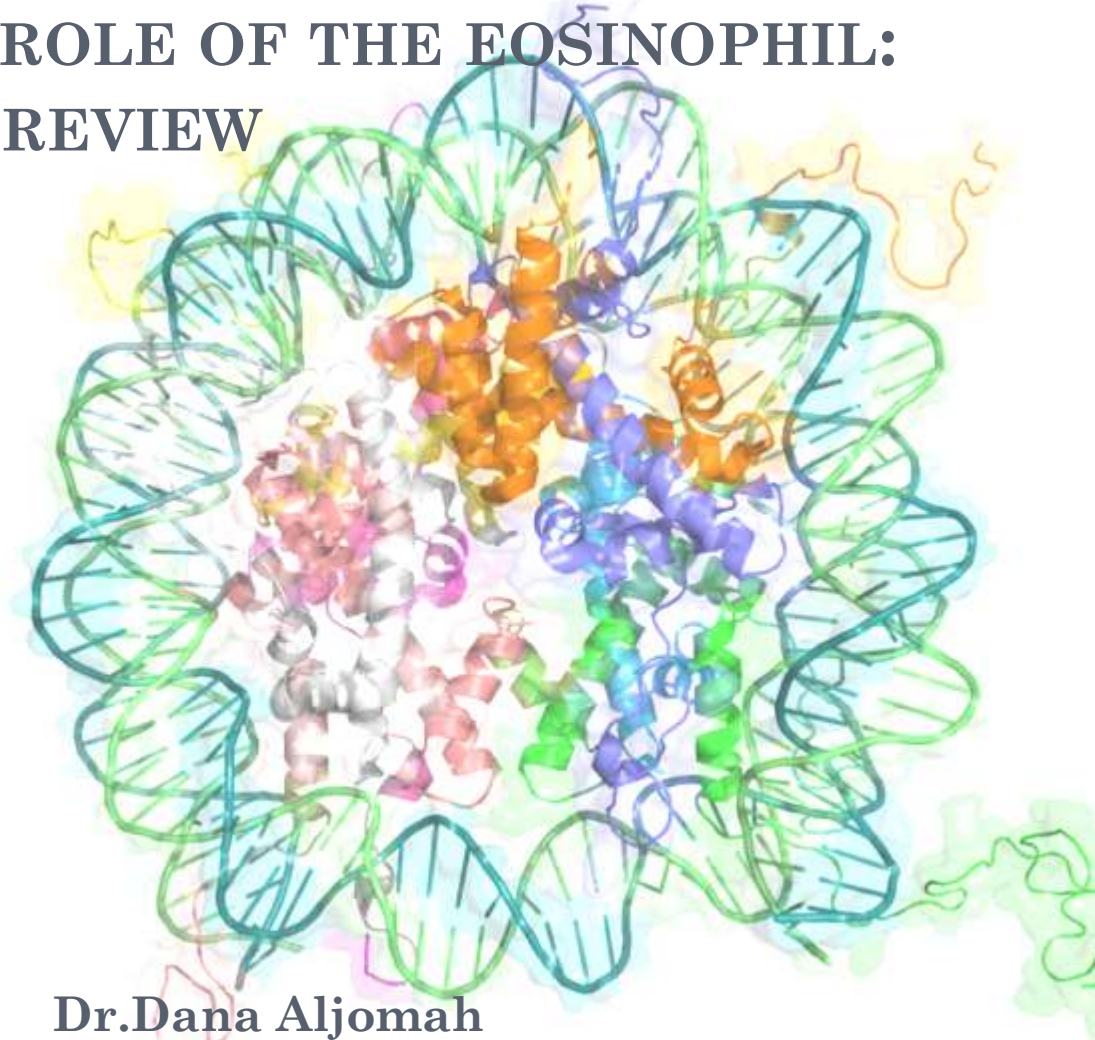


# EPIGENETICS OF CHRONIC RHINOSINUSITIS AND THE ROLE OF THE EOSINOPHIL: ARTICLE REVIEW



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ORIGINAL ARTICLE

# Epigenetics of chronic rhinosinusitis and the role of the eosinophil

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# INTRODUCTION

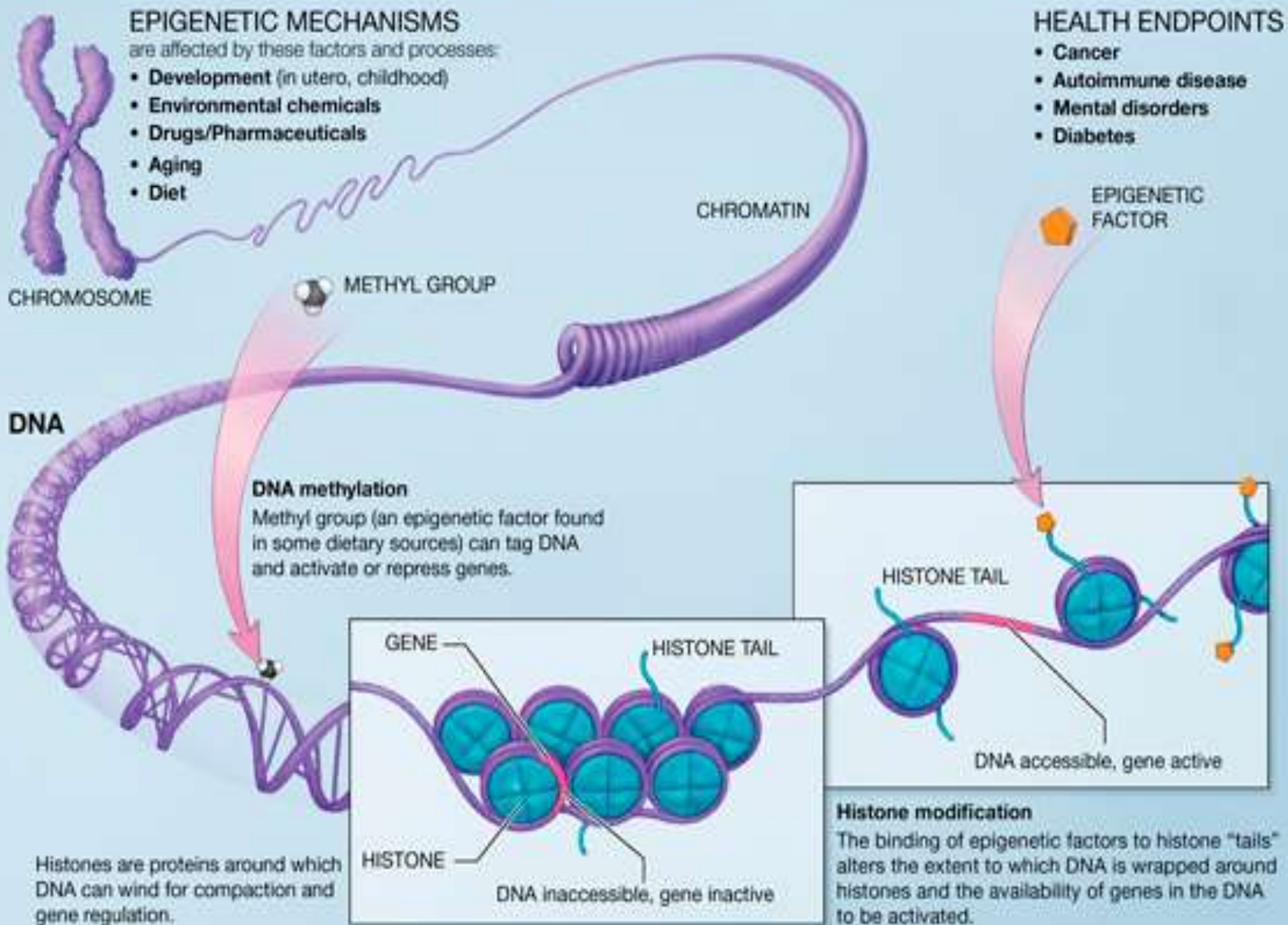
- Chronic rhinosinusitis (CRS) is one of the most prevalent diseases.
- In the United States , over 15% of the general population affected.
- 2 major forms can be differentiated:
  - CRS with nasal polyps (CRSwNP) .
  - CRS without nasal polyps (CRSsNP).



# EPIGENETICS

- the study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence .
- It refers to functionally relevant modifications to the genome that do not involve a change in the nucleotide sequence.
- Examples of such changes are DNA methylation and histone modification, both of which serve to regulate gene expression without altering the underlying DNA sequence.





# CRS WITH NASAL POLYPS

- Characterized by polypoid edema and tissue eosinophilia, and is dominated by T-helper 2 (Th2) cytokines.
- Up to 70% to 90% of patients with CRSwNP demonstrate abundant tissue eosinophilia, which is absent to a large degree in CRSsNP.
- Eosinophils release toxic mediators such as
  - Eosinophilic cationic protein (ECP),
  - Eosinophilic peroxidase (EPO)
  - Major basic protein.



- EPO and myeloperoxidase (from neutrophils) are capable of generating hypobromous acid (HOBr) and hypochlorous acid (HOCl), respectively.
- These hypohalous acids function well as antimicrobial agents; however, they can also cause substantial collateral damage to normal host tissues.
- Hypohalous acids may react with DNA, resulting in an array of damaged bases including 5-chlorocytosine (5ClC) and 5-bromocytosine (5BrC).



