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Focused Feature: NPC epidemiology and genetics

Nasopharyngeal carcinoma as a paradigm of cancer genetics

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Abstract

The unusual incidence patterns for nasopharyngeal carcinoma (NPC) in China, Northeast India, Arctic Inuit, Peninsular and island Southeast Asia, Polynesian Islanders, and North Africans indicate a role for NPC risk genes in Chinese, Chinese-related, and not-obviously Chinese-related populations. Renewed interest in NPC genetic risk has been stimulated by a hypothesis that NPC population patterns originated in Bai-Yue / pre-Austronesian–speaking aborigines and were dispersed during the last glacial maximum by Sundaland submersion. Five articles in this issue of the *Chinese Journal of Cancer*, first presented at a meeting on genetic aspects of NPC [National Cancer Center of Singapore (NCCS), February 20–21, 2010], are directed towards incidence patterns, to early detection of affected individuals within risk populations, and to the application of genetic technology advances to understanding the nature of high risk. Turnbull presents a general framework for understanding population migrations that underlie NPC and similar complex diseases, including other viral cancers. Trejaut *et al*. apply genetic markers to detail migration from East Asia through Taiwan to the populating of Island Polynesia. Migration dispersal in a westward direction took mongoloid peoples to modern day Northeast India adjacent to Western China (Xinjiang). NPC incidence in mongoloid Nagas ranks amongst the highest in the world, whereas elsewhere in India NPC is uncommon. Cao *et al*. detail incidence patterns in Southeast China that have occurred over recent decades. Finally, Ji *et al.* describe the utility of Epstein-Barr virus serostatus in early NPC detection. While genetic risk factors still remain largely unknown, human leukocyte antigen (HLA) genes have been a focus of attention since the discovery of an HLA association with NPC in 1973 and, two years later, that NPC susceptibility in highest-risk Cantonese involved the co-occurrence of multi-HLA locus combinations of HLA genes as chromosome combinations, or haplotypes (e.g. HLA-A2–B46), whereas in relatively lower-risk non-Cantonese Chinese (Hokkiens, Teochews) they appeared to act independently, a strength of association reflecting the 30–50-fold difference in incidence between highest risk Cantonese and lowest-risk Indians. The prototypic haplotype HLA-A2–B46 extends over megabases. An upstream DNA segment (near HLA-DPA1), has close similarity to Gorilla, with no obvious homology to Chimpanzee in current databases, suggesting that a reticulate model of primate evolution may be more appropriate than simple phylogeny. The DNA variation level in this segment is high enough for it to be a hominin remnant. HLA-B46 arose in mongoloids and remains largely limited to Chinese so the question arises as to whether the hominin candidate segment indicates an eastward trek of *Homo neanderthalensis* or the survival of much earlier *Homo erectus*? In 2011 sequencing technologies have finally caught up with the requirement to separate parental haplotypes. Recently achieved chromosome separation for whole genome di-haploid genetic and epigenetic analysis of parental inheritance in single individuals will reveal interacting patterns of multi-locus haplotypes as humans move in and through successive environments, thus providing definitive information on the genetic affinities between extant populations, and of the migrations that have led to the global distribution of modern Homo. The challenge can now be met of seeking HLA-associated locations both within and outside the HLA complex on each of the pair of chromosomes. More broadly, for every disease, genetic risk detection will require resolution of the diploid genome as a di-haplome. In the context of NPC, HLA genetic risk complete autosomal di-haplomic sequencing will enable testing of the Wee unitary origin hypothesis of NPC risk even among populations with no apparent mongoloid affinity.

