

•Perspective•

Is nasopharyngeal cancer really a “Cantonese cancer”?

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[Abstract] Nasopharyngeal cancer (NPC) is endemic in Southern China, with Guangdong province and Hong Kong reporting some of the highest incidences in the world. The journal *Science* has called it a “Cantonese cancer”. We propose that in fact NPC is a cancer that originated in the Bai-Yue (“proto-Tai-Kadai” or “proto-Austronesian” or “proto-Zhuang”) peoples and was transmitted to the Han Chinese in southern China through intermarriage. However, the work by John Ho raised the profile of NPC, and because of the high incidence of NPC in Hong Kong and Guangzhou, NPC became known as a Cantonese cancer. We searched historical articles, articles cited in PubMed, Google, monographs, books and Internet articles relating to genetics of the peoples with high populations of NPC. The migration history of these various peoples was extensively researched, and where possible, their genetic fingerprint identified to corroborate with historical accounts. Genetic and anthropological evidence suggest there are a lot of similarities between the Bai-Yue and the aboriginal peoples of Borneo and Northeast India; between Inuit of Greenland, Austronesian Mayalo-Polynesians of Southeast Asia and Polynesians of Oceania, suggesting some common ancestry. Genetic studies also suggest the present Cantonese, Minnans and Hakkas are probably an admixture of northern Han and southern Bai-Yue. All these populations have a high incidence of NPC. Very early contact between southern Chinese and peoples of East Africa and Arabia can also account for the intermediate incidence of NPC in these regions.

Key words: Nasopharyngeal neoplasm, Bai-Yue, genetics, origins, populations, ethnic groups

Introduction

Nasopharyngeal cancer (NPC) is endemic in southern China, with Guangdong province^[1] and Hong Kong^[2] reporting some of the highest incidences in the world. The journal *Science* has called it a Cantonese cancer^[3]. We suggest that NPC became known as a Cantonese cancer as a result of work by John Ho and others from Hong Kong and Guangzhou^[4] which has raised the profile of NPC, and secondly because of the high reported incidence of NPC in Hong Kong and Guangzhou.

However, in this paper we propose that in fact NPC is a cancer that originated in the Bai-Yue (“proto-Tai-Kadai” or “proto-Austronesian” or “proto-Zhuang”) peoples and was transmitted to the Han Chinese in southern China through intermarriage. To this end, we first review the populations with a high or intermediate incidence of NPC. We then use timelines together with anthropological, genetic, historical, and other data

to demonstrate how the different populations may be interconnected. Finally, we formulate a working hypothesis that may explain how different populations and ethnic groups in which NPC is prevalent all descended from a common ancestor.

Populations with high incidence of nasopharyngeal cancer

Southern Chinese

The southern Chinese have one of the highest incidences of NPC in the world. In Hong Kong^[2], the age-standardized incidence rate (ASR) was 20.2 per 100 000 males, and 7.8 per 100 000 females during the period of 1995-1999. In Guangzhou city, the ASR was 22.2 per 100 000 for males and 9.9 per 100 000 for females in 2002.

In the historical literature of the Book of Former Han (Hanshu in Chinese, written in 111 CE) and the Records of The Grand Historian (Shiji in Chinese, written in 109-91 BCE), there was an area inside current Guangdong province named Bai-Yue, meaning ‘hundred of tribes residing in the area of Yue’^[5]. One of the major tribes continuously inhabiting this area is called Zhuang, and this tribe is also currently the largest ethnic minority population in China, with a population of 17 million^[6]. Linguistic studies have found that modern Cantonese spoken by the people

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in parts of Guangdong province, parts of Guangxi province, and in the Hong Kong Special Administrative Region is a mixture of the ancient Zhuang's languages and the ancient Han Chinese of central China^[5].

By applying molecular genetics analyses involving 13 East Asian-specific Y-chromosome biallelic markers and 7 Y-chromosome short tandem repeat markers, Chen *et al.*^[7] demonstrated that there are three major components in the Zhuang minority, with the Y-chromosome haplogroups O* and O2a populations constituting the original component and the Y-chromosome O1 haplogroup population being imported into eastern Zhuang only at a later stage. The study also showed that from the northern Han Chinese population, the Y-chromosome O3 haplogroup was subsequently brought into the Zhuang population at an even later stage.

The boat-dwellers in the Pearl River delta area and Xijiang river basin (also known as the Tanka people), who are the descendants of the Bai-Yue, have a very high NPC incidence rate. In a study in the 1970s by Min *et al.*^[5] these people were found to have a crude NPC mortality of 22.36 per 100 000. In 1939, the historian Song-Shi Xu (徐松石) drew a map of the grouped areas in Guangdong province named by Zhuang's linguistic character '都' for the purpose of studying the areas where the Zhuang minority are concentrated. Interestingly, this map almost overlaps with the highest NPC incidence areas found in the study of Min *et al.*^[5]

For centuries, imperial decrees had forbidden these boat-dwellers in Pearl River delta and Xijiang river basin (the Tanka people) from marrying Han Chinese, from being educated, or from residing on land. This policy was believed to be the result of their ancestors (a Bai-Yue southern aboriginal group) fighting against the Han Chinese Emperor during the Qin Dynasty era (around 200 BCE), losing the battle, and subsequently becoming fugitives^[8]. This official discrimination only ended in 1912 when the Provisional Constitution of the Republic of China was adopted. This group could thus be thought to be of 'pure' Bai-Yue stock in contrast to the other Southern Chinese.