- These modified forms of cytosine (5BrC and 5ClC) may result in the aberrant methylation of cytosine during DNA replication.
- Cytosine methylation patterns in DNA comprise an epigenetic code for controlling gene activity and have been linked to differential gene expression.
- Methylation of cytosine can lead to transcriptional silencing of genes and altered gene expression without changes in the genomic sequence, whereas the absence of cytosine may lead to gene transcription.



- Inflammatory cell infiltrates are characteristically found in both CRSsNP and CRSwNP suggesting that inflammation may influence disease pathogenesis.
- However, the role of both neutrophils and eosinophils in the etiology of CRSwNP is yet to be established.



- The study hypothesize that eosinophils, which are predominantly found in CRSwNP, may lead to DNA modification and gene silencing through the production of 5BrC and may explain the difference in presentation between CRSwNP and CRSsNP.
- In this study, the goal is to determine the presence of 5BrC, 5ClC, and methylated cytosine in CRSwNP compared to controls.



# PATIENTS AND METHODS

- Ages 16 and 80 years.
- Prospectively recruited for this study.
- Selected into 2 groups, CRSwNP and normal controls.
- Only those who failed medical management and required endoscopic sinus surgery were included in the study.
- Nasal polyps were confirmed by nasal endoscopy and (CT).



- **Patients were excluded if they had a history of**
  - allergic fungal sinusitis,
  - atopy
  - allergic rhinitis,
  - Samter's triad,
  - cystic fibrosis,
  - known immune deficiency,
  - Kartagener's syndrome,
  - inverted papilloma,
  - sinonasal tumor,
  - antrochoanal polyp



- Patients selected for the control group were undergoing endoscopic transsphenoidal surgery for benign pituitary tumors and did not have symptomatology, imaging, or endoscopic findings consistent with CRS.
- Controls with allergic rhinitis were also excluded.



# Results

- 17 patients,
  - 14 with CRSwNP .
  - 3 normal control.
- Ten patients in the CRSwNP underwent revision sinus surgery with an average of 1.66 previous surgeries.
- Seven out of the 14 patients with CRSwNP had asthma and none of the controls.
- All patients were nonsmokers.



**TABLE 1.** Halocytosine content in polyp and normal human samples

Sample	5mC/C%	5BrC/10 <sup>6</sup> Cs	5ClC/10 <sup>6</sup> Cs	Group
1	4.2% ± 0.05%	531 ± 118	710 ± 30	CRSwNP
2	4.0% ± 0.02%	273 ± 89	166 ± 29	CRSwNP
3	3.8% ± 0.01%	269 ± 52	720 ± 51	CRSwNP
4	4.2% ± 0.05%	136 ± 52	57 ± 50	CRSwNP
5	4.1% ± 0.20%	148 ± 1	242 ± 11	CRSwNP
6	4.0% ± 0.02%	152 ± 10	131 ± 27	CRSwNP
7	3.9% ± 0.05%	294 ± 108	302 ± 153	CRSwNP
8	4.2% ± 0.04%	307 ± 22	313 ± 84	CRSwNP
9	4.2% ± 0.02%	198 ± 35	295 ± 61	CRSwNP
10	3.8% ± 0.04%	326 ± 42	279 ± 90	CRSwNP
11	4.5% ± 0.13%	324 ± 51	319 ± 129	CRSwNP
12	4.3% ± 0.02%	287 ± 15	423 ± 34	CRSwNP
13	4.1% ± 0.05%	151 ± 13	97 ± 30	CRSwNP
14	4.5% ± 0.47%	236 ± 12	264 ± 43	CRSwNP
15	3.9% ± 0.02%	50 ± 10	160 ± 25	Control
16	4.3% ± 0.10%	61 ± 9	264 ± 33	Control
17	4.1% ± 0.13%	86 ± 20	321 ± 93	Control

5BrC = 5-bromocytosine; 5ClC = 5-chlorocytosine; 5mC = 5-methylcytosine; CRSwNP = chronic rhinosinusitis with nasal polyps.

- The level of 5BrC in the polyp tissue (CRSwNP) was **significantly higher** than that in the normal controls
- The average level was approximately **5times** that observed in the normal controls.*
- Levels of 5ClC in polyp tissues were also **slightly elevated** when compared to controls
- No** significant differences between CRSwNP and controls were noted in 5mC levels.

## CONT.

- There was no statistical difference between the levels of 5Brc and 5ClC in those patients with polyps on and off oral steroids.
- There was also no difference in the levels of 5ClC or 5BrC between those with and without asthma.



# CONCLUSION

- Epigenetic aberrations that influence innate epithelial immunity as a result of activated eosinophils may play a major role in the pathogenesis of CRSwNP and account for the difference in disease presentation between CRSwNP and CRSsNP. Further studies are needed that define the role of 5BrC and 5ClC in the pathogenesis of CRS.



**\*Achoo\***