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Genetic aspects of nasopharyngeal carcinoma (NPC) were the focus of a meeting at the National Cancer Center of Singapore (NCCS) on February 20–21, 2010. Manuscripts arising from presentations at that meeting will be published in the *Chinese Journal of Cancer* (*CJC*). Readers of a cancer journal may be surprised that a sociologist of science receives a place of prominence in the five papers published this month. The reason is that population incidence is a central enigma of all cancer occurrences. NPC has a highly unusual global geographic distribution, and thus provides a particular opportunity for hypothesis generation and testing. A hypothesis proposed by Wee *et al.*[1] prompted the Singapore meeting and has injected renewed enthusiasm into NPC genetic risk inquiry. This unitary NPC origin hypothesis proposes that the population pattern of NPC occurrence can be explained by a genetic lesion originating in Bai-Yue–speaking ("proto–Tai Kadai" or "pre-Austronesian" or "proto-Zhuang") aborigines that were dispersed by Sundaland submersion following the last glacial maximum[1]. Dispersal from the putative founding population occurred in all directions: Northeast for the Arctic Inuit, Southeast for more proximal Land Dyak Bidayuh–speakers of East Malaysia and further distant Maori and Polynesian Islanders, West to the Northeast of India, and South to island Southeast Asia. The articles in this edition of the *CJC* are directed towards incidence patterns, the application of genetic technologies to understanding the advent of NPC high risk populations, and to early detection of affected individuals within these populations.

The relevance of Turnbull's article[2] to NPC is that understanding the bizarre global geographic incidence patterns, including east and north African populations, requires the unravelling of the diaspora of populations that exhibit high NPC risk through tracing the differing paths of artefacts, language and limited genetic biomarkers that currently lead to conflicting stories. Turnbull[2] presents a general framework for considering human population migrations which is central to testing the Wee unitary NPC origin hypothesis and exhorts us to remember that understanding human movement involves more than just the usual archaeological, cultural-linguistic and genetic processes. He reminds us of the social dimensions, and argues that the totality of interacting components can be conceived of either as an emergent complex adaptive system in action, or as being unifiable in a grand synthesis; and that such conflicting approaches should be held in tension with one another. Indeed, there is good reason to consider social practices since the Bai-Yue aboriginal origination hypothesis arose as a result of Wee's sociological insight that several high NPC incidence populations all practised a similar form of bamboo pole dance (tinikling). As Wee *et al.*[1] detailed, common ancestry between the Bai-Yue and other high NPC risk aboriginal peoples (of Borneo, Northeast India, Arctic Inuit, Austronesian Malayo-Polynesians of Southeast Asia, and Polynesians of Oceania) is supported by other shared cultural characteristics. Whether increased NPC occurrences among populations in east and north Africa that are not obviously related to Chinese share the expected genome-wide risk pattern variations will be a definitive test of any global unifying genetic hypothesis. Wee's preferred mechanism has the female as the more important bearer of transmission, noting that there appears to be a step-wise reduction in age-standardised rate (ASR) with every migration and intermixing of high risk and low risk populations as a "genetic dilution" (personal communication, 2010). He clarifies his hypothesis as "2 hits" involving an X-linked recessive mutation as the "1st hit", and Human leucocyte antigen (HLA) immunity as the "2nd hit". He identifies involvement of the X-chromosome with Epstein-Barr virus (EBV) infections, citing Systemic Lupus Erythematosus and X-linked lymphoproliferative disorder. Wee suggests that, while the EBV infection in the "1st hit" is innocuous, the inability to mount an HLA-based effective immune response would result in an uncontrollable proliferation of EBV-infected cells, initiating the carcinogenic cascade that results in NPC. There are probably multiple pathways that allow this step to occur, accounting for the different HLA haplotypes in different patients (personal communication, 2010).

In this *CJC* edition Trejaut *et al.*[3] apply genetic markers to detail migration from East Asia through Taiwan resulting in the populating of Island Polynesia. This is followed by NPC incidence descriptions of the Northeast Indian provinces adjacent to Western China (Xinjiang)[4]. The incidence of NPC in the mongoloid Nagas is amongst the highest in the world, contrasting starkly with that of other populations in Assam and elsewhere in India where NPC is rarely seen, with an incidence level even lower than that in Caucasians (0.5/100 000–2.0/100 000 per year)[5]. Among the Land Dyaks in Sarawak, East Malaysia, occurrence is similar to, if not higher than, that in the Nagas[6]. Cao *et al.*[7] detail incidence patterns in south eastern China, and changes that have occurred over recent decades. This review should be read in conjunction with other articles on incidence changes indicating that environmental and lifestyle changes play an important role in the declining incidence of NPC over time in some populations[8]. Finally, Ji *et al.*[9] describe the utility of EBV serostatus in early NPC detection.