Another area in China with a high incidence of NPC is in Sichuan province. Historical accounts suggest that the Qing Emperor Kang Xi, after a tour of the land found that Sichuan province grossly depopulated as a result of wars. He encouraged the Hakkas who were living in poverty in the coastal areas of Guangdong province to emigrate to Sichuan province with the promise of financial assistance. This became known as the forth migration of the Hakkas^[9].

Hmong

Originally an ethnic minority group in southern China, the Hmong (also known as the Miao ethnic minority in China) moved south and now inhabit the mountainous regions of northern Vietnam and Laos, where they engage in slash-and-burn farming. Because of their allegiance to the U.S.A. during the Vietnam conflict, some of these Indochinese Hmong were forced to flee to Thailand. In the early 1980s, thousands of Hmong were relocated to California and Minnesota. A study of the cancer incidence among these American Hmong^[10] showed an NPC ASR rate of 16.0 per 100 000 males and 6.9 per 100 000

females (1988–2000). The Hmong are a distinct group from the Bai-yue but were previously physically located next to the Bai-yue populations in south China, and intermarriage between the two groups could have resulted in an increased incidence of NPC in the Hmong.

Bai-yue descendants

Borneo Aborigines The Bidayus are the aboriginal Dayaks of Borneo. They are believed to have originated in Yunnan. A study by Devi *et al.*^[11] showed that the ASR of NPC amongst Bidayus is 29.4 per 100 000 males and 10.6 per 100 000 females (1996–1998). In the East Malaysian State of Sabah, the Kadazan-Dusun-Murut (KDM) ethnic minority group has a higher incidence of NPC than the Chinese population, which is predominantly Hakkas^[12].

Northeastern Indians NPC is generally considered to be uncommon in India. According to Cancer Incidence in Five Continents the ASR is 0.8 per 100 000 (2002) in Chennai (Madras)^[13]. However the Kohima district in Nagaland State recorded an ASR of 19.4 per 100 000 (2002)^[14], which is similar to the high rates found in southern Chinese populations. The Nagas are considered to be of Mongoloid stock. They are supposed to have arrived at different time periods and from different directions to settle in the northeastern highlands bordering India and Burma. Some of these populations have remained isolated and retained their identity, which is reflected in their unique genetic profiles^[15].

The other Northeastern Indian populations are the Dai (also known as Tai) ethnic minority immigrants (descendants of a Bai-Yue subgroup) from South China. In India, they are known as Ahom, Aiton Khamti, Phake, Khamyang, and Turung. The Ahom are the most predominant Dai group in India. They came to Northeastern India in the early part of the thirteenth century CE and have ruled Assam for six centuries (1228–1826). They lost their power to the East India Company's government in the wake of the Anglo-Burmese war in 1826 CE^[16]. Mitochondrial DNA (mtDNA) analyses have shown that these northeastern Mongoloid tribal groups have closer genetic affinities with East Asian groups than with other Indian groups^[17]. The reported ASR of NPC in parts of northeast India is 7.4 per 100 000 (Imphal West district in Manipur State; 2001–2002)^[14].

Southeast Asians The incidence of NPC in Vietnam shows an interesting pattern, with the ASR in Hanoi (10.3 per 100 000 in 1995–1996) being twice that in Ho Chi Min City (5.1 per 100 000 in 1995–1996)^[18]. The North Vietnamese Kinh population (the majority ethnic group in North Vietnam) is believed to be of dual ethnic origin, descendants of an Austro-Asiatic stock who subsequently intermarried with the Bai-Yue people of south China^[19]. South and central Vietnam, on the other hand, was formerly part of the Kingdom of Champa, an Indianised kingdom of Mayalo-Polynesian origin whose language, 'Cham', is part of the Austronesian family. According to one study, Cham is related most closely to modern Acehnese^[20] and Malay^[21]. The ASR of NPC among male Malays in Malaysia (another ethnic group classified under the "Mayalo-Polynesian" stock) is 4.8 per 100 000 (compared with 18.1 per 100 000 for the male Chinese in Malaysia in 2003)^[22].

The Filipinos are another Mayalo-Polynesian stock whose language is classified under the Austronesian language family. The Malays of peninsular Malaysia and Indonesia are of the same stock and are believed to have been derived from migrations from the Philippines. The ASR of NPC in the Philippines is 8.6 per 100 000 males (1993–1995) [13,23]. The Taiwanese aborigines (believed to be of similar ancestral Mayalo stock, but who remained isolated) have an incidence of NPC higher than that of the Han Chinese in Taiwan—who are predominantly from Fujian Province[24].

The origins of the Thais remain an anthropological mystery. Linguistically they belong to the Tai linguistic family[25-27] and are believed to have originated from the Bai-Yue of South China. The Mon-Khmers, who were of Austro-Asiatic stock and who were believed to have originated in India, originally occupied Thailand[28]. The proto-Thai ancestors displaced the Mon-Khmers but assimilated their culture, and to this day there remain many similarities between the Thai and Khmer cultures. The ASR of NPC among male Thais is just below 5 per 100 000 (1997)[29]. The ASR of NPC in northeast India is about 7.4 per 100 000 (2001-2002) [14]. Unlike the Zhuangs, their other major Bai-Yue cousins who remained in the “Sinosphere”, the Thais were taken up in the “Indosphere”.

