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（Supervisor：Professor ○○○○）

Introduction:

Materials and Methods:

Results:

Discussion:

*Notes: Summarize your dissertation with 2 pages of A4 (using 12 point, Times New Roman font, single space. Total number of words should not exceed 1000）*

(Example)

Abstract of the Dissertation submitted by CHANTAL AMA AGBEMABIESE

**Title: Interspecies transmission of rotaviruses and its evolutionary implication: a view from Africa**

Japanese title:ロタウイルスの種間伝播とその進化論的考察―アフリカからの視点

[Chantal Ama Agbemabiese](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Agbemabiese%2C+Chantal+Ama), [Minh Quang Nguyen](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Nguyen%2C+Minh+Quang), [Punita Gauchan](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Gauchan%2C+Punita), [Osamu Nakagomi](https://onlinelibrary.wiley.com/action/doSearch?ContribAuthorStored=Nakagomi%2C+Osamu)

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Department of Infection Research,

Nagasaki University Graduate School of Biomedical Sciences

Supervisor: Professor Osamu Nakagomi, MD, PhD

**Introduction**

Rotavirus A (RVA) is a leading cause of diarrhoea in children and many animal species worldwide. Safe and efficacious, live-attenuated vaccines were developed based on the molecular epidemiology of rotavirus strains in developed countries and rolled out gradually in developing regions in the world including sub-Saharan African countries. The rotavirus genomes are diverse and evolve through rapid point mutations, genetic reassortment and interspecies transmission. As rotavirus strains circulating in Africa are considerably different from the ones circulating elsewhere in the world, the prevalence of unusual strains such as G8, G6P[6] and P[6] strains are high. These unusual genotypes at a glance, are indicative of animal rotavirus origin. While there is always a vague speculation that frequent rotavirus interspecies transmission events occur in Africa because people and animals live in close proximity, precise studies making use of the tools of molecular epidemiology and molecular phylogeny to decipher the evolutionary history of the novel strains are limited.

**Materials and Methods**

I carried out three molecular epidemiology studies that are included in this thesis. In the second study, contrary to the general notion of frequent RVA interspecies transmission events occurring in Africa, it was noted that the genome of G2P[4] strains from Ghana - the potential donor strains of the DS-1-like backbones to many unusual strains in Africa including G6P[6] strains discussed above, evolved by utilizing a step-wise lineage replacement strategy similar to the pattern described for global G2P[4] strains by Doan et al. Third, the genome of a G8 strain, an epidemiologically important genotype on the African continent detected for the first time in Japan, was analyzed to understand how it was generated, how it relates to G8 detected elsewhere in the world, and to determine the host species origin of its genes. Forth, I aimed to explore the major observations made in the preceding chapters to understand the specific features of the circulating rotavirus strains on the African continent and discussed the role played by prevalent P[6] VP4 genes in reference to the abundance of the Lewis-negative phenotype in Africa.

**Results**

In the first study, I showed that the G6 VP7 possessed by G6P[6] strains in Africa as well as Europe originated from a single ancestral VP7 from a human G6P[9] strain around the year 1998 and not directly from bovine G6 strains or bovine-like human G6P[14] strains. Also, it was discovered that the G6 VP7 gene after crossing the host species barrier from cattle to human in the distant past, underwent an accelerated evolutionary rate, a phenomenon which could constitute a post-transfer adaptation process in the new host. Of note was a frequent expansion of the E2 NSP4 gene at the sub-genotype level in African G2P[4] strains leading to African specific lineages such IX and X in the NSP4 gene. However, this diversity was explained by frequent intra-genotype reassortment events involving regional DS-1-like rotavirus strains such as G2P[6], G3P[6] and G6P[6] strains of human host species origin and not direct introduction of genotype 2 rotavirus genes from animal rotaviruses.

The G8 rotavirus of human host species origin was the only one reported in Japan although infection with G8 strains was a common phenomenon in children on the African continent. This strain was concluded to have been generated by genetic reassortment where co-circulating G2P[4] strains in Japan obtained the VP7, VP1 and NSP2 genes from unknown ruminant G8 RVA strains. Although this strain was detected on a different continent from Africa, the genetic composition and the origin of the genes reflect an attempt of an animal strain to establish itself in the human population by acquiring the genetic backbone of DS-1-like strains believed to be already adapted to the human population.

Most importantly, however, what appeared to be African specific G8 VP7 lineages were divided at least into two lineages, namely: the Cameroonian and Malawian lineages, and while their origin was of bovine, after crossing the host species barrier, they seemed to have been transmitted only from human to human which was made possible by the acquisition of either the human RVA Wa-like or DS-1-like genetic backbone. Those G8 strains that gained the Wa-like genetic backbone seem to have died out from Africa after prevailing for some time on the continent. Also noted were the ever-diversifying NSP4 lineages within the E2 genotype which were mostly due to the introduction of the NSP4 sequences of animal rotavirus origin; these lineages were however short-lived with limited geographical distribution.

**Discussion**

I postulated a hypothesis that while proximity of people and animals in Africa provides abundant opportunities for animal rotaviruses to cross species barriers into humans, many of such events terminate as dead-end infections without establishing a human to human transmission chain and only a few interspecies transmission events do so after gaining human rotavirus backbone genes through genetic reassortment. Even in such successfully established interspecies transmission cases, the lifespan of such novel lineages within human rotavirus is rather short and limited geographically as they might have been out-competed by the co-circulating parental strains. Nevertheless, such interspecies transmission events coupled with genetic reassortment provide the source of rich genetic diversity, whether transient or permanent, in African rotavirus strains we observe today.

(857 words)