From the viewpoint of NPC genetics, there is now 37 years of evidence that genetic elements associated with HLA within the major histocompatibility complex (MHC) are major contributors to differential NPC risk among southern Chinese[10]. As early as 1975 it was established

that NPC susceptibility in highest risk Cantonese involved the co-occurrence of multi-HLA locus combinations of HLA genes as chromosome combinations, or haplotypes (e.g. HLA-A2-B46), whereas in relatively lower risk non-Cantonese Chinese (Hokkiens, Teochews) they appeared to act independently, a strength of association reflecting the 30–50-fold difference in incidence between highest risk Cantonese and lowest-risk Indians[11].

HLA genetics in NPC was recently reviewed as a commentary to the Bai-Yue hypothesis [12]. Within the MHC, the HLA genes are of dominant importance in immuno-inflammatory biogenetics. However, it is essential to remember that the known functions of other MHC genes concern fundamental cellular processes, whereas that of the majority of MHC genes remain to be revealed. Yes, NPC does occur before 30 years of age but it is predominantly a disease of older age so the roles of other reproductively transmitted genes have to be considered. For instance, a recent genome-wide association study (GWAS) identified a further three new susceptibility genes [13]. This large GWAS, comprising approximately 5 000 patients and 5 000 controls of southern Chinese descent, has established beyond any doubt that the HLA complex is a primary location of NPC risk, comprising multiple risk regions, with the "top single nucleotide polymorphism (SNP)" having amongst the highest statistically significant value of any published GWA study.

The challenge now is to identify location(s) both within and outside the HLA complex that underlie such genetic associations, and to determine whether they are required to be present on both of the pair of chromosomes as simple or compound obligate recessive traits[14], or whether a single, dominant, gene lesion dose is sufficient. Recent studies have confirmed the original report that HLA genetic involvement in NPC concerns multilocus haplotypes[11], and requires the characterisation both of extended haplotypes and of intra-haplotypic relations between primary locus alleles [15-17]. Further analysis of the GWAS SNP data patterns is revealing the utility of age of onset-cohort SNP stratification for detection of fine genome-mapped clusters of interval SNPs having highly significant associations with unexpected genomic areas (unpublished observations by Simons MJ, Bei JX, Cui Q, Lei JJ, Satterley K, Tait BD, and Zeng YX, 2011).

The HLA connection with NPC has an additional intrigue. Among the thousands of HLA gene varieties or alleles, one, named Singapore-2 when it was first discovered [18], later assigned as HLA-B*46:01, arose in Chinese aborigines by a rare mechanism [19] some tens of thousands of years ago and has an intimate but unresolved association not only with NPC [12,20] but also with some autoimmune diseases[21,22]. HLA-B*46:01 allele is inherited with a range of alleles at HLA loci on either side of the HLA-B locus as extended haplotypes. Analysis of the type and frequency of these multi-locus extended haplotypes provides an indication of genetic affinities of carrier populations (unpublished observations by Yuliwulandari R, Simons MJ, and Tokunaga K, 2011). However, there are inherent errors in assignment of haplotypes based on linkage disequilibrium estimation. For instance, a pedigree study of Chinese Han families revealed that 65% (235) of 362 three-locus haplotypes were observed only once ("singletons") [23]. This corresponds to 45% of individuals having two singleton haplotypes, a situation which precludes di-haplotype assignment by any likelihood estimation. It is thus mandatory to utilise pedigrees or haploid DNA for accurate di-haplotype assignment in population affinity studies.