Polynesians, Maoris, Hawaiians and Chamorro The Polynesians and Maoris have an intermediate risk of NPC[30]. The incidence in New Zealand Maori population is 1.90 per 100 000 (1978–1982) [31]. The Polynesians are Austronesians believed to have originated from either the Taiwanese aborigines or from mainland South China. The incidence of NPC in the ethnic Hawaiian male is 1.9 per 100000 (1988–1992) [32]. According to GLOBOCAN 2002[33], the incidence of NPC amongst Polynesians is similar. In Guam, the Chamorro ethnic Polynesians have an NPC ASR of 13.6 per 100 000 (1998– 2002) [34]. The Chamorros are believed to have derived directly from Taiwan or the Philippines rather than from insular Southeast Asia unlike the other Polynesians.

Inuit

Lanier *et al.* [35] reported one of the highest rates of NPC in the world among both male and female Inuit, and NPC was the most common cancer afflicting Inuit from 1969 to 1988. The reported ASR was about 16.6 per 100 000 males and about 8.7 per 100 000 females.

East Africa

The incidence of NPC in Kenya is high, although no actual ASR has been calculated [36]. NPC constituted 5.8% of all malignant cancers according to a Sudan Cancer Registry study[37]. According to GLOBOCAN 2002[33], the incidence of NPC in East Africa is the highest in Africa except for North Africa.

Timelines for the origins of these populations

Pre-Holocene Migrations

Ke *et al.* [38] performed Y-chromosome analysis on 12 127 male individuals from 163 populations across Southeast Asia,

Oceania, East Asia, Siberia, and Central Asia, genotyping for three biallelic markers (YAP, M89, and M130). Each of the 12 127 samples genotyped carried one of the three polymorphisms (YAP1, M89T, or M130T). In other words, they all fall into the lineage of M168T that was originally derived from Africa. Hence, all surviving East Asian populations today could trace their origins to Africa.

35 000 Years ago

Edmondson[27] (Figure 1) writes that some 35 000 years ago, a group carrying the Y-chromosome Haplogroup O (M175) marker made use of the Dzhungarian Gap and moved into East Asia. The ice age and high mountains isolated this group in East Asia. Some of their descendants remained in Southeast Asia and formed the Austro-Asiatic (Bai-pu) populations and mixed with the Negritos (ethnic groups in Southeast Asia who share physical features with African pygmy, who had arrived with the first wave of migration out of Africa).

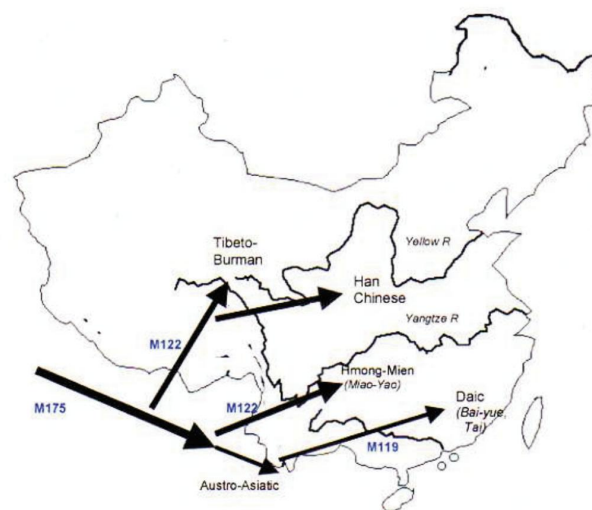


Figure 1 Ancient migration patterns in China

Some of those arrived at Yunnan and moved further north; this group carried the Y-chromosome Haplogroup O-3 (M122) marker. Some of these veered off at the Yangtze Basin and formed the Miao-Yao (ancestors of the Hmong) population, while the remainder continued further north to the source of the Yellow River, where they also divided. One group—the Tibeto-Burman—remained at the Yellow River source, but the Huaxia (the ancestors of the Han Chinese) followed the course of the Yellow River downstream to Henan and Shaanxi provinces.

Those who did not turn north carried the M119 marker (Y-chromosome Haplogroup O-1A). They moved into northern Thailand, Laos, and Vietnam and then looped north, crossed the Red River basin, and followed the seacoast up to the mouth of the Yangtze River near Shanghai. Chinese historians referred to these people as the Bai-Yue, and their settlements extended from Shanghai to the Sino-Vietnam border area in Yunnan province.

A recent study by Li *et al.* [39] examined the Y chromosome on human remains from archeological sites along the Yangtze

River. There was a high frequency of O-1 at the Liangzhu Culture sites around the mouth of the Yangtze, linking this to the modern Austronesian and Daic populations, while O-3d was found at the Daxi site in the middle reaches of the Yangtze, suggesting that the Daxi people may be the ancestors of the modern Hmong-Mien population.

Su *et al.*^[40] in a study of over 900 male DNA samples showed that southern populations in eastern Asia are much more polymorphic than northern populations, which have only a subset of the southern haplotypes. This pattern affirms the hypothesis that the first settlement of modern humans in eastern Asia occurred in mainland Southeast Asia and subsequently a great migration took place towards northern China and Siberia.

