In this perspectives paper, we discuss fertilization strategies for *Taenia saginata* and *Taenia saginata asiatica* as well as heterogeneity in *Taenia solium*, the causative agent of human cysticercosis. Two different genotypes of *T. solium* (Asian and Afro/American) were confirmed by mitochondrial DNA analysis approximately two decades ago. Since then, outcrossings of the two genotypes have been identified in Madagascar where the two genotypes are distributed sympatrically. Outcrossings were confirmed by the presence of discordance between mitochondrial and nuclear DNA. Since multiple tapeworm infections are common in endemic areas, outcrossing events likely occur quite frequently. Therefore, mitochondrial DNA from *T. solium* specimens collected from humans and pigs in endemic areas should be analyzed. If variations are found between specimens, nuclear DNA analysis should be performed to confirm the presence of discordance between mitochondrial and nuclear genes. Additional outcrossings likely add complexity to understanding the existing genetic diversity. Serological surveys are also recommended since serodiagnostic glycoprotein can also differentiate between the two genotypes. Viable eggs from different genotypes or from hybrids of two different genotypes should be used for experimental infection of pigs or dogs in order to observe any pathological heterogeneity in cysticercosis development. Although genetic diversity of *T. solium* is expected to result in clinical heterogeneity of cysticercosis in humans and pigs, there is currently no evidence showing that this occurs. There are also no comparative experimental studies on this topic. Therefore, studies evaluating the link between parasite heterogeneity and clinical outcome are warranted.
pigs. Cysticercosis, including NCC, is not only found in traditional remote/rural areas with known T. solium transmission, but cases can also be diagnosed in non-endemic areas, including big cities in developed countries. Cases in non-endemic regions are often related to T. solium tapeworm carriers who have immigrated for work or are found in individuals who have a history of travel to an endemic region for work or leisure [2].

There are numerous review articles focusing on human traits related to the pathological diversity of T. solium infections [2]. The objective of this article is not to provide a similar overview, but instead to offer a perspective on diversity in pathology due to the parasites, with a special focus on Asia and the Pacific.

**Historical Background on Human Taenia Species**

The genus Taenia consists of nearly 50 species [3]. Most taenid species develop into adult tapeworms in carnivorous mammals [3-10]. The pork tapeworm, Taenia solium, and the beef tapeworm, Taenia saginata, are exceptional in that they require humans as definitive hosts [4]. The worldwide distribution of T. solium and T. saginata has been well documented. In 1993, “Taenia asiatica” (a sister species of T. saginata) was first described by a research group based in Korea as the third Taenia species that infects humans [11]. Although Fan et al. in Taiwan [12,13] morphologically identified this novel (“Taiwan Taenia”) tapeworm as a new species, the scientific community called for molecular evidence in support of the new species designation [14,15]. As a result, many international experts considered “T. asiatica” to be a form of T. saginata, Taenia saginata asiatica, due to only minor genetic differences. These differences are likely due to intraspecies variation between the two parasites [14-20]. All known specimens of “T. asiatica” [11] have been found in Asia and most “T. asiatica” isolates found outside of Taiwan and the Philippines are believed to be descendants of T. saginata and “T. asiatica” hybrids [20-24]. It is not clear if pure “T. asiatica” are still distributed in Taiwan and perhaps distributed in the Philippines. In this article, we refer to this parasite as a local variant of T. saginata (ie, T. saginata asiatica) [14-20].

Molecular studies on the discordance between mitochondrial (mt) and nuclear (nc) genes have revealed the presence of outcrossing in Taenia tapeworms in the human intestine. Tapeworms are hermaphroditic organisms and self-fertilization occurs if there is infection with a single worm. However, fertilization by either selfing or outcrossing can occur when a host is infected with multiple worms. Pioneer work on outcrossing (hybridization) between “T. asiatica” and T. saginata was reported by Okamoto et al. [21-24]. Outcrossing of different T. solium genotypes has also been confirmed in Madagascar by Yanagida et al. [25]. Hybridization may occur more frequently than once believed [26], since tapeworms are known to be mobile within the intestine and are often active in association with the host’s circadian rhythms [27]. There do appear to be differences in the life span of the different human Taenia in the human intestines. The longevity of adult T. solium has been estimated to be no longer than 3 to 5 years in humans ([28-32]; Li et al. unpublished). In contrast, both T. saginata and T. saginata asiatica have been shown to survive approximately 50 years in China where all three are sympatrically distributed ([32]; Li et al. unpublished) and T. saginata asiatica has been shown to have a similar life span in North Sumatra, Indonesia where it is exclusively endemic [33].

