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Genetic Predisposition Factors and Nasopharyngeal Carcinoma Risk: A Review of Epidemiological Association Studies, 2000–2011

Allan Hildesheim[1] and **Cheng-Ping Wang**[2]

[1]Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA

[2]Department of Otolaryngology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

Abstract

While infection with Epstein-Barr virus (EBV) is known to be an essential risk factor for the development of nasopharyngeal carcinoma (NPC), other co-factors including genetic factors are thought to play an important role. In this review, we summarize association studies conducted over the past decade to evaluate the role of genetic polymorphisms in NPC development. A review of the literature identified close to 100 studies, including 3 genome-wide association studies (GWAS), since 2000 that evaluated genetic polymorphisms and NPC risk in at least 100 NPC cases and 100 controls. Consistent evidence for associations were reported for a handful of genes, including immune-related HLA Class I genes, DNA repair gene *RAD51L1*, cell cycle control genes *MDM2* and *TP53*, and cell adhesion/migration gene *MMP2*. However, for most of the genes evaluated, there was no effort to replicate findings and studies were largely modest in size, typically consisting of no more than a few hundred cases and controls. The small size of most studies, and the lack of attempts at replication have limited progress in understanding the genetics of NPC. Moving forward, if we are to advance our understanding of genetic factors involved in the development of NPC, and of the impact of gene-gene and gene-environment interations in the development of this disease, consortial efforts that pool across multiple, well-designed and coordinated efforts will most likely be required.

Introduction

Nasopharyngeal carcinoma (NPC) is known to be strongly associated with Epstein-Barr virus (EBV) infection. However, since EBV infection is nearly ubiquitous and NPC development rare, it is widely acknowledged that EBV infection is not sufficient to induce cancer and that other cofactors play an important role in NPC pathogenesis.[1,2] Co-factors thought to be important in the development of NPC include both exogenous exposures (such as consumption of dietary nitrosamines, occupational exposure to wood/wood dusts, and cigarette smoking) and host genetic susceptibility factors.[1,2] The strong role for viral infections, exposure to chemical carcinogens, and underlying host genetic susceptibility in

Correspondence to: Allan Hildesheim, Infections and Immunoepidemiology Branch, DCEG, NCI, 6120 Executive Blvd, Room 7066, Rockville, MD 20852, USA (hildesha@mail.nih.gov).

NPC pathogenesis makes NPC an ideal candidate for studies aimed at better understanding the interplay between these various factors and cancer risk.

Advances in genotyping technologies over the past 10–15 years have accelerated the rate of growth in our understanding of the genetics of numerous diseases, including cancers.[3–8] In fact, large-scale genome-wide association studies (GWAS) have reported more than 150 associations for two dozen cancers. In several instances, specific chromosomal regions have been found to be associated with a constellation of tumors, as in the case of 8q24 (region where MYC resides) and cancers of the prostate, breast, colon, bladder, ovary and chronic lymphocytic leukemia; and 5p15.33 (TERT-CLPTM1l locus) and cancers of the brain, bladder, testis, pancreas, lung, and skin.[3,5] Based on these results, fine mapping studies are ongoing to define the specific loci involved and their functions, efforts that promise to lead to a better understanding of the molecular mechanisms involved in carcinogenesis and, possibly, to clinical applications aimed at secondary prevention or treatment.

Given these technological advances, the opportunity exists to systematically investigate genetic risk factors for NPC. However, because NPC is a rare tumor in most parts of the world, most studies of NPC genetics to date have been relatively modest in size. Furthermore, most studies of NPC genetics to date have focused on a limited number of specific candidate genes, with few efforts to conduct large-scale studies that are well-powered to identify modest effects associated with common polymorphisms and to fully explore the complete genome and/or to comprehensively explore specific biological pathways of interest.

As a starting point for future efforts to better characterize genetic risk factors for the development of NPC, this review focuses on 1) summarizing genetic association studies of NPC conducted since 2000, 2) identifying gaps in our understanding in this area, and 3) proposing approaches that might help fill these gaps in an accelerated fashion moving forward.

Scope and Organization of Review

We focus this review on studies published since 2000, since this is the period when PCR-based technologies became widely available for high-throughput epidemiological studies. Those interested in results from studies conducted before that time are referred to previously published reviews.[1,2,9,10] Furthermore, this review focuses on association studies, since they comprise the majority of NPC genetic studies conducted to date. Family-based linkage studies, while informative, are not the focus of this review and readers are referred to another paper in this NPC issue by JX Bei, WH Jia, and YX Zeng on familial studies and some of the sentinel NPC family studies for information on this topic.[11–14]

Papers selected for review were identified via Pubmed literature searches conducted at the time this review was initiated and again in early November 2011. Search terms used include “nasopharyngeal carcinoma and genetics”, “NPC and genetics”, nasopharyngeal carcinoma and epidemiology”, “NPC and epidemiology”, “nasopharyngeal carcinoma and HLA”, “NPC and HLA” and “nasopharyngeal carcinoma and polymorphism”. Searches were restricted to English language publications published between the years 2000 and the time this review was drafted (November 2011). 2,176 papers identified via these searches were reviewed. Studies with no control group (i.e., case-only studies) were excluded, as were studies that had fewer than 100 cases and 100 controls. A total of 81 papers that fulfilled our criteria were included in this review. Review of reference list from these papers resulted in the identification of an additional 2 paper, so that the total number of papers considered in this review was 83.