The two prototypic haplotypes A2-B46-DR9 and A33-B58-DR3 are known to confer risk for NPC but for different ages of onset [24]. While both extend over megabases (unpublished data by Shen M, Chia JM, Chan SH, and Ren EC), it is unclear how far centromeric in the HLA complex the primary haplotypes, or variants thereof, extend. In seeking to characterize any association with the main centromeric loci, HLA-DPA1 / HLA-DPB1, the heterodimeric combination of HLA-DPA1*04:01 / DPB1*13:01 was found to be a common accompaniment of HLA-B*46:01[25]. At least three groups have sequenced intron and intergenic components of the DPA1*04:01 allele and observed a high level of sequence variation[25,26] (the third is by Wood JM, Simons MJ, and Ashdown ML, 2004 in GenBank: nucleotide). Over a length of at least 8 kb, the HLA-DPA1*04:01 sequence has more SNPs than are present in the sum of the remaining 27 HLA-DPA1 alleles and as such is possibly unique among human patterns (unpublished observations by Simons MJ and Varney MD, 2011). This segment recombines at sites including junctions with repeat sequences as befitting a Mendelian unit of genetic inheritance. It has close sequence similarity to Gorilla, with no obvious homology to Chimpanzee in current databases. Together these two observations suggest that a reticulate model of primate evolution may be more appropriate to represent genomic segmental inheritance than simple phylogeny. As an ancient highly polymorphic sequence, an association with earlier hominins needs to be considered. Recent evidence of genetic mixture between Neanderthals and modern humans was interpreted as favouring gene flow from Neanderthals into modern humans when they first left sub-Saharan Africa because Neanderthals were found to be equally distantly related to all non-Africans [27]. However, the HLA-DPA1 sequence shows sufficiently high divergence to allow the possibility of later interbreeding with modern humans in western Asia [27].

Explanation will have to take account of the fact that the sequence is concentrated in southeast Asia[26], including in modern day Dai speakers that have descended from the Bai-Yue, so there are questions concerning hominid migration, and whether the sequence represents the eastward trek of *Homo neanderthalensis* or even the survival of much earlier hominin, *Homo erectus*.

Turnbull [2] also alerts us to the need to recognise competing hypotheses at many levels, not only concerning NPC risk population migrations during which recombination and other rearrangement mechanisms result in separation of causative elements and marker traits, as reflected in loss of Chinese-associated HLA markers in descendant populations, but also at the level of molecular mechanisms. For instance, in addition to genomic genetics as factors in NPC causation, there are two other main candidate categories: (1) infection with, and altered immune responsiveness to, EBV[28-30]; and (2) deleterious dietary substances and practices[31-33].

EBV infection is especially important, at three levels. The first level is the utility of EBV infection response in identifying individuals at high NPC risk[9]. The contribution is not in itself sufficient to achieve cost-effective, clinically useful value, even among highest NPC risk normal family members of multiple case families [34], let alone in the general population, since only a small proportion of infected individuals present with EBV-specific IgA seropositivity, but it does provide a majority biomarker contribution to early detection[28]. A recent publication concerning host homologous recombination repair (HRR) system participation in EBV lytic replication suggested a potential mechanism to influence EBV reactivation status and thus seropositivity[35]. Variant alleles of six HRR system-affecting genes could well supplement EBV-specific IgA seropositivity towards "gap closure" of early NPC detection clinical utility.

Such an EBV seroimmunity status contribution could be further supplemented towards "gap closure" by risk-conferring HLA alleles detected, not by routine sequence based typing, but by microarray chip-bearing tag SNPs. This could be achieved by utilising a risk score concept that selects a range of HLA alleles from alleles rare or absent in NPC (such as HLA-A*31:01 in Chinese, HLA-A*23:01 in Tunisians, HLA-B*44:03:2 in Thais) at the one extreme, to the components of high risk haplotypes at the other, in a manner similar to celiac disease risk identification[36,37].

The second level of EBV consideration is whether the HLA associations involve EBV peptide presentation or other direct involvement of HLA alleles as cell surface-presenting immune receptors/ligands, or whether the connection is indirect, reflecting linked genetic lesions referred to as disease-association (DA) or disease-susceptibility (DS) loci[11,38].