20 000 Years ago

Li *et al.*^[41] further postulated that fragmentation of southern Chinese populations began around 20 000 years ago, when ethnically specific haplogroups were formed and genetic exchange was almost cut off. A natural disaster in the form of the peak of a glacial age is thought to be the cause of the sudden end of genetic mixing. The freezing weather reduced communication between populations and altered their conditions of survival. The various groups were forced to move to different areas segregated by the cordilleras of southeastern China. This geographical separation and the resulting cultural differentiation continued over the next 10 000 years to form the present diversity of populations represented by the Daic, Hmong-Mien, and the Austro-Asiatic of South China (Figure 2). Around 8000 years ago, two very important archaeological cultures, Hemudu and Daxi, formed in the region of the Daic and the Hmong-Mien, respectively.



Figure 2 Ethnic divisions in southern China before the Han’s southward expansion

(Map reproduced with permission from Li *et al.*, 2007^[41], Mitochondrial DNA diversity and population differentiation in southern East Asia © 2007- Reproduced with permission from John Wiley & Sons, Inc.)

Dashed lines are the ethnic divisions. Dotted lines are the province borders. Dashed dotted lines are the country borders. Solid lines are rivers and sea lines. Important cordilleras between ethnic areas are marked in the map.

The Inuit are a group of culturally similar indigenous peoples inhabiting the Arctic regions of Canada, Greenland, Russia, and Alaska. While their origins remain a mystery, their physical

characteristics suggest an Asian origin^[42]. Harvald^[43] examined polymorphisms such as lactose and sucrose malabsorptions (which are rare in Western populations) and suggested that the gene pool of Inuit is in many respects similar to that of East Asian populations.

Human leukocyte antigen (HLA) studies^[44] suggest genetic relationships among the Taiwan aborigines, northern Asians, and Oceanians. HLA A24-Cw8-B48, A24-Cw10-B60, and A24-Cw9-B61, commonly found in many Taiwan indigenous tribes, have also been observed in Maori, Papua New Guinea Highlanders, Orochons, Mongolians, Inuit, Japanese, Man, Buryat, Yakut, Tlingit, Tibetans, and Thais. These findings suggest the Inuit are related to Asians.

Larson *et al.*^[45] examined DNA samples obtained randomly from the Greenlandic population to analyze the size and AGG interspersed pattern of the FMR1 (CGG)_n region. The (CGG)_n allele sizes in the Greenland population showed a narrow distribution, similar to that reported for Asian populations. The data also indicated that some (CGG)_n alleles have remained stable for 15 000–30000 years, since the population of the New World arrived from Asia via the Bering Strait. Brace *et al.*^[46], looking at human cranio-facial data, suggested that the Inuit and the Na-Dene-speaking Athabaskans (the most recent groups to have left northeast Asia for the New World) show strong resemblance to the Chinese-related populations of mainland Asia.

Thus, genetic studies support the historical expansions of these East Asian populations to Polynesia and the arctic regions perhaps 15 000 years ago, just prior to the most recent submergence of the Bering land bridge.

10 000 Years ago

Sundaland, Tunghailand and Nanhailand Before the last ice age, continental Asia extended to Japan and Taiwan through two coastal landmasses known as Tunghailand and Nanhailand (from the Gulf of Tonkin to Japan) and to Borneo and Java through Sundaland (now the Gulf of Siam and Java Sea); now all are under the sea after the rise in sea levels (Figure 3). The original southern China aborigines (proto-Bai-yue) probably wandered freely along this coastal region, but after the ice age and the following rising sea levels, they became isolated on the islands of Taiwan, Hainan, Borneo, and islandic Southeast Asia. Some of these people were also believed to have migrated north and across the Bering Strait into Alaska, Greenland, and the Americas.

Soares *et al.*^[47] used complete mtDNA genome sequencing to identify some earlier processes that had a major role in the demographic history of Southeast Asia. Haplogroup E was demonstrated to be an important component of mtDNA diversity in the region. It evolved in situ over the last 35000 years and expanded dramatically throughout Islandic South East Asia (ISEA) around the beginning of the Holocene, when the ancient continent of Sundaland was being broken up into the present-day archipelago by rising sea levels. It reached Taiwan and Near Oceania within the last approximately 8 000 years. This suggests that global warming and sea level rises at the end of the Ice Age, 15 000 to 7000 years ago, were the main forces shaping modern



Figure 3 Southeast Asia before the last ice age (Map reproduced from Google Earth)

human diversity in the region.

The Nagas The Nagas are an ethnic hill tribe living in the hills bordering northeastern India and Myanmar. Of Mongoloid stock, they speak a Tibeto-Burman language. Some scholars have noted similarities between the Nagas and the aboriginal peoples of Borneo and the Philippines. Like the Bidayus (Land Dayaks) of Borneo, the Nagas have also one of the highest ASR of NPC in the world.

The origins of the Naga people remain a mystery; although folklore and folk tales suggest that they may have originated in Southeast Asia. According to Pou,^[48] the movement of the Naga population was first southward from the Asiatic mainland and then from the Archipelago eastward to the Pacific. Then, however, they retreated in a northwest direction to the Naga Hills. This might have occurred when the sea levels rose and inundated the Sunda shelf at the end of the last ice age, forcing the people inland and uphill. Their love of marine shells (for a hill tribe) may perhaps be construed to point to some bygone settlement near the sea.