GWAS studies were reviewed separately. For candidate gene/candidate pathway studies, we grouped studies into the following categories to organize our presentation: studies of immunerelated genes (HLA Class I/II genes evaluated separately), studies of phase I/II metabolism genes & DNA-repair genes, and studies of other genes.

Summary of the Literature

A total of 83 published papers were identified that fulfilled our criteria for inclusion in this review. Among these, three studies reported results from agnostic GWAS, 9 reported results from studies that evaluated the association between HLA genes and NPC, 32 reported results from studies that evaluated other genes involved in immune response and NPC, and 15 reported results from studies that evaluated genes involved in phase I/II metabolism & DNA repair and NPC. The remaining studies reported findings from efforts that evaluated other genes, including genes involved in cell cycle control, cell adhesion/migration, angiogenesis, and DNA methylation. Each is discussed, in turn, below.

GWAS studies

The three GWAS studies of NPC published to date are summarized in Table 1. The largest GWAS of NPC to date consisted of a discovery phase that included 1583 cases and 1894 controls from Southern China and Singapore and two validation studies that together consisted of 3507 NPC cases, 3063 controls and 279 family trios from Southern China. The other two published GWAS were considerably smaller, with discovery phases that included less than 300 cases and controls each. The most consistent finding across these studies was the confirmation that genes within the Major Histocompatibility Complex (MHC) region on chromosome 6p21, where the human leucocyte antigen (*HLA*) genes are located, are strongly associated with NPC. In addition to HLA genes themselves, other genes, including the *GABBR1* and *HCG9* genes had suggestive evidence for association, although it is currently unclear whether either of these genes are causally linked to the development of NPC.[15] Other, less consistent findings from the GWAS efforts suggested associations between genes located on chromosomes 3q26, 3p21, 9p21, and 13q12. These inconsistent findings for regions other than those in the MHC are likely reflective of the modest sample size for the various GWAS published to date, and highlight the need for larger, pooled efforts in the future to achieve study sizes that are sufficiently powered to more deeply explore the associations between common genetic polymorphisms that, while important, confer modest risk of disease.

Immune-related genes

There is an extensive literature dating back to the 1970s suggesting an important role for *HLA* genes in the etiology of NPC.[1,2,9,10] Much of that work is based on low resolution (2-digit) *HLA* typing, which has since been replaced by more extensive high resolution testing capable of identifying specific *HLA* alleles (4-digit typing). Our search identified 9 publications since 2000 that evaluated classical *HLA* class I (*A, B* and C) and II (*DRB1, DQA1, DQB1,* and *DPB1*) genes and their association with NPC. Of these, three studies were excluded because either genotyping or the analysis was performed at the low resolution, 2-digit level.[16–18] Results for the remaining studies are summarized in Table 2. Consistent with the older literature, studies conducted since 2000 largely confirmed the association between specific *HLA* alleles and NPC risk. Since many of the *HLA* alleles found to be associated with NPC are rare outside of China and individuals of Chinese ethnicity, confirmation of these associations in studies of individuals of non-Chinese descent has been difficult. Within studies conducted among individuals of Chinese ethnicity, strong linkage disequilibrium patterns observed across *HLA* genes on chromosome 6p21 have made it difficult to determine whether the associations are explained by the specific alleles, by

extended *HLA* haplotypes, or by non-*HLA* genes in the region that are in close linkage disequilibrium with *HLA* genes.

While the strong population differences in *HLA* distribution combined with the strong linkage disequilibrium patterns in *HLA* within populations make the study of *HLA*-disease associaitons difficult, the fact that the GWAS efforts summarized earlier in this review point to this region of the genome as having the strongest evidence for association with NPC suggests the need for further study in this area. To be fruitful, however, those studies will need to be large and to involve varied population groups to enable us to disentangle the genetic complexity in this region.

In addition to classical *HLA* genes, numerous other immune-related genes have been investigated for their association with NPC. Interest in the connection between immune-related genes and NPC is a logical extension of the fact that NPC is closely linked to infection with EBV, and that immune response to this nearly ubiquitous virus is likely to be an important predictor of NPC risk. Immune-related genes that have been explored for their association with NPC include immune genes located within the MHC region where *HLA* genes are located, and genes that code for cytokines/chemokines and innate immune-related molecules believed to be important in the host response to and control of viral infections. As summarized in Table 3, while many genes have been evaluated in the past decade, nearly all have been evaluated in a single study and the studies conducted to date have been modest in size, typically containing no more than a few hundred cases and a comparable number of controls. Furthermore, for the few genes that have been evaluated in more than one study, results have often been conflicting (e.g., *HLA-E*, TNF-α, IL-10, IL-18, and *FAS*). In the future, larger, more comprehensive evaluations with built-in independent replication will be required to further our knowledge of the role of immune-realted genes in the development of NPC.