If T. saginata asiatica [11] is considered a variant or strain of T. saginata, [14-20], it is easy to understand why this parasite does not cause cysticercosis in humans since the condition does not occur with T. saginata [17,18,20,34,35]. Previous studies have shown that, in mice with severe combined immunodeficiency (SCID), T. saginata asiatica can develop into cysticerci of similar size and morphology to those produced by T. saginata [36]. At this time, there is no molecular evidence to support calling “T. asiatica” an independent species [11]. Instead, molecular evidence has shown only a minor difference between the two parasites, suggesting intraspecies variation [14-17,19,20].

**Clinical Heterogeneity of T. solium Cysticercosis in Humans and Pigs**

Almost all cases of human cysticercosis (CC) are caused by the larval (metacestode) stage of T. solium. However, there are reports of at least eight additional Taenia species, including Taenia crassiceps, occasionally resulting in CC in humans [37-40]. Taenia solium is the only species of Taenia, with a human definitive host, known to cause CC including NCC in humans [20,34,35]. While no human CC cases due to T. saginata or T. saginata asiatica have been identified, there is still some speculation that T. saginata asiatica might cause hepatic CC in people living in areas where T. saginata asiatica is endemic [41]. That being said, as T. saginata asiatica is a local variant of T. saginata widely distributed in Asia, it is not believed that CC due to T. saginata or T. saginata asiatica occurs in humans [41]. More recently, serological analysis for CC has been carried out in regions of China where the two human Taenia species and T. saginata asiatica are known to be sympatrically distributed [32]. However, serological evaluation of patients with T. saginata asiatica taeniasis has thus far produced no antibody response [32]. In addition, animal models for T. saginata asiatica or T. saginata taeniasis have not been evaluated [36,42].

Taenia solium cysticerci develop mainly in the cen-
nal nervous system, eyes, striated muscle, heart muscle, and subcutaneous tissue. In the brain, most larvae are found in the parenchyma. Clinical manifestations are pleomorphic and depend on the location, number, and stage of the parasite and the host’s immune response. There are numerous reports discussing the heterogeneity of clinical presentations in humans [2,43-49]. In contrast, there have been no or few studies relating clinical heterogeneity to the genetic heterogeneity of *T. solium* [25,38]. The main goal of this perspectives paper is to discuss the available reports, which suggest a link between clinical heterogeneity and parasite genetic heterogeneity [6,38].

**History of Emergence of Human Taenia**

Human *Taenia* tapeworms are believed to have emerged along with the domestication of swine and cattle [8,50]. In general, these parasites are thought to have switched from carnivorous definitive hosts to primate definitive hosts on two separate occasions. As briefly summarized by Nakao et al. [6], recent molecular approaches have shown different histories for *T. solium* and *T. saginata* (and *T. saginata asiatica*), which are believed to be only distantly related to *T. solium*. *Taenia saginata asiatica* is a local variant of *T. saginata* [14-17,19] and most “*T. asiatica*” specimens have been identified as hybrid-derived descendants of *T. saginata* and “*T. asiatica*” [21-24]. In contrast, *T. solium* is found in the same clade as *Taenia hyaenae* and *Taenia crocutae* [3,5].

According to previous studies [3,4,6], the pork tapeworm, *T. solium*, is believed to have emerged as a human parasite in Africa predominately through a “human-wild suid” cycle (hunting), although some transmission via a “human-human” cannibalistic cycle has been proposed [3,5]. The only modern data that could provide insight to this potential cycle are from Papua New Guinea where both kuru and NCC were identified in the first half of the 20th century [51-56].

The wild boar (*Sus scrofa*) is widely distributed in the Paleartic region. During boar domestication in Asia, Anatolia, and Europe, pigs became obligatory intermediate hosts, and the modern synanthropic “human-pig” cycle was established [3,5-7,38]. The current geographic distribution of *T. solium* likely emerged approximately 500 years ago and was largely influenced by European colonization. Pigs were brought into Latin American countries by Spanish and Portuguese colonists. Similarly, domestic pigs were brought to sub-Saharan African countries by various European groups [57-60]. While Europe is no longer considered endemic for *T. solium*, introduction of the parasite is always a risk from tapeworm carriers arriving from endemic regions [61-63]. Therefore, CC cases can occasionally occur in non-endemic countries due to contamination by a tapeworm carrier [1,38,61-63].

**Dogs as Alternative *T. solium* Intermediate Hosts**

Although pigs are the primary intermediate hosts for *T. solium*, dogs have also been infected with the larval stage of this parasite. A dog with *T. solium* cysticerci throughout its body, including the brain, was confirmed through necropsy and serological testing in Papua, Indonesia. In this region, pigs and dogs live closely together and have ready access to human feces through the practice of open defecation [64]. Although dog meat is not consumed worldwide, it is consumed in some Asian countries. Therefore, in some regions, dogs may contribute to the local parasite life cycle [64]. Due to the ability of dogs to act as aberrant intermediate hosts, they may be well suited for *T. solium* experimental infection studies along with pigs (see below).