Naga scholars^[49] also believe that there are socio-cultural similarities between the Nagas and the tribes of the southern seas (Philippines, Malaysia, Indonesia, Taiwan, and so forth). The customs and traditional practices by Nagas—such as dormitory system, houses on stilts, tattooing, platform burial, looms, terraced rice fields, and so forth—resemble those practiced by tribes in the southern seas. McGovern describes the similarities of the Nagas to the Dayaks and Kayans of Borneo, the Bataks of Sumatra, to certain groups of Formosa (Taiwan) and to other groups in Philippines. Hazarika *et al.*^[50] suggests that there are similarities in the Neolithic cultures of northeast India and South China and Southeast Asia.

Zhuang minority ethnic group Barlow^[51] describes the Zhuang minority ethnic group in Southern China as also having practices like tattooing, houses on stilts, terraced rice fields, bamboo pole dances, and so forth. Their ancestors may be the ancestors of the aboriginal peoples of Southeast Asia and northeast India, before the ice age and rising sea levels isolated these communities.

Hainan minority ethnic group Hainan was originally connected to mainland China, but became isolated with the rise in sea levels. Genetic studies suggest that these aborigines descended from early migrants who entered East Asia during the last Ice Age, and have remained isolated since then^[52]. In a paper written by missionary doctors in 1940, these aborigines had the highest incidence of “gland cancer”—even higher than in Guangdong and Hong Kong^[53].

Post-Holocene Migrations

6 000 Years ago

There are many theories on the origins of the Polynesians. One hypothesis, known as the express-train model^[54], postulates that the Polynesians descended from farmers who sailed from Taiwan. Kayser *et al.*^[55] proposed a “slow boat” model, suggesting an original expansion of “Austronesians” out of south China/Taiwan, expanding along the coasts of New Guinea and mixing with the Melanesians, before slowly expanding into the rest of Polynesia. On the other hand, Su *et al.*^[56] in a study of over 500 Y chromosomes from 36 populations living in Southeast Asia, Taiwan, Micronesia, Melanesia, and Polynesia, postulated that Southeast Asia provided a genetic source for two independent migrations, one toward Taiwan and the other toward Polynesia through ISEA. This was supported by Li *et al.*^[57] investigating 1500 Y chromosomes, which suggested that Indonesian lineages (Western Austronesians) did not derive from Taiwan aborigines but rather from Daic speaking ethnic (descendants of the Bai-Yue) populations (Figure 4).

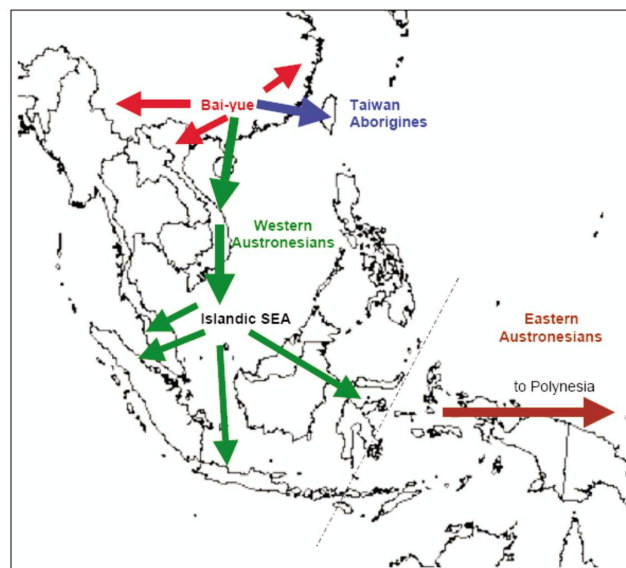


Figure 4 Origins of the Polynesians (Map modified from and reproduced with permission from the authors Li *et al.* 2008^[57])

Another piece of evidence that the Polynesians derived from mainland Southeast Asia is a report by Larson *et al.*,^[58] who studied the mtDNA of pigs and concluded that all so-called wild pigs currently found in the lesser Sunda chain and New Guinea (East of the Wallace Line) are descendants of introduced

domesticated *S. scrofa*, which in turn, trace their mitochondrial genetic heritage to mainland Southeast Asia. Since pigs do not swim, it is likely that these pigs must have followed human migration to Polynesia

A study of Y-chromosome haplotypes of Maoris by Underhill *et al.*^[59] demonstrated a mixture of European, Melanesian, and Southeast Asian (Austronesian) origins and showed a complex interrelationship between the different ethnic groups throughout their history, supporting the theory of gene dilution from the original South China ancestors.

2500 Years ago

Genetic differences between the Northern Han and Southern Han Chinese Zhang *et al.*^[60], in their article “Genetic studies of human diversity in East Asia”, wrote that “The spread of culture in human populations can be explained by two alternative models. The demic diffusion model involves mass movement of people, while the cultural diffusion model refers to cultural impact between populations. Historical records show that the Hans originated from the ancient Huaxia tribes in northern China and experienced a continuous expansion into southern China over the past two millennia.”