Phase I/II metabolism and DNA-repair genes

In addition to immune-related genes, there has been interest in the evaluation of the association with NPC of genes involved in the activation and detoxification of chemical carcinogens and in the repair of DNA damage they cause. This interest stems from the known association with NPC of environmental carcinogens, particularly those derived from exposure to dietary or tobacco nitrosamines or to occupational exposure to wood dust and possibly formaldehyde. These chemical carcinogens are activated into reactive intermediates by phase I xenobiotic enzymes (e.g., Cytochrome P-450 enzymes) and these reactive intermediates are detoxified by phase II enzymes (e.g., Glutathione s-transferase enzymes). DNA damage generated by these chemical carcinogens are often repaired by the host DNA repair mechanism. Given this, the study of whether genetic polymorphisms in genes involved in activation of chemical carcinogens, in their detoxification, and in the repair of DNA damage they cause seems natural.

Results from studies that have evaluated the association between genes in these pathways and NPC are summarized in Table 4. As was the case for studies of immune-related genes, while several genes have been evaluated in the past decade, many have been evaluated in a single study and the studies conducted to date have typically been modest in size, containing no more than a few hundred cases and a comparable number of controls. Furthermore, for the few genes that have been evaluated in more than one study, results have often been negative across studies (e.g., *GSTM1*, *GSTP1*, and *GSTT1*) or conflicting (e.g., *CYP2E1*, *hOGG1*, and *XRCC1*). A few studies that included both a discovery and an independent validation stage warrant highlighting. Guo and colleagues[19] conducted a study that evaluated candidate polymorphisms in the *CYP2E1*, *GSTP1*, *MPO*, and *NQ01* genes within a total of 571 cases and 859 controls. A lack of evidence for an association with NPC was

observed for all SNPs evaluated within these four genes (five SNPs total). Jia and colleagues[20] conducted parallel family-based association (2499 individuals within 546 families) and case-control (755 cases and 755 controls) studies that evaluated 8 tag-SNPs within *CYP2E1*. In this study, no individual SNP was found to be significantly associated with NPC in both the family-based and case-control studies, although within the case-control study the authors report limited evidence for an association between several of the SNPs evaluated and NPC in sub-analyses restricted to young smokers (175 cases and 156 controls). Finally, Qin and colleagues[21] evaluated a comprehensive set of 676 tag-SNPs within 88 genes in the DNA-repair pathway in a total of 2323 cases and 2052 controls. Results from this study identified two SNPs within the *RAD51L1*, a gene involved in homologous recombination DNA repair, for which consistent and significant evidence for an association was observed. In the future, it will be interesting to see whether well-powered studies are able to replicate this initial finding for *RAD51L1* and if so whether functional data directly supporting this association are observed.

Other genes

Genes within various other functional pathways have been evaluated for their association with NPC, including genes involved in cell cycle control, cell adhesion/migration, angiogenesis, and DNA methylation. Results from these studies are summarized in Table 5. As was observed for studies of immune-related genes, genes involved in the metabolism of chemical carcinogens, and those involved in repair of DNA damage, the majority of genes listed in Table 5 were evaluated in single studies and studies conducted to date have typically been modest in size. For the genes that were evaluated in more than one study, results were negative across studies (e.g., *MMP9*) or conflicting (e.g., *MMP1* and *VEGF*). A few genes for which consistent evidence for an association with NPC were reported warrant discussion. These include two genes involved in cell cycle control, *MDM2* and *TP53*, and one gene involved in extracellular matrix and cellular migration, *MMP2*. *MDM2*, a negative regulator of *TP53*, was evaluated in three independent studies[22–24] totaling 1478 cases and 1997 controls. In all three studies, a consistent association was observed for SNP rs2279744 (nucleotide 309) and NPC. Similarly, three studies totaling 731 cases and 1155 controls evaluated the association between polymorphisms in the *TP53* gene (SNP rs1042522; codon 72) and NPC.[23,25,26] In two of these three studies, evidence for a significant association with NPC was observed.[23,25] In the third study,[26] while a significant association was not evident, carriage of the risk allele was associated with a near 2-fold increase in risk of NPC, consistent in magnitude and direction with results from the other two studies. Finally, the association between a polymorphism in the promotor region of *MMP2* (SNP rs243865; nucleotide −1306) and NPC risk was evaluated in three independent populations.[27,28] In one study that included a discovery (593 cases and 480 controls) and a validation (239 cases and 286 controls) phase, evidence for an association between SNP rs243865 and NPC was reported.[28] This association was further reproduced in a separate study conducted among 370 NPC cases and 390 controls.[27]