The third level for consideration is the role of EBV in cancer genesis. A striking instance of the complexity is the association of EBV with both NPC and salivary adenocarcinoma in the Inuit. Among multiple NPC case Inuit families, increased cancer proneness is to both of the EBV-associated tumors [39], whereas in Chinese only NPC is observed [40]. Furthermore, EBV seroreactivity has a different pattern from Chinese in that the very high prevalence of anti-VCA IgA precludes the utility of this antibody for NPC screening among Inuits [41]. This is an example of how a complex disease like NPC can have a definable genetic origin and be carried as a genetic marker by a specific population yet the risk distinction, here between risk-originating Chinese and descendant Inuits, and between Arctic-at-risk Inuit and Siberian-not-at-risk Inuit, is not a simple story of genetic determination and geographic spread. The high risk of carcinoma of the nasopharynx and salivary glands observed in Arctic Inuit populations is maintained after migration to the low incidence area of Denmark, indicating that genetic factors acting early in life are etiologically important for these cancers[42].

It needs to be remembered that genetic variations arise in a single individual. For the changes to become sufficiently established to account for an effect on a population, the operation of positive selection is required on the reproductive age group. The question is—what are the selective processes, and what are their genic targets and mechanisms? Whether origination occurs in a single location, as in the Wee unitary NPC origin hypothesis, or is geographically distributed, evolutionary time provides ample opportunity for the emergence of a multiplicity of genetic defects in different locations within the MHC and elsewhere in the genome. Recombination and other genomic rearrangements is a sufficient explanation for dissociation of linkage between candidate HLA markers and yet-to-be-discovered "causal" variants, together with balancing selection[43] so it should surprise no one that, although HLA-B*46:01 is not present in medium NPC occurrence populations such as Maori and Polynesian islanders, Taiwan Paiwan aborigines and Maghreb North Africans, HLA-B*46:01–linked genetic lesions may still be found to be shared between disparate NPC risk populations.

The major contributions of the recent GWAS were to highlight the well-established HLA associations, and to reveal three new genomic locations [13]. Collectively, all these genes can contribute alleles towards useful diagnostics of disease risk and of early disease occurrence. In addition, the GWAS revealed genetic individuality even between individuals who were interval-HLA locus typed as homozygous over megabases because they differ in SNP haplotypes between canonical HLA locus allele types. Thus two individuals who share common HLA "haplotypes" such as A2-B46-DR9 and A33-B58-DR3, even as apparent

homozygotes, are dissimilar at intervening loci [44]. The situation is not different from that at other genetic loci where it is common practice to group separated SNPs at protein-coding sequences as "haplotypes". While it is widely assumed that phase-true "haplotypes" will be able to be assembled by ever more sophisticated bioinformatic algorithms, only phase-discrete analysis by separate chromosome sequencing between and through protein-coding DNA provides certainty of characterisation of the entire inherited diplotype. Thus definition of the genetic elements conferring risk for every disease will require resolution of the diploid genome as a di-haplome. Aside from the importance to classification of cis- and trans- phase in NPC genetic analysis, it also follows that even di-haploid matching for transplantation is incomplete unless the inter-HLA genotype is defined.

Such a whole genome di-haploid typing strategy for "complete" autosomal archaeogenetic population profiling will also enable an interpretative tension to be held between the dichotomy of a phylogenetic arborescent framework and a reticulate form of modelling that is independent of complications arising from population selective pressures or of neutral drift.

For the purpose of utilising DNA to study populations at differential disease risk, and here to testing of the unitary origin hypothesis of NPC risk among seemingly unrelated populations, it will soon become technically and cost-feasible to separately sequence 46 chromosomes for whole genome di-haploid genetic and epigenetic typing. Thus it can be anticipated that a full di-haplomic account will better enable resolution of interacting patterns of haplotypes in a process of co-production of humans moving in and through their environments. Indeed, the first reports of the feasibility of achieving a completely phased genome following chromosome sorting and separation have just been published[45,46]. Then it will be easily possible to examine the MHC as a multi-locus microgenome to qualify the simplistic concept of a single major gene risk for NPC, while scanning the remaining 99.9% for evidence consistent with further, multifactorial, genetic contributions to NPC risk. Since HLA multilocus haplotypes occur as risk factors, they can be applied to supplement male Y chromosome and female inherited mitochondrial gene types in the characterisation of Chinese and Chinese descendant populations. Di-haploid analysis of parental inheritance in single individuals will provide definitive information of the genetic affinities between extant populations, and therefore of the migrations that have led to the global distribution of modern Homo sapiens.

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