REVIEW

The genetics of Barrett's esophagus: a familial and population-based perspective

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Conflicts of Interest: none

Abstract

Barrett's Esophagus (BE) is intestinal metaplasia of the lower esophagus and a precursor lesion for esophageal adenocarcinoma (EAC). Both are important health issues as they have rising incidences in the Western World. Improving the management of BE relies on understanding the underlying biology of this disease, but the exact biological mechanisms have been difficult to determine. BE is generally thought to be an acquired condition that develops secondarily to chronic gastro-esophageal reflux. However, multiple reports of familial clustering of patients with BE and/or EAC suggest a possible inherited predisposition to BE may be driving this condition, at least in a sub-set of patients. Identifying the genetic variants that predispose to BE in these families would open up the possibility for blood-based screening tests that could inform decision-making in regard to surveillance strategies, particularly for relatives of patients with BE and/or EAC. Perhaps more importantly, understanding the genetic mechanisms that predispose to BE may provide valuable insights into the biology of this condition and potentially identify novel targets for therapeutic intervention. Here we review the current evidence for a genetic predisposition to BE and discuss the potential implications of these findings.

Introduction

Barrett's esophagus (BE) is an acquired metaplasia of the esophageal epithelium that confers increased risk of developing esophageal adenocarcinoma (EAC). The cellular and molecular mechanisms that underlie the pathogenesis of BE and its progression to EAC are unclear but are integral to understanding its biology (1). Known risk factors for BE include gastroesophageal reflux, male gender, Caucasian ethnicity and obesity (primarily central adiposity) (2). There is also evidence for a genetic component. There are numerous reports of familial clusterings of two or more first or second degree relatives with BE or EAC (which is assumed to have been derived from BE) (3-5), and up to 7% patients with BE report a first or second degree relative with BE/EAC (6), suggesting an underlying genetic predisposition and potential inheritance of BE/EAC in some patients.

BE is the eponymous name for the metaplastic change of the esophageal mucosa from the normal stratified squamous epithelium to an intestinal-like columnar epithelium. It occurs in the distal esophagus and is presumed to be an adaptive response to chronic exposure to noxious refluxing gastric contents including acid and bile. Although in itself a benign condition, BE is widely considered to be a pre-neoplastic lesion that represents the first stage in development of EAC (7). The progression of BE to cancer is a multi-step process in which the metaplastic epithelium is thought to sequentially develop low-grade dysplasia (LGD), high grade dysplasia (HGD), and, eventually, invasive adenocarcinoma (Figure 1). The underlying drivers of this process are not clear but appear to involve a progressive increase in mutational load including loss of tumor suppressor genes such as CDKN2A and TP53 and the subsequent acquisition of more general genomic instability and oncogenic events (8-10).

The diagnosis of BE requires both endoscopic and histologic evidence of metaplastic columnar epithelium within the esophagus. Although columnar mucosa, including gastric-, cardia- and intestinal-types, can all be recognized in the esophagus during endoscopy, only

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histologically confirmed specialised intestinal-type columnar epithelium, as defined by the presence of goblet cells, has been clearly linked to an increased risk of malignant progression and is required for a diagnosis of BE (11, 12). However, this strict definition is not universally accepted and in British guidelines, the presence of goblet cells in the metaplastic columnar epithelium is not essential for the diagnosis of BE (13, 14). In addition, recent studies show that any length of BE (measured proximally from the gastro-esophageal junction) confers a risk of EAC (11), and those with longer length have increased lifetime risk of EAC (15).

The overall incidence of BE in the general population is difficult to calculate as the condition can be clinically silent and a definitive diagnosis of BE requires specialised investigations (upper gastrointestinal endoscopy and histological confirmation). Despite these challenges, early endoscopic studies detected BE in 5-13% of patients undergoing endoscopy for reflux symptoms, and in 1-2% of those in whom endoscopy was performed for any clinical indication (16-19). More recent studies randomly selected individuals from the community to reduce recruitment bias, and determined a 1-2% prevalence of histologically confirmed BE in asymptomatic individuals (19, 20). Modelling based on the incidence of EAC estimated the prevalence of BE to be as high as 5% in the US population (21). Of note, while the incidence of squamous cell carcinoma of the esophagus is much higher in Asian compared to Western populations, the estimated prevalence of BE/EAC in Asian countries such as Korea, Japan and China, at approximately 1% is lower than their Western counterparts (22-26). Importantly, recent publications show that there is an increasing incidence of BE independent of the volume of endoscopic testing (27), with this rise particularly evident in males less than 40 years of age, possibly due to increasing rates of obesity (28).