Conclusions and Future Outlook

As summarized herein, over the past decade, close to 100 association studies containing more than 100 NPC cases and 100 controls have been conducted to evaluate genetic factors potentially associated with NPC risk. Consistent evidence for associations were reported for a handful of genes, including immune-related HLA Class I genes, DNA repair gene *RAD51L1*, cell cycle control genes *MDM2* and *TP53*, and cell adhesion/migration gene *MMP2*. However, for most of the genes evaluated, there was no effort to replicate findings and studies were largely modest in size, typically consisting of no more than a few hundred cases and controls. The small size of most studies and the lack of attempts at replication

have limited progress in understanding the genetics of NPC. For the genes listed above for which some consistency in the reported listerature exists, well-designed and powered confirmatory studies are needed. In addition, given the modest statistical power of studies conducted to date and the fact that most studies have evaluated arbitrary candidate genes/polymorphisms, it is likely that additional genetic factors yet to be defined are involved in NPC development. Identification of these additional factors will, again, require carefully designed (both with respect to the selection/implementation of genetic testing and with respect to the epidemiological design) and well-powered studies. Finally, even the initial GWAS studies conducted to date have been modest in size, making it possible to identify with confidence only those regions within which strong effects are observed (e.g., MHC region on chr 6p21). Moving forward, if we are to advance our understanding of genetic factors involved in the development of NPC and of the impact of gene-gene and gene-environment interations in the development of this disease, consortial efforts that pool across multiple, well-designed and coordinated efforts will most likely be required.

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Table 1

Summary of GWAS studies for NPC

Author/Yr	Country	Sample Size (# Cases/# Ctrls)	Genotyping Platform	Main Findings:		
				SNP	Chromosome	Locus
Bei[29] **(2010)**	China	Discovery: 1583/1894 Validation 1: 3507/3063 Validation 2: 279 Trios	Illumina Human610-Quad & Human1M-Duo	rs2860580 rs2894207 rs28421666 rs9510787 rs6774494 rs1412829	6p21 6p21 6p21 13q12 3q26 9p21	*HLA-A* *HLA-B/C* *HLA-DQ/DR* *TNFRSF19* *MDS1-EVI1* *CDKN2A-CDKN2B*
Tse[30] **(2009)**	Taiwan	Discovery: 277/285 Validation 1: 339/696 Validation 2: 296/944	Illumina Human Hap550v3_A	rs2517713 rs2975042 rs9260734 rs29232 rs3869062 rs5009448 rs3129055 rs9258122 rs16896923 rs2267633 rs2076483 rs29230	6p21 6p21 6p21 6p21 6p21 6p21 6p21 6p21 6p21 6p21 6p21 6p21	*HLA-A* *HLA-A* *HCG9* *GABBR1* *HCG9* *HCG9* *HLA-F* *HLA-F* *HCG9* *GABBR1* *GABBR1* *GABBR1*
Ng[31] **(2009)**	Malaysia	Discovery: 111/260 Validation: 168/252	Illumina HumanHap550v3	rs2212020 rs189897	3p21 3p21	*ITGA9* *ITGA9*

Table 2

Classical HLA Class I/II genes and NPC

Author /Yr	Country	Sample Size (# Cases/ # Ctrls)	Genes Targeted	Typing Method	Main Findings									
					*A*0207*	*A*1101*	*A*3303*	*B*4601*	*B*5801*	*DRB1*0301*	*DQB1*0201*	*DQB1*0302*	*DPB1*0401*	Other alleles
Tang[32] (2010)	China	356/629	*HLA-A HLA-B HLA-C*	PCR-SSOP	(+)	(−)	(+)	(0)	(+)	N/T	N/T	N/T	N/T	*HLA-A*0206* (+) *HLA-B*5502* (−) Protection tended to be observed for individual alleles; risk for haplotypes.
Yu[33] (2009)	Taiwan	301/1010 (481 siblings, 212 spouses, 317 unrelated)	*HLA-A HLA-B*	SBT; PCR-SSOP	(+)	(−)	(+)	(0)	(+)	N/T	N/T	N/T	N/T	*HLA-B*3802* (+) *HLA-B*4601* protective in absence of HLA-*A* 0207*
Karanikiotis[34] (2008)	Greece	101/300	*HLA-DQA1 HLA-DQB1*	PCR-SSP	N/T	N/T	N/T	N/T	N/T	N/T*	(0)	(0)	N/T	*DQA1*0103* (−) *DQA1*0201* (−)
Li[35] (2007)	Tunisia	136/148	*HLA I*	SBT	N/D	N/E**	N/E**	N/D	N/E**	N/T	N/T	N/T	N/T	*HLA-B14* (−) *HLA-Cw08*(−) *HLA-B18* (+) *HLA-B51* (+) *HLA-B57* (+) *HLA-B14/Cw08* (−)
Butsch Kovacic[36] (2005)	Taiwan	213/200	*HLA-Cω*	PCR-SSOP	N/E***	N/E***	N/E***	N/E***	N/E***	N/E***	N/E***	N/E***	N/E***	*HLA-Cω*0302* (+) *HLA-Cω*0401* (−)
Hildesheim[37] (2002)	Taiwan	366/318	*HLA-A, HLA-B, HLA-DRB1, HLA-DQB1, HLA-DPB1*	PCR-SSOP	(+)	(−)	(0)	(+)	(+)	(+)	(+)	(−)	(0)	*HLA-A*0201* (0) *HLA-A*3101* (−) *HLA-B*13*(−) *HLA-B*39*(−)

PCR-SSOP (sequence-specific oligonucleotide probe), PCR-SSP (sequence specific primer), SBT (sequence based typing), N/T (Not tested), N/D (Not detected), N/E (Not evaluated).

