

# World Journal of *Clinical Cases*

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## Exome analysis for Cronkhite-Canada syndrome: A case report

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### Abstract

#### BACKGROUND

Cronkhite-Canada syndrome (CCS) is a rare, non-genetic disorder characterized by multiple gastrointestinal polyps, and ectodermal lesions such as alopecia, fingernail atrophy, and skin mucosal pigmentation. Unfortunately, the pathogenesis of CCS is currently unknown.

#### CASE SUMMARY

Here, we describe the case of an elderly female with diarrhea, fatigue, and hair loss, who experienced abdominal pain for over half a year and was found to have multiple gastrointestinal polyps. She was diagnosed with CCS and was treated with albumin supplementation and prednisone, and her electrolyte imbalance was corrected. Following treatment, her symptoms significantly improved. To elucidate the role of potential genetic events in the pathogenesis of CCS, we performed exome sequencing using an extract of her colorectal adenoma.

#### CONCLUSION

Our data revealed multiple somatic mutations and copy number variations. Our findings provide a novel insight into the potential mechanisms of CCS etiology.

**Key Words:** Whole exome sequencing; Cronkhite-Canada syndrome; Somatic mutations; Case report

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**Core Tip:** Cronkhite-Canada syndrome (CCS) is a rare, non-genetic disorder characterized by multiple gastrointestinal polyps, ectodermal lesions including alopecia, fingernail atrophy, and skin mucosal pigmentation. However, its pathogenesis is unclear. We performed exome sequencing in an elderly female patient and obtained somatic mutations in the hope that these data could provide a genetic perspective on the pathogenesis of CCS.

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## INTRODUCTION

Cronkite and Canada reported the first case of Cronkhite-Canada syndrome (CCS) in 1955, which was characterized by multiple gastrointestinal polyps, ectodermal lesions including alopecia, fingernail atrophy, and skin mucosal pigmentation[1]. Unfortunately, despite much research, the pathogenesis of CCS remains unknown. Some studies have reported an association between CCS and immune factors, especially infiltration of IgG4-positive plasma cells[2]. To date, there is no standard treatment for CCS; however, some studies have recommended glucocorticoid therapy for partial symptom relief[3]. Herein, we describe the case of an elderly female with the diagnosis of CCS. As part of her treatment regimen, she received albumin supplementation and prednisone, and her electrolyte disturbance was corrected. After 15 days, her symptoms, namely, hypokalemia and diarrhea, significantly improved. To elucidate the role of potential genetic events in the pathogenesis of CCS, we performed exome sequencing using DNA extracted from a colorectal adenoma. Our data revealed multiple somatic mutations and copy number variations. We are the first to identify 3 novel genetic mutations (*USP24*, *KCNQ5*, and *FKBP10*) in a CCS patient. Moreover, we demonstrated that the *HPSE2*, *SPATA7*, and *ZC3H18* genes had markedly elevated copy numbers. Given this evidence, we hypothesized that these specific gene mutations and copy number variations are associated with the pathogenesis of CCS.

## CASE PRESENTATION

### Chief complaints

An elderly female patient sought treatment for diarrhea, fatigue, and hair loss, as well as abdominal pain for half a year at the Department of Gastroenterology on October 11, 2019.

### History of present illness

She reported diarrhea 4-5 times daily, watery stools, no blood, and abdominal pain under the xiphoid process, not related to eating. Physical examination revealed obvious emaciation, alopecia, and nail atrophy.

### History of past illness

Her past medical history is unremarkable.

### Personal and family history

Her family history is unremarkable.

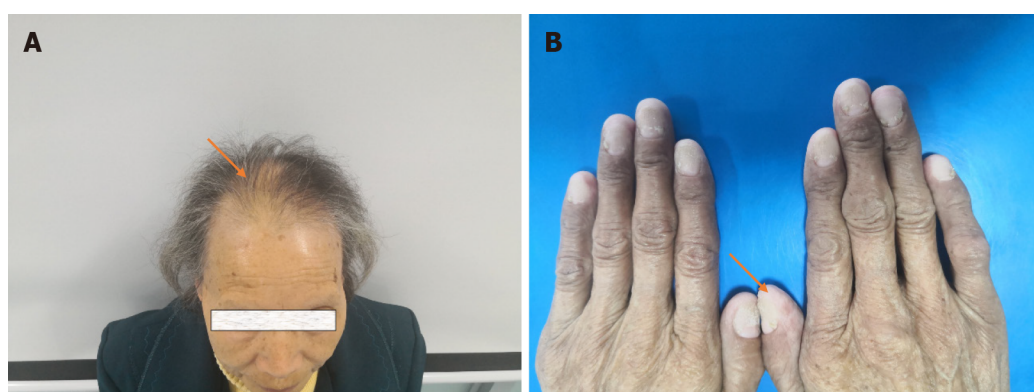
### Physical examination

Physical examination revealed obvious emaciation, alopecia, and nail atrophy (Figure 1).