The diagnosis of BE is important because of its malignant potential. Non-dysplastic BE has been shown to confer a 20 times higher risk of developing EAC compared to population

controls (29, 30). The incidence of EAC in patients with non-dysplastic BE is 6 per 1000 patient-years of follow up (30-34), which equates to a 0.1% risk per year, or a 5 - 10% lifetime risk (depending on age at diagnosis), of progressing to EAC (35). Nevertheless, it has been observed that with a relatively low rate of malignant transformation and a mean age of 60 – 70 years at diagnosis for BE, those with BE usually do not die from EAC but often from competing causes (31, 36, 37). Hence, it has been suggested that the diagnosis of non-dysplastic BE does not affect mortality rates related to EAC (38). However, these studies do not take into account lead time and the age of diagnosis, where younger patients are more likely to die from the condition rather than pre-existing co-morbidities. Conversely, if dysplasia is identified in BE, then estimates of progression rates to EAC are higher. This is reported as 0.6% per year for low grade dysplasia (39, 40), and 5.6% per year for high-grade dysplasia (41). There is expert agreement on the benefit of treating dysplastic BE, but the absolute effect on reducing the incidence of EAC is yet to be quantified (42). Importantly, the incidence of EAC (43) has mirrored the increasing incidence of BE (28) over the past 30 years.

Evidence for a genetic predisposition to BE

Whilst it is well accepted that BE is a metaplastic process that occurs in response to the exposure to noxious luminal contents (44), the exact cellular and genetic mechanisms involved in this process are still unclear. There are two lines of evidence for a genetic component in BE: firstly, the clinical observation of familial clustering as a surrogate for genetic inheritance in a subgroup of affected cases, and secondly, the association of disease with observed genetic variants.

Familial BE

A small but important subgroup of BE cases are observed to cluster in families (Table 1). The earliest reports of familial clusterings of BE noted multiple siblings with BE/EAC (45-47)

including one case of identical twins diagnosed with BE at a similar age (48), which suggested that the same genetic variant/s may have predisposed them to BE. Later reports presented larger families with BE/EAC (3, 49, 50), with multi-generational distributions of BE/EAC cases observing an autosomal dominant pattern of inheritance within these families and earlier age of diagnosis when compared with sporadic BE (Table 1). In these reports, EAC is included in the BE-spectrum of disorders, with the underlying assumption that EAC derives from a premalignant BE stage (51).

To improve recruitment of BE families, subsequent studies were conducted to systematically recruit cases through hospital case series (52-54). These studies indicate that between 5-7% of BE/EAC cases report a family history of either disease (6, 52), while Chak et al. reported a higher prevalence of BE/EAC in relatives of cases of BE when compared with controls without BE (24% versus 5% $p < 0.005$) (55, 56). The individual risk of BE in relatives was calculated at approximately 20% in some families (4), but this risk is likely an overestimate due to recruitment bias as not all relatives were investigated. Taken together, these studies suggest that a familial predisposition to BE/EAC may occur in a small but not insignificant number of cases, and individual risk of BE in these families is substantially higher than the general population.

Features of familial BE also suggest a contributing genetic component in these cases. Drovolic et al. reviewed common features in a case series of 70 BE/EAC families, and noted consistent observations including early age of diagnosis (mean age of ~51 years for familial BE (57) vs. 65 years for sporadic BE (58)). These observations were affirmed in a study of 20 BE/EAC families by Sappati Biyyani et al. (4) and in other studies (Table 1). Furthermore, Chak et al. reported a significant lower proportion of males (75% vs. 83%), lower average body mass index (28.6 kg/m^2 vs. 29.6 kg/m^2), and less reported reflux (55% vs. 66%) in familial BE compared with sporadic BE (59). These clinical features show a trend that is in

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contrast to the expected risk factor profile seen in population-based BE, suggesting a larger contribution of genetic factors in these families.

There is a well-established relationship between gastro-esophageal reflux disease (GERD) and BE, where the exposure of the esophageal lining to noxious acid and bile promotes the metaplastic process (60). It is therefore possible that it is GERD that is inherited and that BE is simply an indirect consequence. Certainly some studies have noted an association of BE with GERD in BE families (52, 61, 62) although others found that GERD was not a universal clinical feature of familial BE (53). In addition, there were similar (rather than higher) rates of GERD symptoms in relatives of patients with familial BE when compared with a cohort of relatives of sporadic BE cases (56). As GERD is not always observed in patients with BE, and, as there is also an unusually high rate of progression from GERD to metaplasia in BE families (53), this suggests that even if there is an increase in GERD, additional genetic factors may be required for the development of BE.