To test this hypothesis of demic diffusion, Wen *et al.*^[61] examined genetic variations on both the non-recombining region of the Y chromosome (NRY) and mitochondrial DNA (mtDNA) in 28 Han populations in China. According to the NRY data, northern Hans and southern Hans share similar haplogroup frequencies. The M122-C mutation is prevalent in almost all the Han populations studied (53.8% in northern Hans and 54.2% in southern Hans), while M119-C and M95-T, prevalent in southern natives (SNs), and are more frequent in southern Hans (19%) than in northern Hans (5%). Some haplogroups prevalent in southern natives, such as O1b-M110, O2a1-M88 and O3d-M7, are only observed in some southern Hans. According to the mtDNA lineages, northern Hans and southern Hans are significantly different in their mtDNA lineages. The frequency of northern East Asian-dominating haplogroups (A, C, D, G, M8a, Y and Z) is 55% in northern Hans, which is much higher than that in southern Hans (36%). In contrast, the frequency of the haplogroups dominant in southern natives (B, F, R9a, R9b and N9a) is much higher in southern Hans (55%) than in northern Hans (33%).

These observations of Wen *et al.*^[61] are consistent with historical records, in which the continuous southward migration of the Hans caused by warfare and famine is mentioned. Taking this genetic and historic evidence into account, it can be concluded that the migration into South China is one of the main causes of the expansion of Han culture.

Origins of the Cantonese People, the Vietnamese People, and the Zhuang minority ethnic people Meacham^[62] has argued that the South China Sea may have risen sharply about 4 000 BCE, inundating a coastal strip as much as one hundred miles deep. This process may have covered all remains of extensive middle Neolithic cultures that are presumed to have preferred the richer marine environment. This period also encompasses the emergence of local southern cultures from their relatively less differentiated early Neolithic identities.

According to Barlow^[51] in *The Zhuang: A Longitudinal Study of Their History and Their Culture*:

The term Bai-Yue, meaning literally “the One Hundred Yue” is a classical Chinese name for a variety of peoples believed to belong loosely to one group, the Yue. As stated in the classical Chinese text the Han Shu, “From Jiaozhi [Vietnam in present day] to Guaiji (Zhejiang in present day) is seven or eight thousand li. The Bai-Yue live everywhere.” The term Yue can also refer to a geographic region and to a feudal state as well as to the ethnic group. The Yue peoples were neighbours of the Zhou and the state of Yue [sometimes referred to as Gu Yue (Ancient Yue) to differentiate it from later Yue polities] was one of the feudal states of the Spring and Autumn period (770–475 BCE). It was destroyed by Chu in 334 BCE. The state of Yue is said by classical Chinese historians to have emerged from the Yue peoples and then to have united the Bai-Yue. After their state was destroyed, the Bai-Yue continued to survive in their ancestral domain, the south and east of China, but lost their common identity; some were absorbed by the Han and others became disparate minority peoples after the unification of China by Han Wu Di (141–87 BCE). Peoples termed “Yue” extended both into the southern interior of China, and north into today's Fujian, Zhejiang, Jiangsu, and Jiangxi provinces.

By the Song Dynasty, Han Chinese impact upon the Bai-Yue (now known as Zhuang) was much deeper than in any previous period. Far more Han Chinese took up residence in the region than in the past, exposing Zhuang people to the social values and institutions of Confucian society in an unprecedented manner.

It was during the Tang and Song dynasties that major waves of Han Chinese literati migration to the South occurred. The migration came in waves, inter-mixing with existing local populations at different time periods and to different extents, causing a spectrum of Chinese populations to occur, evolving into the present-day Cantonese, Hakka and Chaozhou groups in Guangdong.

(Meacham^[63] supports this theory of the origins of the Cantonese.)

Jin *et al.*^[25], in a study of over 100 East Asian populations, concluded that a significant proportion of southern Chinese populations carry a signature of Daic-speaking populations. Chen *et al.*^[7] drew the same conclusions when he examined the Y chromosome of the Zhuang population. Lin *et al.*^[64] analyzed the HLA data of both the Minnan and Hakka by constructing phylogenetic trees and plotting corresponding analyses, and they compared the results of the most common HLA haplotypes with data from other populations. Genetically they showed affinities to southern Asian populations. This corresponds historically with the fact that the Minnan and Hakka are the descendants of the southeast coastal indigenous population (Bai-Yue) of China.

While most Yue peoples were eventually sinicized, the Kam-Tai—ie Zhuang, Buyi, Dai, Sui (Shui), Kam (Dong), Hlai (Li), Mulam, Maonan, Ong-Be (Lingao), Thai, Lao, Shan, and Vietnamese peoples—retained their original ethnic identities. Some of these peoples also have their own nation-states today.