### Laboratory examinations

Laboratory tests revealed the following: (routine blood examination) white blood cells:  $10.03 \times 10^9/L$ , hemoglobin: 95 g/L, and platelets:  $151 \times 10^9/L$ ; (liver function) albumin 25 g/L; (electrolytes)  $Na^+$ : 128 mmol/L,  $K^+$ : 2.8 mmol/L.





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**Figure 1** Signs in the patient with Cronkhite-Canada syndrome. A: The patient had typical symptoms of hair loss (orange arrow); B: The patient had typical nail atrophy (orange arrow).

### Imaging examinations

She underwent gastroenteroscopy, which revealed multiple small polyps in the gastrointestinal tract (Figure 2).

### Further diagnostic work-up

**DNA samples:** This study was performed in accordance with the guidelines of the Ethics Committee of the Mianyang Central Hospital. DNA was extracted from a sample of the patient's colonic adenomas and normal colon tissue. The samples were obtained *via* endoscopic mucosal resection and were preserved in liquid nitrogen.

**Whole exome sequencing:** Genomic DNA  $\geq 1.5$   $\mu$ g from colonic adenomas and normal colon tissue was used for whole exome sequencing library construction. The Agilent liquid chip capture system was employed for the efficient enrichment of human DNA in all exon regions. Upon library construction, Qubit2.0 was used for preliminary quantification, and the library was diluted to 1 ng/ $\mu$ L. Subsequently, Agilent 2100 was utilized for detection of the library insert size to ensure library quality (the effective concentration of the library was  $> 2$  nmol/L). Next, PE150 high-throughput sequencing was performed based on the Illumina HiSeq platform. Finally, the library and capture experiment were constructed using the Agilent SureSelect v5 kit, according to the manufacturer's instructions.

**Quality control:** Upon collection of the original sequenced reads (Sequenced Reads), Cutadapt software was used to remove the adapter and reads with N (N denotes that the base information cannot be determined) ratio  $\geq 10\%$ . In addition, the read pairs were discarded if the low-quality bases (quality score  $\leq 5$ ) accounted for 50% of the entire single read. Furthermore, quality controls (including, sequencing error rate distribution, base quality distribution, and GC content distribution) were performed, based on the selected filtered reads using the above methods.

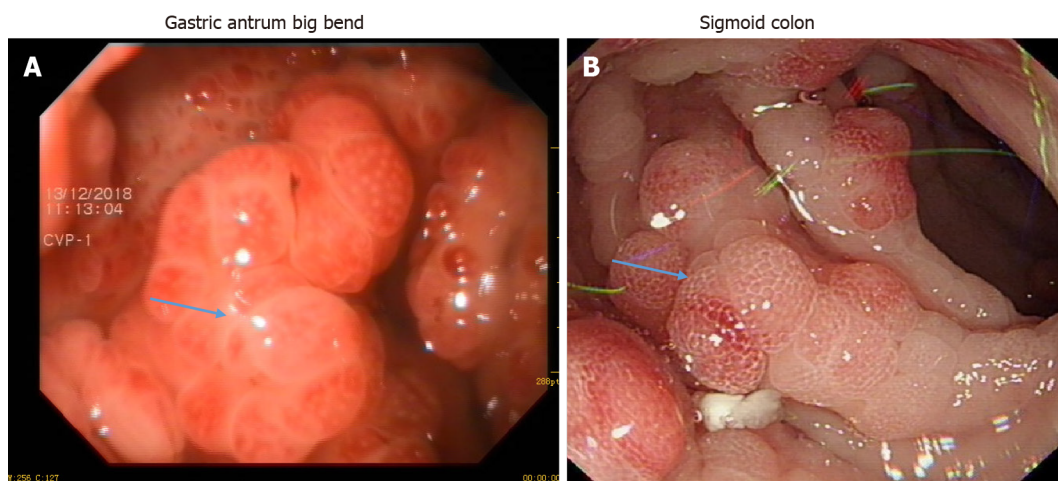
**Data analysis:** The BWA (v0.7.15) software was used to map the sequenced reads to the human reference genome GRCh37 (hg19). Picard software was used to remove the sequence generated by PCR-duplication. The somatic single nucleotide variations (SNVs) and InDel detection were performed using the GATK (v4.1.0.0) and muTect2 software, respectively. The ANNOVAR software (Mon, 17 Jul 2017) was used to annotate gene mutations. Lastly, the control-free software (v11.4) was used for copy number variation analysis.