Of course, there are a number of important issues that need to be considered when interpreting the results of these familial studies. While some studies have used a strict definition of three or more affected relatives (i.e. proband plus 2 or more others) to define familial BE (53), others included families with just two affected relatives (proband plus one other) (52, 54), which has a higher probability of occurring by chance. Relatives with EAC are included in the definition of familial BE as it is assumed that EAC arises from BE (51) but it is possible that familial EAC may be distinct from familial BE. Also, the definition of BE itself may have under-estimated the number of BE cases in each family. For example, earlier studies of BE, particularly those prior to 2000, required a 3cm minimum length of BE and thus patients with less than a 3 cm segment would have been excluded.

Other confounding factors also need to be considered in studying the clinical and genetic characteristics of familial BE. Firstly, there is potential for phenocopies to complicate the analysis. A low but significant incidence of BE in the general population (63) raises the possibility that some members of any given family may have sporadically developed BE independent of any underlying familial predisposition. Secondly, the temporal nature of BE development means the condition is age dependent and young relatives may carry a predisposition variant but are yet to develop the disease. This means that family members found not to have BE by endoscopy may still develop BE at an older age. If wrongly classified as unaffected, this would reduce the penetrance results for any variants studied. Thirdly, families often have similar lifestyle exposures, and a common environmental factor may be the cause of familial BE rather than a genetic predisposition. Careful analysis of the pattern of disease within families, particularly the multi-generation nature and the age of onset of disease may determine if a genetic factor is the likely contributor. Finally, recruitment bias may also play a part, with the method of recruitment of families likely to influence whom and at what age cases were diagnosed. Indeed, recruitment bias may explain the earlier age of diagnosis reported for familial BE compared with sporadic BE by additional surveillance and detection of BE in young family members who may not otherwise have been investigated.

Genetics of Familial BE

While there is a clear familial association for a sub-group of BE patients, the actual gene, or genes, responsible for the inherited predisposition have not been identified. Analyses of pedigrees in the familial BE case series have generally supported a monogenic autosomal dominant mode of inheritance (4, 57). Consistent with early individual case reports, a large study by Sun et al. (5) examined 881 BE/EAC pedigrees and concluded that the underlying

pattern of inheritance was most consistent with an autosomal dominant model with incomplete penetrance.

Two studies attempted to identify the genetic factor responsible for familial BE using a traditional linkage analysis of multiple affected family members. Although shared genetic regions were identified on Chromosome 2, 12, and 19, no specific candidate genes were identified (55, 64). Another published linkage study of BE/EAC sibling pairs followed by a fine mapping association study identified specific single nucleotide polymorphisms in *MSR1* (8p), *ASCC1* (10q) and *CTHRC1* (8q), implicated macrophage function and inflammatory pathways (65), but these variants have not been validated in other BE cohorts. The advent of high-throughput, massively parallel (next-generation) sequencing opens up a new strategy for searching for high-risk genes in families with inherited disease. By comparing the genomic sequence of multiple affected family members, inherited variants shared by these individuals can be identified and used in a standard segregation analysis with all family members (affected and unaffected) to identify those variants that specifically segregate with the condition. The first study utilising this approach has recently been reported in abstract form and identified a variant in an uncharacterised gene, FBE-1, as a potential genetic predisposing factor in familial BE (66). Further details on the function and role of the gene harbouring this variant have yet to be reported.

Genetics of Non-Familial BE

Evidence for a genetic contribution to BE has also been identified in the non-familial context. Early studies used a candidate gene approach, and a number of potential susceptibility genes have been reported (Table 2). However, the odds ratios for these polymorphisms were all low or moderate, indicating a low level of susceptibility. In addition, these variants have yet to be validated in independent replication cohorts.

More recently, two Genome Wide Association Studies (GWAS) of BE have been reported (67, 68). GWAS screen thousands of un-related cases and controls to identify common germline variants that have a stronger association with the disease than controls. The first GWAS tested almost 7000 cases and over 17000 controls from the United Kingdom, the United States, the Netherlands and Australia (67). They identified two variants associated with the risk of BE, one within the major histocompatibility complex locus on chromosome 6 (6p21, rs9257809) and the other on chromosome 16 (16q24, rs9936833) close to the gene *FOXF1* (Table 3). The second GWAS compared 2390 EAC cases with 3175 BE cases and 10120 controls and identified three further areas of genetic association - 19p13 (rs10419226) and 9q22 (rs11789015), within genes *CRTC1* and *BARX1* respectively*,* and 3p14 (rs2687201) which is close to the gene *FOXP1* - as well as confirming the previously reported association with *FOXF1* (68) (Table 3), which has been subsequently validated in an independent case-control study (69). If regions of association have an odds ratio (OR) high enough it could justify use in population based genetic screening for BE. However, in these studies the associations were too low to be of any clinical significance in isolation. For example, the variant 16q24 rs9936833 close to *FOXF1* had an OR of just 1.14 (95% CI = 1.10–1.19) (67), which implies only a small degree of genetic contribution, with additional factors likely to be required in the development of BE. An additional factor may indeed be another genetic variant, thus raising the possibility of a polygenic inheritance pattern.

