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REVIEW ARTICLE

Is Pouch Specific to Colon and Not Ileum?

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Abstract: ***Background*:** Congenital Pouch Colon (CPC) is an anorectal anomaly with an incidence of 3.5:1 in males and females, respectively. We have earlier reported CPC to be quite prevalent in north Indian tertiary care centers.

***Objective*:** In this article, we deliberate on the possible causes associated with CPC bringing the manifestation of the disease. In addition, we throw insights on the effective role of this congenital anomaly in Colon and provide systems genomic evaluation by comparing our recent analysis to that of Colon and Ileum based on Next-Generation Sequencing (NGS) studies.

***Conclusion*:** In this commentary article, we argue that a host of epigenetic factors could be the reason why the disease is manifested in colon alone. We further hypothesize on the few unmet challenges linking epigenetics to understand the genetic variants.

Keywords: Congenital pouch colon, anorectal malformation, colovesical fistula, colostomy, imperforate anus, systems genomics.

1. INTRODUCTION

Congenital Pouch Colon (CPC) is a rare variant of high Anorectal Malformation (ARM). The peculiarity of this anomaly is that the colon is malformed with the pouch-like globular dilatation of whole or parts of colon usually ending in a wide fistulous communication to the urinary bladder in males, while in females; they are often persistent with cloaca [1]. Earlier, we reported five types of CPC, common in males comprising about 5-18% of all ARM with few cases reported from other countries as well [2]. Whereas plain abdominal radiographs have been helpful to determine the type of CPC [3], the standard surgical management involves protective stoma initially followed by definitive repair at a later date [4].

Because of the below-mentioned reasons, the likelihood of fecal incontinence following corrective surgery in CPC children is probably higher than those having a high imperforate anus without the pouch colon [5, 6]. Anatomically, CPC has outpouching of the colon. The excised pouch is an abnormal tissue suggested by histopathological examination and immunohistochemistry. There are instances of pouch redilatation in CPC type 1 and 2 in which Coloplasty/ Colography is performed as definitive repair at a later stage which could be due to additional muscle coat seen in CPC type 1 and 2 [7]. Furthermore, pouch excision is rendered by shortening of bowel in most of the cases [8]. Pena reported "total continence" rates of 100% in patients with perineal fistula, 66% in patients with vestibular fistula, 34% in patients with bulbar fistula, 26% in patients with prostate fistula and none with a rectovesical fistula [9]. According to Nelson, in amphibians, birds and mammals the digestive tube has a tendency for enlargement or extension to occur in the area of the function of the small and large intestine further strengthening the dilatation [10]. The colonic part of the physiological hernia elongates less rapidly and has no tendency to become coiled as a small bowel [11]. While the pathogenesis and etiology of the CPC are not well known, wherein epigenetics could be the causal factor [12, 13], we hypothesize this to: (a) the plausible role of epigenetic factors on distribution of CPC in northern India; and (b) CPC morphogenesis restricted to colon only, but not in small bowel.

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2. DISCUSSION

Significant differences exist in the prevalence of most urogenital anomalies in tropical countries. With both genetic and environmental (often clearly defined geographically) factors relevant, the higher incidence of CPC cases in northern India might be attributed to nutritional and dietary patterns in this part of the world. Although there are reports influencing the gut microbiota [14-17], these substances have been possibly shown to affect anorectal functioning with defecation problems [18-21]. Furthermore, mutagenic effects in the form of viral agents could not be ruled out towards causality. For example, Cytomegalovirus (CMV), one of the most common causal agents for congenital infection has been known to cause birth defects and deafness, as with the presence of colonic CMV infection, it was reported to decrease response towards steroids and other immunosuppressive agents [22] causing various cancers such as breast, colon and prostate cancer, neuroblastoma, meduloblastoma, and glioblastoma [23]. Furthermore, such infections have been reported in immunocompetent individuals [24] causing an effect on the tissues such as oesophagus and colon [25].

In the recent past, the Global Disease Burden (GBD) has shifted from communicable to non-communicable anomalies and from early mortality to years lived with disability. The rising burden from disorders such as neurological, behavioral, musculo-skeletal disorders, and congenital anomalies impose new challenges on health systems [26]. Burden of disease studies have been implemented in many countries using the disability-adjusted life years (DALY) to assess major health problems as well as presenting a comprehensive assessment of the worldwide health impact of disease, injury and risk factors (Fig. **1**) [27-29]. However, it is challenging to provide routine quantification of GBD in terms of DALY which would otherwise add value to public health policy for the translation of evidence into policy [30, 31].