The incidence of NPC in Guangxi Zhuang Autonomous

region is the second highest in China but lower than that of Guangdong province [65]. There may be several reasons for this. Firstly, Guangxi can be considered rural, whereas Guangdong is more urban. Only 3% of Zhuangs are thought to reside in cities. Being rural and poor, there may be issues with access to medical care. The main causes of mortality in rural regions are also different from that of urban areas, with respiratory and heart causes being the prime cause of death in rural areas as opposed to cancer in the urban regions [66]. For cancer itself, Guangxi province has the second highest incidence of liver cancers in the whole of China, and liver cancer makes up half of all cancer cases there [65]. This is different from Guangdong, where only about a quarter of all cancer cases is liver cancer. There is thus a distinct possibility that the Guangxi population is succumbing to liver cancer, even before they have a chance to develop NPC. An earlier study by Ho [67] on the boat people of Hong Kong (who are the direct descendants of the Bai-Yue); revealed a two-fold increase in NPC incidence compared with the whole population of Hong Kong, which is predominately Cantonese. While the NPC incidences in Hong Kong and Singapore have gradually decreased over the last 2 decades, the incidence in Sihui and Cangwu counties in South China (where the majority of people are the former Tanka people) has remained stable. One possible reason is the stability of the population at Sihui and Cangwu [68], compared with more recent migrations of Chinese from non-endemic regions in the case of Hong Kong [69] and Singapore [70].

The Vietnamese In 257 BCE, Thục Phán consolidated the Lạc Việt (Luo-yue) tribes with his Âu Việt (Xī Ōu) tribes (both are Bai-Yue), forming Âu Lạc and proclaiming himself An Dương Vương. In 207 BCE, a Chinese general named Zhao Tuo defeated An Dương Vương and consolidated Âu Lạc into Nanyue. In 111 BCE, the Chinese Han Dynasty consolidated Nanyue into their empire.

For the next 1000 years, Vietnam was mostly under Chinese rule. In 938 CE, the Vietnamese defeated Chinese forces at the Bạch Đằng River and regained independence. Between the 11th and 18th centuries, the Vietnamese expanded southward in a process known as *nam tiến* (southward expansion). They eventually conquered the southern kingdom of Champa (Austronesian) and part of the Khmer Empire (Austro-Asiatic). It is thus not surprising that the ASR of NPC in South Vietnam is half that of the north, as there was much more gene dilution as the country expanded southward. A recent study by Hoa *et al.* [19] demonstrated that the Vietnamese population shares HLA patterns with southern Chinese, Thai, Javanese, and Micronesians, while retaining unique characteristics.

Dai Migrations Over several centuries, groups of Dai ethnic minority (also known as Tai; another “Bai-Yue descendant subgroup”) from Yunnan moved steadily into Southeast Asia, and by the thirteenth century they had reached as far west as Assam (India in present-day). Once settled, they became identified in Burma as the Shan and in the upper Mekong region as the Lao.

The Thais (of today) have traditionally regarded the founding of the kingdom of Sukhothai as marking their emergence as a

distinct nation. Tradition sets 1238 as the date when Tai chieftains overthrew the Khmer at Sukhothai, capital of Angkor's outlying northwestern province, and established a Tai kingdom. A flood of migration resulting from Kublai Khan's conquest of Nanchao furthered the consolidation of independent Tai states. Tai warriors, fleeing the Mongol invaders, reinforced Sukhothai against the Khmer, ensuring its supremacy in the central plain. In the north, other Tai war parties conquered the old Mon state of Haripunjaya and in 1296 founded the kingdom of Lan Na with its capital at Chiang Mai.

Communities in contact with China

The Maritime Silk Road (The Spice Route) In 1983, the tomb of the second Nanyue King Zhao Mo (Hu) (also known as Emperor Wen; reigning 137–122 BCE) was discovered at Jiefang North Road, Xianggang Hill in Guangzhou [71]. This was the biggest archeological discovery in the Lingnan area. Some artifacts recovered included a Persian silver box and African elephant tusks [72], suggesting that an ancient sea route that linked the South Yue Kingdom with Persia and Africa already existed in that era.

The ancient city of Petra in Jordan, is supposedly the capital of the Nabataeans, who were an ancient Semitic people, who were the Arabs of southern Jordan, Canaan and the northern part of Arabia. They built up a great trading empire and were thought to have had contacts with China during the period 250 BCE till 250 CE, and were the middlemen between the Orient and the Mediterranean [73].

During the 7th and 8th centuries, the Tang Dynasty had diplomatic relations with about 20 countries and permitted residency in China for foreign merchants doing business in China. As overseas trade gained momentum, a superintendent of maritime trade was appointed in Guangzhou, the largest port in China. Jin Dan, a Tang prime minister marked several main diplomatic routes in “Hainei Huayitu” or “Map of China and Neighboring Countries” and wrote “The Maritime Passage from Guangzhou to Foreign Countries”, which is a description of the voyage from Guangzhou to the Persian Gulf. On the other end, the Arab Ibn Khordadbeh's “Kitab al-masalik wa-al-mamalik”, recorded the voyage from the Persian Gulf to the Pearl River Delta. During the Song and Yuan dynasties (10th to 13th centuries), a large population of Arabs, Persians, Indians, and merchants from the South Seas entered, visited, or settled in Guangzhou [74].

The Ming Navigator Admiral Zheng He made seven voyages down the Indian Ocean to West Asia and East Africa [75]. Each voyage would have over 60 vessels and more than 27 000 people. These voyages stimulated the flow of materials and communications, as well as intermarriage and migration of Chinese people to foreign lands.