* HLA-DRB1 typing was performed but analysis was performed at low-resolution and therefore not considered for this review.

** Not evaluated due to low frequency in population studied.

*** Not evaluated in this manuscript since previously reported in a separate publication.

Table 3

Immune-related (non-classical HLA) genes in NPC

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphic Site(s) Evaluated (Significant Association Reported – Yes/No)
HLA Related Genes					
Hassen[38] **(2011)**	Tunisia	185/177	*HLA-E*	PCR-ARMS/ Candidate	*HLA-E**0103 (No)
Hirankarn[39] **(2004)**	Thailand	100/100	*HLA-E*	PCR-SSOP/ Candidate	*HLA-E**0103 (Yes)
Ghandri[40] **(2011)**	Tunisia	186/189	*HLA-G*	PCR-RFLP/Candidate PCR-ARMS /Candidate	1074A/T (No) 1597delC (No) 1537 C/A (No)
Jalbout[41] **(2003)**	Tunisia	140/274	*HSP70-2*	PCR-RFLP/Candidate	Pst I P1/P2 (Yes)
Douik[42] **(2009)**	Tunisia	130/180	*MICA*	PCR-RFLP/Candidate	454 A/G (Yes)
Tian[43] **(2006)**	China	218/196	*MICA*	PCR size-sequencing/Candidate	MICA*A5.1 (Yes) MICA*A9 (Yes)
Hassen[44] **(2007)**	Tunisia	209/165	*TAP1*	PCR-ARMS /Candidate	Ile333Val (Yes) Asp637Gly (Yes)
Sousa[45] **(2011)**	Portugal	123/627	*TNF-α*	PCR-SNP Genotyping/Candidate	−308G/A (Yes)
Jalbout[41] **(2003)**	Tunisia	140/274	*TNF-α*	PCR-RFLP/Candidate	−308 G/A (No)
Cytokine and Chemokine Genes					
Yang[46] **(2011)**	China	248/296	*IL-1*	PCR-RFLP/Candidate	−889C/T (No) rs3783553 (Yes)
Zhu[47] **(2008)**	China	**113/144**	*IL-1B*	PCR-RFLP/Candidate	−31T/C (No) −511C/T (Yes)
Wei[48] **(2010)**	China	**180/200**	*IL-2*	PCR-RFLP/Candidate	−330 T/G (Yes) 114 T/G (No)
Ben Nasr[49] **(2007)**	Tunisia	160/169	*IL-8*	AS-PCR/Candidate	−251T/A (Yes)
Wei[50] **(2007)**	China	280/290	*IL-8*	PCR-SSP/Candidate PCR-RFLP/Candidate	678T/C (No) −251T/A(Yes) −353A/T (No) −738T/A (No) −845 T/C (No)
Farhat[51] **(2008)**	Tunisia	160/197	*IL-10*	AS-PCR/Candidate	−1082G/A (No)
Wei[52] **(2007)**	China	198/210	*IL-10*	PCR-RFLP/Candidate	−592A/C (No) −819 T/C (No) −1082 G/A (Yes)

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphic Site(s) Evaluated (Significant Association Reported – Yes/No)
Ben Chaaben[53] (2011)	Tunisia	247/284	*IL-12p40*	PCR-SSOP/Candidate	rs 3212227 (Yes)
Wei[54] (2009)	China	302/310	*IL-12B*	PCR-RFLP/Candidate	rs 3212227 (Yes)
Gao[55] (2009)	China	206/373	*IL-16*	PCR-RFLP/Candidate	rs4072111 (No) rs4778889 (No) rs11556218 (Yes)
Nong[56] (2009)	China	250/270	*IL-18*	PCR-RFLP/Candidate	rs187238 (No) rs1946518 (Yes)
Farhat[57] (2008)	Tunisia	163/164	*IL-18*	PCR-RFLP/Candidate	rs187238 (No) rs1946518 (No)
Wei[54] (2009)	China	302/310	*IL- 27p28*	PCR-RFLP/Candidate	rs153109 (No) rs181206 (No) rs17855750 (No)
Farhat[51] (2008)	Tunisia	160/197	*IFN-γ*	AS-PCR/Candidate	874T/A (No)
Wei[58] (2007)	China	108/120	*TGF-β1*	PCR-RFLP/Candidate	−509C/T (Yes) 869T/C (Yes)
Innate Immune Response Genes					
Xu[59] (2010)	China	444/464	*DC-SIGN*	SBT/All SNPs	−116G/T (No) −190A/G (No) rs735239 (No) rs735240 (Yes) rs2287886(Yes) rs4804803(No)
He[60] (2007)	China	434/512	*TLR3*	SBT/Candidate	829A/C (Yes) 13766C/T (No) rs3775291 (No) rs5743312 (No)
Song[61] (2006)	China	486/529	*TLR 4*	PCR-ARMS/Candidate	11350G/C (Yes) 11449C/T(No)
Zhou[62] (2006)	China	487/580	*TLR10*	PCR-ARMS/Tag-SNPs	rs10856837 (No) rs11096955 (No) rs11096956 (No) rs11466651 (No) rs11466652 (No) rs11466653 (No) rs11466655 (No)
Butsch Kovacic[36] (2005)	Taiwan	295/252	*KIR genes*	PCR-SSP/Candidate	activating KIRs (No) inhibitory KIRs (No)
Other Immune-Related Genes					
Hirunsatit[63] (2003)	Thailand	175/317	*CR2IVS2*	PCR-RFLP/Candidate	−848C/T (No)