In addition, as mentioned earlier, from our recent histological findings, we revealed the distortion of submucosal and muscularis external linings in diseased condition as compared to normal colon tissue [7]. Although the preliminary reports complementing histopathological studies followed by comparative proteomic analysis indicate a remarkable difference in the expression of few muscular protein coding genes between the normal and affected tissue colon and poorly formed keratin in affected tissues, we argue that there could be enormous effect of poorly formed keratin filaments in the pouch colon patients leading to disrupted muscle fibres (Table **1**) as compared to normal colon. This could be correlated with pouch formation as elasticity of the

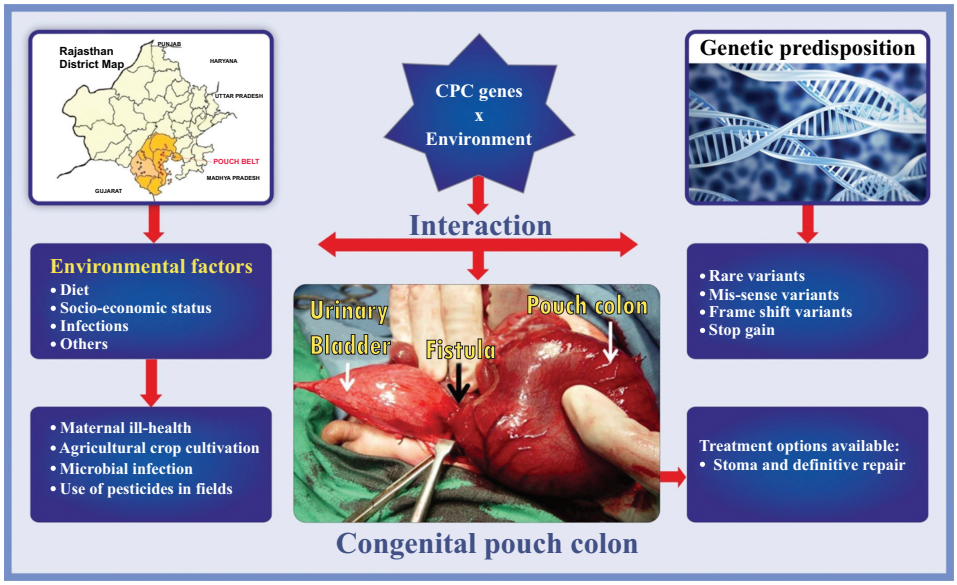

Fig. (1). Pictographic representation of genes and its influence on environment for manifestation of CPC [32].

Table 1. Comparative expression level of proteins between normal and affected colon tissue.

S.No.	Protein	Normal Colon	Affected Colon
1	Keratin-II	High	Low
2	Actin	High	Low
3	Zing finger protein	High	Low
4	GBP-5 (Human guanylate binding protein-5)	Low	High

Fig. (2). Flowchart depicting the methodology.

tissue is impaired due to distortion of mesentric cell linings. Furthermore, from 20 samples that we analysed for karyotyping, we have observed structural aberration in only one sample inherent to polymorphic variation increasing the length of heterochromatin region of chromosome 9 (unpublished (Fig. **2**)).

The preferential role of colon not ileum, could be attributed to the role of Fibroblast Growth Factor Receptor Type 4 (FGFR4) gene to have a high impact frame shift mutations from our Whole Exome Sequencing (WES) study [32]. Furthermore, it is known to be highly expressed in caecum, rectum and colon serving as an internal/localized tissue expression but not seen in small intestines or ileum [33]. Whereas Gli2, Gli3 and FGFR type mutations have been documented to cause a variety of ARMs, its association with Sonic Hedgehog signaling (SHH), all-trans-retinoic acid signaling (ATRA) pathways to colon augments the hypothesis that the pouch is indeed associated with colon, not necessarily ileum [34]. In addition, Wnt/β-catenin pathway is shown to be expressed and essential for intestinal homeostasis in a large number of studies which gives a subtle reason for the role of colon towards aggravated pouch [35].