The eastern coast of Africa is known as the Porcelain coast, and the Austronesians were known to have sailed and settled in Madagascar [76,77]. The Fa Mao were descendants of over 400 Chinese sailors who were shipwrecked off Pate Island in Kenya and who decided to settle there and marry the local women. Kenya has one of the highest incidences of NPC in East Africa [78]. According to GLOBOCAN 2002 [33], East Africa has a

higher incidence of NPC than the rest of Africa except for North Africa. Aden (Ah Dan) and Hormuz (Hulumosi) were important transit ports for Zheng He's fleet, and still today retain many Chinese artifacts. It is interesting that Aden (now Yemen, which has an important seaport since ancient days) has a high incidence of NPC^[79,80], whereas Oman^[81], which is just next to Aden, has a low incidence.

Gavin Menzies, in his book *1421: The Year China Discovered the World*^[82], wrote that Zheng He's treasure ships carried concubines recruited from the floating brothels of Guangzhou^[83]. They belonged to an ethnic group called the "Tanka". These people were believed to have been descended from the Bai-Yue from the time of the Qin and Han dynasties and have always remained on the fringes of Chinese society both geographically and socially^[8]. As mentioned in the beginning of this paper, and in the study by Ho^[67], this group has a very high NPC rate.

There was thus a lot of contact between the East African, Arabian peoples and the Chinese across the Spice Routes and also in the maritime cities like Guangzhou in South China. It is highly plausible that these merchants intermarried with Chinese women and brought them back to their homeland.

Conclusions and Hypothesis

That NPC originated from the Bai-yue people

Genetic and anthropological epidemiology suggest that there are a lot of similarities between the ethnic minorities of the Southeastern China region and the aboriginal peoples of Borneo and northeast India; the Inuit of Greenland, and the Polynesians of Oceania, suggesting perhaps some common ancestry. Besides their genetic similarities, there are also certain cultural and linguistic similarities among these diverse groups. Another characteristic shared by these groups of people is their fairly high incidence of NPC.

Genetic studies also suggest that the Han population can be roughly divided into northern and southern Han, with the division roughly at the Yangtze River. While the Y chromosome is more homogenous, the mtDNA of the southern Han shows some admixture with the southern aborigines or Bai-Yue people. This is supported by the history of the Kingdom of Nanyue. Thus, the present-day Cantonese are probably an admixture of northern Han men and southern Bai-Yue women. The Kinh ethnic group of Vietnam has a dual origin, from the Bai-Yue as well as the Austro-Asiatic populations of Indochina. The Thais are also believed to have derived from both the Bai-Yue and the Mon-Khmer, an Austro-Asiatic stock.

Taken together, we propose that the high incidence rates of NPC in these populations have resulted, in part, from a genetic trait that can be traced back to the Bai-Yue as the reference population. The "NPC susceptibility gene(s)" was probably carried by the female Bai-Yue and transmitted to the Cantonese, East African, and Arabian peoples through intermarriage. Subsequent migrations of these proto-Austronesians to Southeast Asia and Oceania, and north across the Bering Strait have resulted in an abnormally high incidence of NPC in these

ethnic groups.

Given our hypothesis, it is easy to understand that the Cantonese, being a northern Han minority migrating south and assimilating into the resident majority Bai-Yue population, would have a high incidence of NPC. Whereas, when the Bai-Yue themselves migrated south and assimilated with the indigenous Austro-Asiatic majority in Vietnam, the incidence of NPC in North Vietnam is practically half that in Guangzhou, and similarly the incidence drops even further in South Vietnam with further gene pool dilution. (The incidence of NPC in Hong Kong has also gradually decreased over the last 25 years, and while we can attribute this partially to changes in lifestyle, another plausible reason could be the gene dilution from more recent emigration^[69].)

While the rest of indigenous Southeast Asia has an incidence similar to that of South Vietnam, reflecting the admixture of the Bai-Yue and the Austro-Asiatic, there are however pockets of high incidence of NPC amongst, for example, the Bidayuhs of Borneo, the Nagas of Northeast India, the Inuit of Greenland and the Tanka boat people of the Pearl River Delta. The latter may be due to the "genetic isolation" of these communities with the rise of sea levels during the last ice age; and "imperial decrees". The Polynesians have an even lower incidence, having derived from Southeast Asia but later having their gene pool diluted through mixing with Melanesians and more recently with European settlers.

The incidence of NPC in the "porcelain coast" of East Africa may be explained by the even smaller scale of migration of the gene pool to these regions through trade between the East African and Arabian peoples and China which flourished since the early days of the Spice Route. The maritime route, was in part through the ports of southeastern China, which led to very early mixing between the Arabians and East Africans with the Southern Chinese.

In conclusion, the hypothesis that NPC did not originate from the Cantonese, but rather from the Bai-yue, may account for the high incidence of NPC in the many diverse populations around the world, whose ancestry can be traced back to this reference population. How this gene actually contributes to NPC carcinogenesis currently remains unknown, although the ubiquitous association of NPC with the Epstein Barr virus, might point to some form of viral or immune susceptibility, rather than a direct carcinogenic effect.

At this point, we also observe that there appears to be a possible female transmission as evidenced by the fact that the Cantonese are essentially northern Han male majority intermarrying with southern Bai-Yue women; the female Tanka courtesans on the flower boats of the Pearl River delta; and the matrilineal society in ancient Austronesian societies^[84]. There is also evidence that mtDNA somatic mutations are common in NPC^[85]. Of interest is also that the Nagas have Y chromosomes which are Tibeto-Burman, but mtDNA signatures which are southeast Asian^[86].

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Conflicts of interest

The authors declare no conflicts of interest.

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