Semin Cancer Biol. Author manuscript; available in PMC 2013 April 1.

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphic Site(s) Evaluated (Significant Association Reported – Yes/No)
Xiao[64] (2010)	China	457/485	*CTLA-4*	PCR-RFLP/Candidate	rs231775 (Yes)
Cao[65] (2010)	China	582/613	*FAS*	PCR-RFLP/Candidate	−1377G/A (Yes)
Zhu[66] (2010)	China	237/264	*FAS*	PCR-RFLP/Candidate	−670A/G (No)
Bel Hadj Jrad[67] (2006)	Tunisia	170/224	*FAS*	PCR-RFLP/Candidate	−670A/G (Yes)
Cao[65] (2010)	China	582/613	*FASL*	PCR-RFLP/Candidate	−844T/C (Yes)
Zhou[68] (2009)	China	163/203	*NFKB1*	PCR-RFLP/Candidate	−94 ins/del ATTG (Yes)
Hirunsatit[63] (2003)	Thailand	175/317	*PIGRIVS3*	PCR-RFLP/Candidate	−156G/T(No)
Hirunsatit[63] (2003)	Thailand	175/317	*PIGR*	PCR-ARMS /Candidate	1093G/A (No)

AS-PCR (allele-specific), PCR-ARMS (amplification refractory mutation system), *CR2* (complement receptor 2), *CTLA-4* (cytotoxic T-lymphocyte antigen 4), *DC-SIGN* (dendritic cell-specific intercellular adhesion molecule 3 grabbing non-integrin), *FASL* (FAS ligand), *HSP* (heat shock protein), *IL* (interleukin), ins/del (insertion/deletion), *IFN-γ* (interferon-gamma), *KIR* (killer cell immunoglobulin-like receptor), *NFKB1* (Nuclear factor-κB), *MICA* (Major histocompatibility complex (MHC) class I chain–related A), PCR-SSOP (sequence-specific oligonucleotide probe), PCR-SSP (sequence specific primer), SBT (sequence based typing), *PIGR* (Polymeric immunoglobulin receptor), RFLP (Restriction fragment length polymorphism),*TAP1* (transporter part of the antigen processing 1 gene), *TGF-β1* (Transforming growth factor-β1), *TLR* (Toll-like receptor), *TNF-α* (Tumor Necrosis Factor Alpha)

Table 4

Phase I/II metabolic activation/detoxification and DNA repair genes in NPC

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphic Site(s) Evaluated (Significant Association Reported – Yes/No)
Phase I/II Metabolic Activation/Detoxification Genes					
Cheng[69] **(2003)**	Taiwan	337/317	*CYP1A1*	PCR-RFLP/Candidate	m1/m2 (No)
Guo[19] **(2010)**	China	Discovery: 358/629 Validation: 213/230	*CYP2E1*	TaqMan PCR & SBT/Candidate	rs2031920 (No) rs6413432 (No)
Jia[20] **(2009)**	China	Discovery: 2,499 individuals (w/in 546 families) Validation: 755/755	*CYP2E1*	TaqMan PCR/Tag-SNPs	rs915906 (No)* rs915908 (No) rs1536826 (No)* rs2249695 (No)* rs3813865 (No)* rs3827688 (No)* rs8192780 (No)* rs9418990 (No)*
Yang[70] **(2005)**	Taiwan	103/553	*CYP2E1*	PCR-RFLP/Candidate	c2 (No)
Kongruttanachok[71] **(2001)**	Thailand	217/297	*CYP2E1*	PCR-RFLP/Candidate	rs2031920 (Yes)
He[72] **(2009)**	China	225/273 100/100	*GSTM1*	PCR-ARMS/Candidate Sequencing/Candidate	1270533T/G (No) C1256088C (No)
Guo[73] **(2008)**	China	350/622	*GSTM1*	PCR-electrophoresis/Candidate	Non-null/null (No)
Cheng[69] **(2003)**	Taiwan	337/317	*GSTM1*	PCR-RFLP/Candidate	Non-null/null (No)
Cheng[69] **(2003)**	Taiwan	337/317	*GSTP1*	PCR-RFLP/Candidate	1a/1b (No)
Guo[19] **(2010)**	China	Discovery: 358/629 Validation: 213/230	*GSTP1*	TaqMan PCR/Candidate	rs947894 (No)
Guo[73] **(2008)**	China	350/622	*GSTT1*	PCR-electrophoresis/Candidate	Non-null/null (No)
Cheng[69] **(2003)**	Taiwan	337/317	*GSTT1*	PCR-RFLP/Candidate	Non-null/null (No)
Guo[19] **(2010)**	China	Discovery: 358/629 Validation: 213/230	*MPO*	TaqMan PCR /Candidate	rs2333227 (No)
Cheng[69] **(2003)**	Taiwan	337/317	*NAT2*	PCR-RFLP/Candidate	Slow/fast (No)
Guo[19] **(2010)**	China	Discovery: 358/629 Validation: 213/230	*NQO1*	PCR-RFLP/Candidate	rs1800566 (No)
DNA Repair Genes					