### Exon sequencing results

Somatic mutation analysis, based on samples from the CCS patient, identified 47 SNVs. 75% of them were nonsynonymous SNVs. In addition, approximately 70% of them occurred in exonic regions (Figure 3). Mutations of the *USP24*, *KCNQ5*, and *FKBP10* genes were identified as deleterious *via* SIFT, LRT, Polyphen2, and Mutation Taster software (Supplementary Table 1). Based on the COSMIC data, the three mutations in genes *USP24*, *KCNQ5*, and *FKBP10* may be novel in CCS. The mutated genes are associated with the regulation of DNA-templated transcription (Figure 4). Our analysis showed that the *HPSE2*, *SPATA7*, and *ZC3H18* genes had markedly elevated copy numbers, while other significant altered fragments were located in the intergenic regions (Table 1).

**Table 1** The identified copy number alterations, as shown by exome sequencing

| Chr | Start    | End      | Gene          | Copy number | Status | Wilcoxon rank sum test <i>P</i> value | Kolmogorov-Smirnov test <i>P</i> value |
|-----|----------|----------|---------------|-------------|--------|---------------------------------------|----------------------------------------|
| 2   | 1.32E+08 | 1.32E+08 |               | 3           | Gain   | 0.02315                               | 0.14375                                |
| 3   | 37095399 | 37000000 |               | 3           | Gain   | 0.00756                               | 0.02719                                |
| 6   | 29910395 | 30000000 |               | 3           | Gain   | 0.01482                               | 0.03778                                |
| 6   | 1.37E+08 | 1.37E+08 |               | 3           | Gain   | 0.03443                               | 0.10684                                |
| 10  | 98711799 | 99000000 | <i>HPSE2</i>  | 3           | Gain   | 0.0104                                | 0.04592                                |
| 11  | 73534113 | 74000000 |               | 1           | Loss   | 0.00139                               | 0.0043                                 |
| 14  | 88442644 | 88000000 | <i>SPATA7</i> | 3           | Gain   | 0.02368                               | 0.06465                                |
| 16  | 3074297  | 3078522  |               | 3           | Gain   | 0.00136                               | 0.0099                                 |
| 16  | 88600346 | 89000000 | <i>ZC3H18</i> | 3           | Gain   | 0.00311                               | 0.00561                                |
| 17  | 2274380  | 2276393  |               | 3           | Gain   | 0.0146                                | 0.03707                                |
| 19  | 38702846 | 39000000 |               | 3           | Gain   | 0.00017                               | 0.00075                                |
| 19  | 47287593 | 47000000 |               | 3           | Gain   | 0.01445                               | 0.03707                                |
| 22  | 28194746 | 28000000 |               | 3           | Gain   | 0.0032                                | 0.00641                                |
| Y   | 1456244  | 1486988  |               | 3           | Gain   | 0.00126                               | 0.0036                                 |
| Y   | 13309548 | 14000000 |               | 1           | Loss   | 0.00059                               | 0.00437                                |
| Y   | 59359925 | 59000000 |               | 3           | Gain   | 0.01688                               | 0.04401                                |