These GWAS were the first studies to indicate direct evidence that BE has a genetic component, and may provide important insights into the biology of the disease. For example, the forkhead (FOX) family of transcription factors are important regulators of foregut development. In particular FOXP1 is known to cooperate with FOXP2 to regulate lung and esophagus development (70). Furthermore, FOXF1 is a target of the Hedgehog signalling pathway, a developmental pathway that we have shown to play a role in the pathogenesis of

BE (71, 72). Interestingly FOXA2, which shares many transcriptional targets with FOXF1, is also regulated by Hedgehog signalling in esophageal embryogenesis and BE (73). Thus, the findings from the GWAS provide further evidence for the importance of developmental signalling pathways, particularly the Hedgehog pathway, in the pathogenesis of BE.

Clinical Implications and Future Directions

The clinical significance of determining the genetic basis of BE is unclear at this time. Identification of a causal and/or predisposing gene(s), although unlikely at present, would open the possibility for a DNA-based personalized risk assessment for developing BE. This would seem a more attractive option than hospital based endoscopy, which is the only current screening tool available. While GWAS analyses have identified several potential genetic variants associated with BE, the odds ratios for these are far too low to have any clinical utility. Familial studies may identify variants with stronger penetrance, but the low prevalence of familial BE is likely to preclude use of such familial variants in more general population-based screening approaches. Nevertheless, identification of specific predisposing variants in individual families would have potential significance within those families; asymptomatic family members carrying the variants might be subjected to more intensive surveillance while those not carrying the variant could potentially avoid regular invasive endoscopic procedures.

Currently, the clinical implications of genetic studies are restricted to acknowledging that familial clustering with an inherited predisposition to developing BE does exist. Thus, management of patients presenting with BE should include diligent attention to any family history and, if multiple family members with BE and/or EAC are identified, endoscopic surveillance of asymptomatic family members should be considered.

Perhaps the greater value in finding genetic drivers or predisposition genes in BE, whether in sporadic or familial BE, are the potential insights this might provide into the underlying biology of BE. Identifying such genes could highlight critical pathways involved in the development of BE that might be pharmacologically targeted to eliminate BE and reduce the risk of progression to cancer. Moreover, unravelling the genetic background of BE and its progression to EAC may help to identify those patients with BE that are at high risk of malignant progression. For these reasons, ongoing studies into the genetic basis of BE are valuable.

Conclusion

The clinical observation of familial clustering of BE, along with results of GWAS analyses, strongly supports the contention that there is a genetic component underlying the development of BE. Identifying the genetic variants that predispose to BE may open up the possibility for personalised DNA based screening tools that could inform decision-making in regard to surveillance strategies, particularly in relatives of patients with BE and/or EAC. Perhaps more importantly, understanding the genetic mechanisms that predispose to BE may provide valuable insights into the biology of this condition and potentially identify novel targets for therapeutic intervention and/or biomarkers for stratifying risk of progression to cancer.

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Table 1 – Published case reports and case series on familial Barrett's esophagus

Author	Year	Number of families	BE (n)	EAC (n)	Age BE diagnosis, mean years	Age EAC diagnosis, mean years	M/F Ratio	Hereditary Pattern[a]
Everhart et al. (45)	1983	1	3	0	23.6	NA	Males only	AD
Gelfand et al. (48)	1983	1	2	0	67.0	NA	Females only	AR/AD
Crabb et al. (46)	1985	1	4	0	59.5	NA	1 to 1	AD
Prior et al. (47)	1986	1	2	0	66.0	NA	Females only	AR/AD
Jochem et al. (74)	1992	1	6	3	43.6	74.0	Males only	AD
Eng et al. (49)	1993	1	7	2	54.3	68.0	2 to 5	AD
Fahmy et al. (75)	1993	4	8	2	62.0	74.0	3 to 2	AD
Poynton et al. (76)	1996	3	6	8	62.0	60.0	5 to 3	AD
Drovdlic et al. (57)	2003	70	121	62	51.0	60.5	2.25:1	AD
Groves et al. (3)	2005	1	7	3	48.1	74.0	4 to 1	AD
Melzer et al. (77)	2006	1	0	3	NA	65.5	Males only	AD
Sappati Biyyani et al. (4)	2007	20	37	17	60.3	60.8	2.2 to 1	AD
Munitiz et al. (50)	2008	1	4	6	46.2	60.5	Males only	AD
Farr et al. (78)	2008	1	4	0	unknown	NA	3 to 1	AD