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphic Site(s) Evaluated (Significant Association Reported – Yes/No)
Qin[21] **(2011)**	China	Discovery stage: 755/755 Validation stage: 1568/1297	88 genes**	Illumina GoldenGate/ Tag-SNPs	*RAD51L1**: rs927220 (Yes) rs11158728 (Yes)
Yang[74] **(2009)**	China	267/304	*ERCC1*	PCR-RFLP/Candidate	rs11615 (No) rs3212986 (Yes)
Zheng[75] **(2011)**	China	1052/1168	*NBS1*	PCR-RFLP/Candidate	rs1805794 (Yes) rs2735383 (No)
Cho[76] **(2003)**	Taiwan	334/283	*hOGG1*	PCR-RFLP/Candidate	Ser326Cys (Yes)
Laantri[77] **(2011)**	Morocco Algeria Tunisia	598/545	*hOGG1*	TaqMan PCR/Candidate	Ser326Cys (No)
Yang[78] **(2008)**	China	153/168	*XPC*	PCR-RFLP/Candidate	Val499 Ala (Yes) Lys939Gln (No) Poly-AT (No)
Yang[79] **(2007)**	China	153/168	*XPD*	PCR-RFLP/Candidate	Lys751Gln (Yes)
Laantri[77] **(2011)**	Morocco Algeria Tunisia	598/545	*XRCC1*	TaqMan PCR/Candidate	Arg194Trp (No) Arg280His (No) Arg399Gln (No)
Yang[79] **(2007)**	China	153/168	*XRCC1*	PCR-RFLP/Candidate	Arg194Trp (Yes)*** Arg280His (No) Arg399Gln (No)
Cao[80] **(2006)**	China	462/511	*XRCC1*	PCR-RFLP/Candidate	Arg194Trp (Yes)*** Arg399Gln (No)
Cho[76] **(2003)**	Taiwan	334/283	*XRCC1*	PCR-RFLP/Candidate	Arg280His (Yes) Arg399Gln(No)
Yang[79] **(2007)**	China	153/168	*XRCC3*	PCR-RFLP/Candidate	Thr241Met (No)

PCR-ARMS (amplification refractory mutation system), *CYP* (Cytochrome), *GST* (Glutathione S-transferase), *MPO* (Myeloperoxidase), *NAT2* (N-acetyltransferase gene 2), *NQO1* (NAD(P)H dehydrogenase, quinone 1), RFLP (Restriction fragment length polymorphism), *ERCC1* (excision repair cross complementing group 1), *hOGG1* (human 8-oxoguanine DNA glycosylase 1), *NBS1* (Nijmegen breakage syndrome 1), *XPD* (xeroderma pigmentosum group D), *XPC* (xeroderma pigmentosum group C), *XRCC1* and *XRCC3* (X-ray repair cross-complementing groups 1 and 3).

*Significant effects were noted in sub-analyses restricted to young smokers.

**For complete list of 676 Tag-SNPs within 88 DNA repair genes evaluated in the discovery stage and 11 SNPs within 7 DNA repair genes that were significant in the discovery stage and evaluated in the replication stage, refer to reference #[21].

***While the studies by Yang and Cao both reported evidence for a significant association between XRCC1 codon 194 polymorphism and NPC risk, the reported associations were in opposite directions.