**PERSPECTIVES**

**Neurocysticercosis with and without Subcutaneous Nodules**

NCC, which is caused by the presence of a cysticercus/cysticerci in the brain, makes *T. solium* one of the most lethal helminth infections [1,62]. Numerous studies have been conducted on clinical outcomes associated with NCC, including evaluation of organ tropism and patient immune response [42-45]. Prior to the commencement of molecular and serological studies, it was known that clinical manifestations associated with CC differed between Latin America and Asia. In the Americas, NCC is typically not accompanied by subcutaneous cysticercosis (SCC), whereas NCC cases in Asia are commonly associated with SCC [18,72,73]. In sub-Saharan Africa, NCC cases without SCC are common. However, NCC cases with SCC are also found in certain regions of Africa [74-76]. Molecular analysis of NCC cases with and without SCC are needed to determine if cyst location is related to genotype (Asian versus Afro/American).

**T. solium Genetic Diversity and Clinical Presentation of Cysticercosis**

Molecular analysis of *T. solium* was first conducted in Mexico [45-48,76], followed by Brazil [49,70,77-79], and Ecuador [80]. These studies showed only minor genetic differences in the parasites between countries, which aligns with the hypothesis that *T. solium* parasites were initially brought to the Americas by early colonists from Europe. In contrast, Vega et al. [81] showed genetic differences between *T. solium* distributed in Mexico and Madagascar. At that time, a Japanese group was also conducting mtDNA analysis on numerous *T. solium* specimens from the Americas, Asia, and Africa [6,7,38,82-87]. This group was able to identify two clades of *T. solium*, which are now considered the Asian and Afro/American
genotypes [7,9,10,25,36,38,76,82-89].

In the early 2000s, Ito et al. [76] found differences in crude antigen profiles between the Asian and Afro/American genotypes of *T. solium*. Analysis of antigenicity by Sato et al. [84,85,87] showed further differences between the two genotypes [38]. Later, Michelet et al. [9] analyzed the mtDNA of 12 *T. solium* cysticerci from 11 different areas in Madagascar and found that only two samples from the former southwestern province of Toliara were of the Afro/American genotype, while the remainder were of the Asian genotype. Yanagida et al. [25] then analyzed a total of 109 samples from Madagascar and confirmed that both genotypes are sympatrically distributed in most areas of the country, including Toliara [25]. This same study confirmed that two cysts from a single pig from Madagascar were heterozygous at all three examined loci, which is of note since pigs can become infected by multiple parasites at the same time [25]. When nuclear gene analysis was performed on these samples using the *Ag2*, *rpb2*, and *pold* genes [86,87], different patterns were identified in homozygote and heterozygote specimens, leading to the conclusion that outcrossing between the Asian and Afro/American genotypes had occurred at least twice [25]. It has been hypothesized that the parasites belonging to the Asian genotype were introduced into Madagascar from Nepal and other areas of the Indian subcontinent [9,25,38].

Differences in the distribution of *T. solium* genotypes among populations in various geographic regions may be attributed to differences in the populations' ethnic and migratory histories. Therefore, the presence of the Asian genotype in Africa might be explained by earlier migration from Asia [9,10,25,38,45,46]. The presence of both the Asian and Afro/American genotypes would then explain the variation in the clinical presentation of NCC patients with SCC (Asian genotype) and without SCC (Afro/American genotype) in different parts of Africa. Molecular analysis of parasite mtDNA from patients with SCC versus those without SCC in mainland Africa, Madagascar, and the Americas should provide further information.

**FURTHER EVALUATION OF THE ROLE OF T. SOLIUM GENETIC DIVERSITY**

While humans have only been documented with adult *T. solium* belonging to a single genotype, the possibility exists that a person could be infected with more than one genotype if they were to consume pork that contains cysts belonging to different genotypes within a few days. While this would most likely occur by consuming pork originating from different animals infected with different genotypes, it is also possible that a single pig could harbor cysticerci belonging to both *T. solium* genotypes in areas where the genotypes are co-distributed [25,45-47].

Thus far, Madagascar is the only country where the two *T. solium* genotypes are known to be sympatrically distributed and hybridization has been confirmed. It is interesting to speculate how parasite genetics would have been impacted if the Asian genotype had been introduced into the Americas or if the Afro/American genotype had been introduced into Asia [38,46]. That being said, in today's mobile world, the possibility of introducing a novel genotype still exists and mtDNA can assist with evaluating NCC infection origin [88-93]. While NCC is much more common in *T. solium* endemic areas, tourism and immigration allow for infection to occur worldwide, including in areas where the majority of the population does not consume pork [61,87,89,93-99].

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