinical presentation, epidemiology, diagnosis, and treatment, emphasizing the complex nature of this condition and the evolving landscape of its management.

CNC, as we've seen, presents with a remarkable diversity of clinical features, spanning across the cardiovascular, dermatological, endocrine, gastrointestinal, and nervous systems. This heterogeneity can make CNC a diagnostic enigma, with its various manifestations often mimicking other medical conditions. As such, heightened awareness and a high index of suspicion are crucial in the clinical evaluation of patients presenting with characteristic features or family history.

The diagnostic journey for CNC is a multi-faceted process, encompassing clinical assessments, genetic testing, imaging studies, and ophthalmological examinations. The discovery of pathogenic mutations in genes such as *PRKAR1A* and *PDE11A*, both integral to the cAMP-protein kinase A (PKA) signaling pathway, has paved the way for more accurate and precise diagnoses. Furthermore, the importance of genetic counseling in CNC cannot be overstated, as it enables informed decision-making, risk assessment, and early detection in affected families.

Managing CNC is a complex endeavor, often requiring a combination of surgical interventions, medical treatments, regular surveillance, and supportive care. For cardiac myxomas, surgical excision remains the standard of care, while endocrine disturbances, such as Cushing's syndrome, may be managed through a variety of interventions, including surgery and medical therapy. Lifelong cardiac and oncological surveillance is indispensable for CNC patients, as the risk of tumor recurrence and the development of new neoplasms persist.

In the ever-evolving landscape of medicine, research is a beacon of hope. The pursuit of a deeper understanding of CNC,

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its genetic basis, and the dysregulated cAMP-PKA pathway continues to yield insights that may someday lead to more targeted therapies and improved outcomes for those living with this condition. Emerging treatment modalities and ongoing studies promise to expand our knowledge and enhance our ability to manage CNC more effectively.

In conclusion, Carney Complex serves as a compelling example of the challenges and opportunities within the realm of rare genetic disorders. Its complexity, rarity, and variable clinical expressions make it a formidable adversary, but through collaboration, research, and personalized care, we are forging a path towards better management and improved quality of life for CNC patients. As we continue to unravel the intricacies of CNC, we draw closer to a future where more precise diagnostics and targeted therapeutics become a reality, offering hope to those affected by this enigmatic condition.

REFERENCES

- I. Bertherat J, Groussin L, Sandrini F, Matyakhina L, Bei T, Stergiopoulos S, Papageorgiou T, Bourdeau I, Kirschner LS, Vincent-Dejean C, Perlemoine K, Gicquel C, Bertagna X, Stratakis CA (2003) Molecular and functional analysis of PRKAR1A and its locus (17q22-24) in sporadic adrenocortical tumors: 17q losses, somatic mutations, and protein kinase A expression and activity. *Cancer Res* 63:5308-19
- II. Bertherat J, Horvath A, Groussin L, Grabar S, Boikos S, Cazabat L, Libe R, René-Corail F, Stergiopoulos S, Bourdeau I, Bei T, Clauser E, Calender A, Kirschner LS, Bertagna X, Carney JA, Stratakis CA (2009) Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. *J Clin Endocrinol Metab* 94:2085-91
- III. Beuschlein F, Fassnacht M, Assié G, Calebiro D, Stratakis CA, Osswald A, Ronchi CL, Wieland T, Sbierra S, Faucz FR, Schaak K, Schmittfull A, Schwarzmayr T, Barreau O, Vezzosi D, Rizk-Rabin M, Zabel U, Szarek E, Salpea P, Forlino A, Vetro A, Zuffardi O, Kisker C, Diener S, Meitinger T, Lohse MJ, Reincke M, Bertherat J, Strom TM, Allolio B (2014) Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *N Engl J Med*. 370:1019-28.
- IV. Cazabat L, Libè R, Perlemoine K, René-Corail F, Burnichon N, Gimenez-Roqueplo AP, Dupasquier-Fediaevsky L, Bertagna X, Clauser E, Chanson P, Bertherat J, Raffin-Sanson ML. (2007) Germline inactivating mutations of the aryl hydrocarbon receptor-interacting protein gene in a large cohort of sporadic acromegaly: mutations are found in a subset of young patients with macroadenomas. *Eur J Endocrinol* 157:1-8
- V. Forlino A, Vetro A, Garavelli L, Ciccone R, London E, Stratakis CA, Zuffardi O.N (2014) PRKACB and Carney complex. *N Engl J Med*. 370:1065-7.
- VI. Groussin L, Horvath A, Jullian E, Boikos S, René-Corail F, Lefebvre H, Cephise-Velayoudom FL, Vantghem MC, Chanson P, Conte-Devolx B, Lucas M, Gentil A, Malchoff CD, Tissier F, Carney JA, Bertagna X, Stratakis CA, Bertherat J (2006) A PRKAR1A mutation associated with primary pigmented nodular adrenocortical disease in 12 kindreds. *J Clin Endocrinol Metab* 91:1943-9
- VII. Groussin L, Kirschner LS, Vincent-Dejean C, Perlemoine K, Jullian E, Delemer B, Zacharieva S, Pignatelli D, Carney JA, Luton JP, Bertagna X, Stratakis CA, Bertherat J (2002) Molecular analysis of the cyclic AMP-dependent protein kinase A (PKA) regulatory subunit 1A (PRKAR1A) gene in patients with Carney complex and primary pigmented nodular adrenocortical disease (PPNAD) reveals novel mutations and clues for pathophysiology: augmented PKA signaling is associated with adrenal tumorigenesis in PPNAD. *Am J Hum Genet* 71:1433-42
- IX. Horvath A, Bossis I, Giatzakis C, Levine E, Weinberg F, Meoli E, Robinson-White A, Siegel J, Soni P, Groussin L, Matyakhina L, Verma S, Remmers E, Nesterova M, Carney JA, Bertherat J, Stratakis CA (2008) Large deletions of the PRKAR1A gene in Carney complex. *Clin Cancer Res* 14:388-95
- X. Huang SJ, Amendola LM, Stern DL. Variation among DNA banking consent forms: points for clinicians to bank on. *J Community Genet*. 2022;13:389-97.
- XI. Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA (2000) Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nat Genet* 26:89-92
- XII. Mateus C, Palangí A, Franck N, Groussin L, Bertagna X, Avril MF, Bertherat J, Dupin N (2008) Heterogeneity of skin manifestations in patients with Carney complex. *J Am Acad Dermatol* 59:801-10
- XIII. Perdigão PF, Stergiopoulos SG, De Marco L, Matyakhina L, Boikos SA, Gomez RS, Pimenta FJ, Stratakis CA (2005) Molecular and immunohistochemical investigation of protein kinase a regulatory subunit type 1A (PRKAR1A) in odontogenic myxomas. *Genes Chromosomes Cancer* 44:204-11
- XIV. Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline

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- mutation. *Nat Genet.* 2016;48:126-33
- XV. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* 2015;17:405-24.