Table 5

Other Genes in NPC

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphism (Association Reported – Yes/No)
Cell Cycle Control					
Ma[81] **(2011)**	China	855/1036	*BIRC5*	TaqMan PCR/ Candidate	rs9904341 (Yes)
Sousa[22] **(2011)**	Portugal	124/509	*MDM2*	PCR-RFLP/Candidate	rs2279744 (Yes)
Xiao[23] **(2010)**	China	522/722	*MDM2*	PCR-ARMS /Candidate	rs2279744 (Yes)
Zhou[24] **(2007)**	China	832/766	*MDM2*	SBT/Candidate	rs2279744 (Yes)
Xiao[23] **(2010)**	China	522/722	*TP53*	PCR-RFLP/Candidate	rs1042522 (Yes)
Sousa[25] **(2006)**	Portugal	107/285	*TP53*	PCR-SSP/Candidate	rs1042522 (Yes)
Tiwawech[26] **(2003)**	Thailand	102/148	*TP53*	PCR-RFLP/Candidate	rs1042522 (No)
Cell Adhesion/Migration					
Ben Nasr H[82] **(2010)**	Tunisia	162/140	*E-cadherin*	PCR-RFLP/Candidate	−160C/A (Yes)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP1*	SBT/Candidate	rs1799750 (No)
Nasr[83] **(2007)**	Tunisia	174/171	*MMP1*	PCR-RFLP/Candidate	rs1799750 (Yes)
Shao[27] **(2011)**	China	370/390	*MMP2*	TaqMan PCR/ Candidate	rs243865 (Yes)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP2*	SBT/Candidate	rs243865 (Yes) rs2285053 (Yes)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP3*	SBT/Candidate	rs3025058 (No)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP7*	SBT/Candidate	rs17880821 (No)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP9*	SBT/Candidate	rs3918242 (No)
Nasr[83] **(2007)**	Tunisia	174/171	*MMP9*	PCR-RFLP/Candidate	rs3918242 (No)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP12*	SBT/Candidate	rs2276109 (No)
Zhou[28] **(2007)**	China	593/480 239/286	*MMP13*	SBT/Candidate	rs17860523 (No)

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphism (Association Reported – Yes/No)
			Angiogenesis		
Ben Nasr H[84] (2009)	Tunisia	180/169	*COX-2*	PCR-RFLP/Candidate	−765G/C (Yes)
Wang[85] (2010)	China	156/161	*VEGF*	PCR-RFLP/Candidate	rs699947 (Yes)*
Nasr[86] (2008)	Tunisia	163/169	*VEGF*	PCR-RFLP/Candidate	rs699947 (Yes)*
			DNA Methylation		
Chang[87] (2008)	Taiwan	259/250	*DNMT3B*	MALDI-TOF based mini-sequencing genotyping/ Candidate	−149C/T (No) −283T/C (No) −579G/T (No)
Cao[88] (2010)	China	529/577	*MTHFR*	PCR-RFLP/Candidate	677C/T (No) 1298A/C (Yes)
			Others		
Li[89] (2011)	China	175/279	*ACE*	PCR-RFLP/Candidate	insertion/deletion (I/D) (No)
Tsou[90] (2011)	Taiwan	176/176	*Cav-1*	PCR-RFLP/Candidate	rs1997623 (No) rs3757733 (No) rs3807987 (No) rs3807992 (No) rs7804372 (Yes) rs12672038 (No)
Feng[91] (2008)	China	201/320	*DLC-1*	PCR-SSCP/Candidate	−29A/T (No)
Gao[92] (2008)	China	173/206	*EGF*	PCR-RFLP/Candidate	rs4444903 (No)
Gao[92] (2008)	China	173/206	*EGFR*	PCR-RFLP/Candidate	rs17337023 (No)
Zhang[93] (2011)	China	798/1019	*TERT*	Hot-PCR	MNS16A L/S (Yes)
Huang[94] (2011)	China	171/176	*VDR*	PCR-RFLP/Candidate	rs1544410 (No) rs10735810 (No)
Zheng[95] (2007)	China	531/480	*N4BP2*	sequencing/Candidate	loc123-e3l-snp2 (No) rs794001-SNP1 (No) rs1442855 (No) rs2252352 (No) rs2271395 (No) rs2347044 (No) rs17439810 (No) rs17511578 (No) rs17511668-SNP2 (No) rs17585937 (No)

Author/Yr	Country	Sample Size (#Cases/#Ctrls)	Genes Targeted	Methods/Approach	Polymorphism (Association Reported – Yes/No)
He[96] (2005)	China	239/286	*PLUNC*	PCR-RFLP/Candidate direct sequencing	rs750064 (Yes) rs2752903 (Yes) rs1998149 (No)

ACE (angiotensin I-converting enzyme), *BIRC5* (Baculoviral inhibitor of apoptosis repeat-containing 5 (also called as survivin)), *Cav-1* (Caveolin-1), *Cox-2* (Cyclooxygenase-2), *DLC-1* (Deleted in liver cancer-1), *DNMT3B* (DNA methyltransferase 3B), *EGF* (epidermal growth factor), *EGFR* (epidermal growth factor receptor), MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight), *MDM2* (Mouse double minute 2), *MMP* (matrix metalloproteinases), *MTHFR* (Methylenetetrahydrofolate reductase), *N4BP2* (Nedd4 binding protein 2), PCR-ARMS (amplification refractory mutation system), PCR-SSCP (single-strand conformation polymorphism), PCR-SSP (sequence specific primer), *PLUNC* (palate, lung, and nasal epithelial clone), RFLP (Restriction fragment length polymorphism), SBT (sequence based typing), *TERT* (telomerase reverse transcriptase), *VEGF* (vascular endothelial growth factor), *VDR* (Vitamin D receptor).

[*] While both studies that evaluated VEGF reported significant evidence for an association with NPC, the reported associations were in opposite directions.