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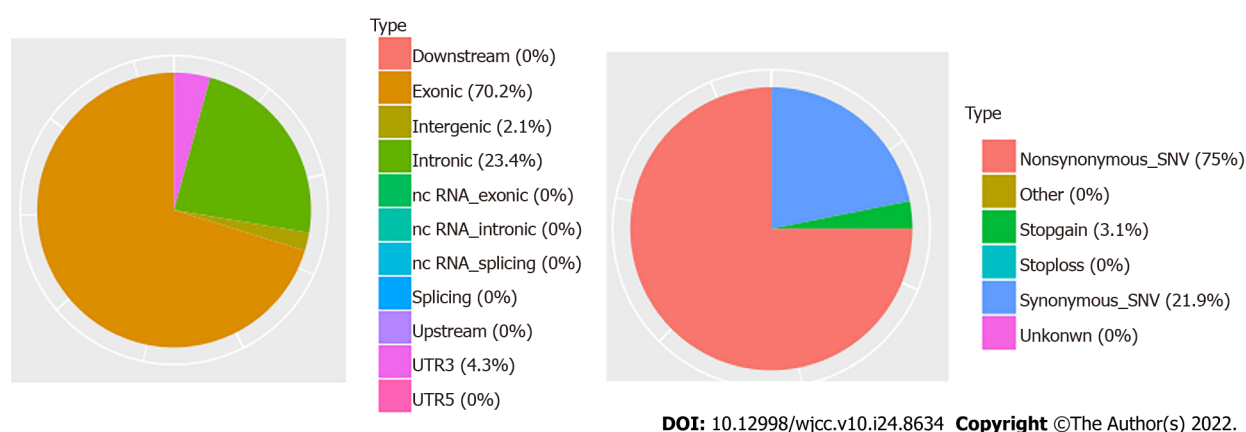
**Figure 2** Endoscopic characteristics of the patient with Cronkhite-Canada syndrome. A: The patient presented with multiple adenomas of the stomach greater curvature (blue arrow); B: The patient presented with multiple adenomas of the colon (blue arrow).

## FINAL DIAGNOSIS

The patient was diagnosed with CCS.

## TREATMENT

As part of her treatment regimen, she received albumin supplementation 10 g/d and prednisone 10 mg/d, and her electrolyte imbalance was corrected.



**Figure 3** The types of somatic single nucleotide variations detected in samples obtained from an elderly female patient with Cronkhite-Canada syndrome.

## OUTCOME AND FOLLOW-UP

Treatment lasted for 15 d and her diarrhea, hypokalemia, and abdominal pain significantly improved.

## DISCUSSION

Approximately 500 cases of CCS are currently described in the literature, with an estimated incidence of 1 in 1 million per year. The average age at CCS diagnosis is early 60s and it is predominantly diagnosed in males[4]. At present, there is no definite treatment plan for CCS. Previous literature reported that glucocorticoids and immunosuppression have certain benefits, and some studies reported that anti-tumor necrosis factor therapy is effective in CCS patients[5]. Our treatment plan and effect are consistent with these published works. However, there are limited studies on the pathogenesis of CCS. Therefore, based on the fact that CCS is an acquired non-genetic disease, we performed exon sequencing of excised diseased and non-diseased tissues from our CCS patient, in an attempt to elucidate CCS pathogenesis. Based on our exon sequencing results, three genes, namely, *USP24*, *KCNQ5*, and *FKBP10* may be related to CCS pathogenesis.

We searched Human Gene Mutation Database (HGMD) and found that *USP24* belongs to a large family of cysteine proteases that function as deubiquitinating enzymes. *USP24* stabilizes the bromine domain protein and promotes malignant lung cancer[6]. In addition, Zhang L *et al*[7] found that *USP24* deubiquitinase regulates DNA damage by directly targeting the tumor suppressor gene p53. Also, the *USP24-Mcl-1* axis may represent a novel strategy in treating acute T cell lymphoma[8], whereas functional studies of the *FKBP10* mutation reported an association with osteogenesis imperfecta[9]. The above two genes are both related to tumor formation and body development. Combined with the clinicopathological characteristics of CCS, we speculated that gene mutations are involved in the formation of multiple intestinal adenomas. The *KCNQ* family protein activates slowly during depolarization and forms heterogeneous channels with the protein encoded by *KCNQ5* gene. *KCN5* dependent potassium channels play an important role in airway smooth muscle relaxation[10]. Given the symptoms of diarrhea and difficult-to-correct hypokalemia of CCS, the *KNQ3* mutation seems to suggest an association.

In terms of copy variation, *ZC3H18* copy number losses are known to contribute to homologous recombination defects in high-grade serous ovarian cancers[11]. *HPSE2* was reported to play an inhibitory role in bladder cancer[12]. Mutations in *SPATA7* are associated with fundus macular degeneration[13]. CCS patients have multiple clinicopathological manifestations, such as, multiple gastrointestinal adenomas, nail atrophy, skin pigmentation, and alopecia, which may be related to the increased copy number of the three genes mentioned above.