To augment our hypothesis, we compared all the 65 variants obtained from our WES analysis for checking the similarity between colon and ileum like genes [32] with known significant differential expression between ileum, colon and publicly available GSE85499 dataset [36, 37]. In addition, the data from the RNA-Seq with various clinical subtypes constituting microarray data of biomarkers of human GI tract regions was collated (Fig. **3**). We observed several missense as well as frameshift variants to be in concordance with colorectal cancer exome datasets [38] besides a few non-coding RNAs especially *lnc-EPB41-1-1* shown to be promiscuously interacting with *KIF13A*, a gene causal to CPC [39]. Furthermore, our microarray findings also show that few non-coding RNAs are differentially expressed in CPC samples [40]. On the other hand, the situation is notably different in ulcerative colitis in adults when compared to the Crohn's disease where there is recurrence [41]. To some extent, this could be the reason perhaps why there is pathogenic effect of colon leading to ulcerative colitis and familial adenomatous polyposis. This tendency is also with the agreement that there are *GBA3* and *HAVCR1* genes involved with small intestine (Fig. **3**). However, one needs to integrate and assess the ontology/pathway "mutated" genes across assorted databases like ClinVar, dbSNP and supplement this information with further experiments. Besides this, the variation in coding sequences resulting in potential changes in protein sequences followed by global enrichment and association network analysis possibly will prioritize genes subtly linked to "rare" events which will be interesting to explore.

CONCLUSION

The CPC associated with ARM is an abnormally developed tissue and needs a better functional outcome of the remaining gut. The crux of the treatment lies on timely diagnosis and planned management. Hence, it is important for gastroenterologists and pediatric clinicians to be aware of the

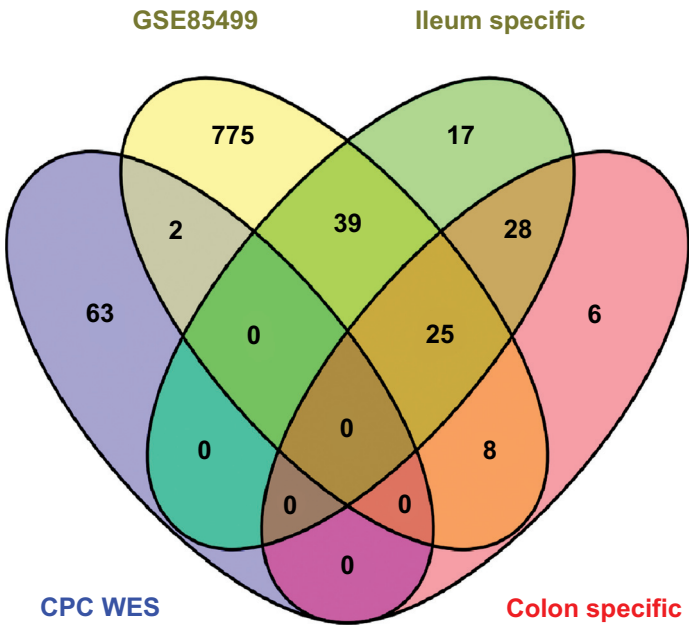

Fig. (3). Comparative study of already reported datasets and whole exome sequencing of CPC.

pathological perspective for proper diagnostic, evaluation and surgical management. The overall mortality of CPC was previously as high as 30-40%, but has now come down to 10-20% due to growing awareness of this condition and improvements in surgical and neonatal care management. We have discussed that prognosis depends on the extent of the malformation and excision of the pouch and end enterostomy associated with maximal survival (92.3%) in good-risk patients. In Next Generation Sequencing (NGS), there has been an increase in the number of samples sequenced using whole genome, transcriptomics (RNA-Seq), whole exome and targeted panels which has resulted in understanding the rare genetic diseases better. Nevertheless, there might be genetic variation observed in non-coding regions and at intersection of precision medicine scale, it is imperative to better understand CPC cases and find causal variants related to the disease. The trio analysis which is underway could subtly provide solutions on the possible assumptions of CPC restricted to colon, not ileum.

LIST OF ABBREVIATIONS

CPC	=	Congenital Pouch Colon
ARM	=	Anorectal Malformation
NGS	=	Next Generation Sequencing
CMV	=	Cytomegalovirus
GI	=	Gastro-intestinal
GBD	=	Global Disease Burden
DALY	=	Disability-adjusted life Years
WES	=	Whole Exome Sequencing
SHH	=	Sonic Hedgehog Signaling
ATRA	=	All-trans-retinoic Acid Signaling

AUTHORS' CONTRIBUTIONS

SG wrote the first draft in discussion with PS and PM. SG, PT, PS, PM, VN, AnS, AmS, NG and SLK wrote sections on discussions. SG, PT and PS prepared tables and figures with guidance from PM. PS, PM and KM proofread the manuscript. All authors read and approved the manuscript before submission.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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