(a) Hereditary pattern is described as AD = autosomal dominant, or AR = autosomal recessive

Table 2 - Investigated candidate predisposition genes for Barrett's esophagus

Gene	Function	Suggested Role in BE development	OR	Reference
CCND1	Encodes Cyclin D1, cell cycle regulation	Proliferation	3.69 (95% CI 1.46-9.29)	Casson et al. (79)
XPC, XPD, XRCC1	DNA repair genes	Genetic instability	Combined Analysis	Tarlarini et al. (80)
EGFR	Musocal protection and repair	Mucosal defence against inflammation	3.0 (95% CI 1.8-9.7)	Menke et al. (81)
GSTP1	Encode enzymes in detoxification, e.g. glutathione S-transferase	Detoxification of free radicals caused by inflammation i.e. esophagitis	2.10 (95% CI 0.99-4.44)	Kala et al. (82)
TNF-B	Inflammation	Mediates inflammatory reaction	1.60 (95% CI 1.07-2.38)	Menke et al. (83)
IL-18	Inflammation	Mediates anti-tumor response	1.26 (95% CI 1.01-1.57)	Babar et al. (84)
IL-1	Inflammation	Mediates inflammatory reaction	0.56 (95% CI 0.33-0.93)	Holla et al. (85)
IGF Axis, IGF-1	Insulin-like growth receptors	Growth hormone implied in obesity	0.43 (95% CI 0.24-0.75)	McElholm et al. (86)

Table 3 – Reported variants associated with sporadic BE in published Genome Wide Association Studies

Chr Locus	rsID	Proximal Gene	Combined OR (95% CI)	Combined p value	Reference
6p21	*rs9257809*	MHC	1.21 (1.13 - 1.28)	4.09×10^{-9}	Su et al. (67)
16q24	*rs9936833*	FOXF1	1.14 (1.10 - 1.19)	2.74×10^{-10}	
19p13	*rs10419226*	CRTC1	1.18 (1.12 = 1.24)	3.55×10^{-10}	Levine et al. (68)
9q22	*rs11789015*	BARX1	0.83 (0.79 - 0.88)	1.02×10^{-9}	
3p14	*rs2687201*	FOXP1	1.18 (1.12 - 1.25)	5.47×10^{-9}	

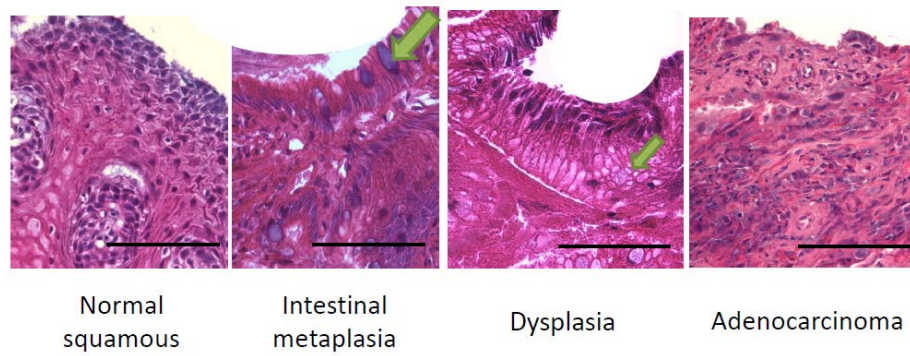| Normal squamous | Intestinal metaplasia | Dysplasia | Adenocarcinoma |

Figure 1 – Histological features of Barrett's esophagus

Haematoxylin and Eosin staining of biopsies taken from the oesophageal mucosa showing the histological features the esophagus with normal squamous, metaplasia (BE), dysplasia and adenocarcinoma (scale bar represents 100 µm). The green arrows mark goblet cells, which are the key feature of intestinal differentiation.

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Title:
The Genetics of Barrett's Esophagus: A Familial and Population-Based Perspective

Date:
2016-07-01

File Description:
Accepted version