However, due to the isolation of individual cases, the sample size of phenotypic alterations, caused by the above gene mutations, needs to be further expanded.

CCS is a rare disease and its etiology is unclear. The autoimmune etiology of CCS was previously proposed, and case reports described beneficial responses to immunosuppressive therapies such as azathioprine, anti-tumor necrosis factor antibodies, cyclosporine, and sirolimus[14,15]. Interestingly, Brigid S. Boland also conducted exome sequencing on tissue from a CCS patient who responded effectively to infliximab, and found that *PRKDC* mutations may be involved. However, this gene was not included in our analysis[14]. This suggests that the data on these mutations require further validation using tissues from a large CCS patient population.

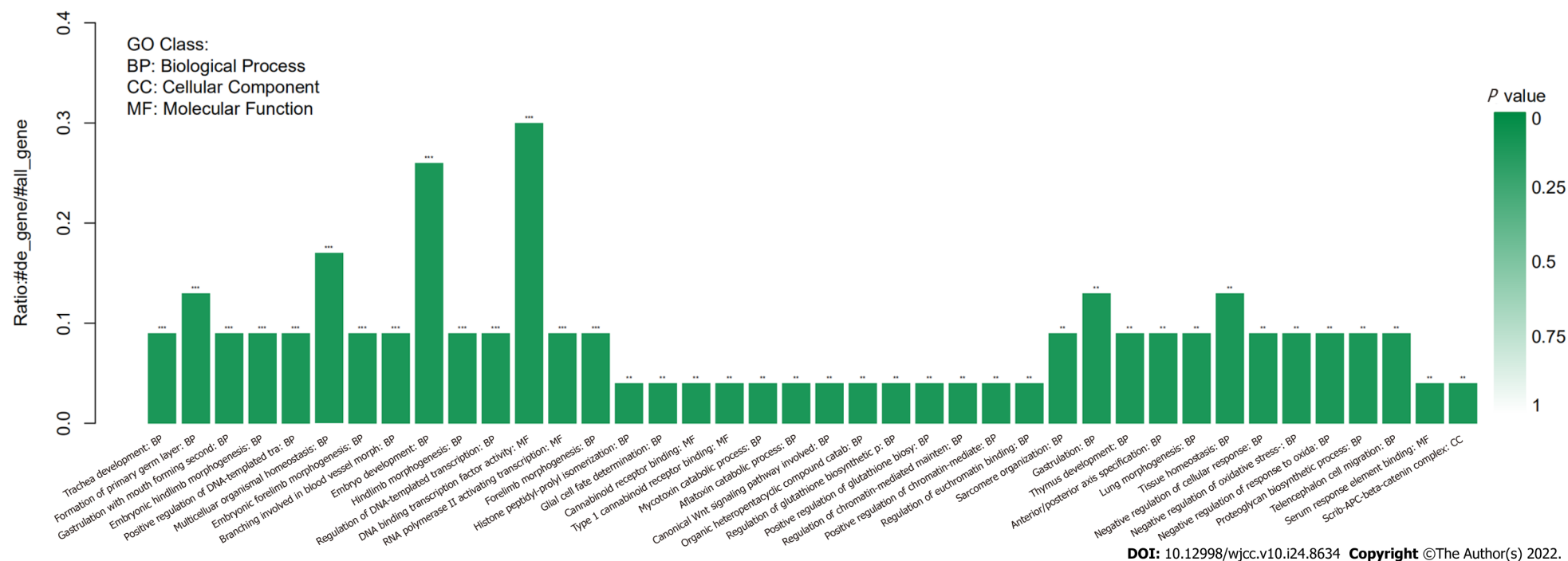


Figure 4 The functional attributes of mutated genes detected in an elderly female patient with Cronkhite-Canada syndrome.

## CONCLUSION

In conclusion, we report a classic case of CCS, which was effectively treated with parenteral nutritional support and glucocorticoids, and we explored the pathogenesis of CCS from the perspective of gene mutation. Based on our analysis, we identified several gene mutations and alterations in gene copy numbers. However, we acknowledge that more genetic and epidemiological research is necessary to understand the complex pathogenesis of this rare but highly fatal disease.

## FOOTNOTES

**Author contributions:** Li ZD and He YJ treated the patient and drafted the manuscript; Rong L and Ji YZ performed the exon sequencing work; Li X helped to search for references; Zhou SF and Li XA performed data retrieval and helped with drafting of the manuscript; all authors read and approved the final manuscript.

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