

INSTITUTE FOR ADVANCED RESEARCH

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 NAGOYA UNIVERSITY

Special Interview

The Academic Journey: from France to Japan ____ Shoichi Sato

Research Highlights

Genetic copy number variation (CNV) analysis of schizophrenia _____ Itaru Kushima

Categorical representation theory and its application to knot theory ____ Yasuyoshi Yonezawa

Exploring imprints of string theory from cosmological observations _____ Yuko Urakawa

For Further progress of the Institute

On December 1st, 2017, we were able to celebrate the 15th Anniversary of the founding of the Institute for Advanced Research (IAR), Nagoya University, by inviting distinguished guests such as Professor Ryoji Noyori (2001 Nobel Prize Winner in Chemistry), Professor Morten Kyrndrup (the Director of UBIAS, University-Based Institutes for Advanced Study, Denmark), Professor Mike Hannon (the Director of the Institute of Advanced Studies, University of Birmingham, UK) as well as Mr. Masami Watanabe (Director of the Promotion Policy Division, Ministry of Education, Culture, Sports, Science and Technology) and the President of Nagoya University, Professor Seiichi Matsuo. Almost 200 people gathered from various fields for this Nagoya University IAR's memorial event, which was held at the Sakata-Hirata Hall on the University campus. Our Institute is one of the oldest IAR/IAS's here in Japan and has been quite active both domestically and internationally.

Internationally, Nagoya University IAR is one of the 6 members of the Steering Committee of UBIAS (out of 37 total members) and has some leading international exchange activities in research and education. In this context, just prior to the 15th Anniversary, we organized and hosted an International IAR/IAS Workshop entitled "Today's IAR/IAS Challenges – Future Perspective (I)", where 20 IAS Directors and deputy-Directors participated from Europe, South-East Asia and South America in order to discuss their own Institutional Young Fellowship Programs. This is the first IAR/IAS international workshop, in which European IAS's and Asian IAS's shared a common discussion table on how we could support and nurture talented and aspiring young researchers from the standpoint of "interdisciplinarity".

Domestically, during the past 8 years, Nagoya University IAR has been coordinating an important University program, the so-called Young Leaders Cultivation (YLC) Program, which has played a crucial role in cultivating and supporting talented young researchers in various fields. The program has so far contributed greatly to converting the outcomes of excellent studies done by IAR young researchers in individual Departments into common property of all members of the University. This year, we have newly appointed eight brilliant young researchers in various fields as "YLC Designated Assistant Professors"

I really hope that readers may find this issue's Special Interview and Research Highlights interesting and thought-provoking as well.

February 2018



Nori SHINOHARA
Director of Institute for Advanced Research



Director
Hisanori SHINOHARA

INSTITUTE FOR ADVANCED RESEARCH LETTER

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Cover Picture :
'In to the deep' by Sachiko Kuroyanagi
(YLC Assistant Professor at Nagoya IAR)

Special
Interview

Shoichi SATO

Dr. Shoichi SATO is a historian studying early medieval Europe renowned for his study of the Frankish history. He was born 1945 in Yamagata, Japan. He graduated from the Faculty of Law at Chuo University in 1976. He completed his Ph.D program without a Ph.D. degree from the Graduate School of Letters, Arts and Sciences at Waseda University in 1976 but received a Ph.D degree in Literature from the same university in 1995. He worked at the Faculty of Law and Economics at Aichi University as an assistant professor (1979-1987), at the School of Letters at Nagoya University as an associate- (1987-1991) and later as a full professor (1991-2009). He was the director of Nagoya-IAR from 2003 to 2004. Now he is a Professor Emeritus at Nagoya University and a member of the IAR Academy. During his career he was a visiting professor at many prominent French research institutions like the Centre national de la recherche scientifique (CNRS) (1995), the Collège de France (2001), the École Pratique des Hautes Études, the École des Hautes Études en Sciences Sociales (EHESS) Paris (2001) and the Université Paris I (2004). He has won numerous awards such as the Collège de France Lecture Medal (2001) and the Japan Academy Prize (2002).

< The Academic Journey: from France to Japan >

— Your area of specialty is European medieval history, especially Francia. What led to this choice?

SATO: I studied law as an undergraduate student. When I applied for university I didn't have any clear plan.

Throughout my middle and high school years baseball was my all-consuming passion. In high school I did little else but baseball. I was a member of the Sakata Higashi High School baseball team (in Yamagata Prefecture), where I was a pitcher and cleanup hitter. When I was in my third year our team narrowly missed playing at the Summer Koshien, the National High School Baseball Championship, after reaching the prefectural semifinals. After that, in around late August, I started thinking about which university I should apply for, when I heard that a law degree was pretty "marketable," and so, without much thought, I chose the department

of law, thinking I could always decide about my future later on. I only had three or four months to prepare for my entrance exams, so I chose a private university, because there were fewer subjects on the exam than at public ones. I applied for the department of law at Chuo University, which at the time boasted the highest success rate for the bar exam, and somehow managed to be admitted to the university on my first attempt.

However, after about a month or two, I realized that I had made the wrong choice. To me the general education subjects were simply the most fascinating. These were at the time taught by part-time instructors from the University of Tokyo, who were first-class. Perhaps as a reaction to doing hardly anything else but baseball until then, I suddenly found myself greatly stimulated intellectually. I decided to study humanities subjects properly at graduate school. I enrolled in a postgraduate course at Waseda University, where I

studied Western history.

Undergraduate law studies didn't disappear completely from my head, though. The disciplines of history and law have always been closely related. The shift from antiquity to the Middle Ages (Roman times to Frankish) also involved a legal shift from Roman law to Germanic tribal law. As a reader of history, I was highly interested in the state of law at such transitional times.

— In 1969, while a postgraduate student at Waseda University, you went to study at the University of Caen in France.

SATO: It was a time when student movements were all the rage, with the fall of the Yasuda Auditorium and other incidents, which made situations at universities very chaotic. I was in the first year of my master's course, but classes weren't always held smoothly in those circumstances. So I considered studying abroad as an alternative. My father, who ran a long-established kimono retailing business, didn't object when I asked him to pay for my studies abroad. I said I will give up my share of inheritance instead.

I studied for about two years in France, which was a very good thing for me. I learned in France what I needed to learn properly before being affected by conventions of Japanese learned society. Europe is, after all, the center of studies in European history. It was highly beneficial that it was in Europe that I learned from a clear slate what to make of history as a discipline, what training the discipline involved, and how to conduct viable research. There were of course drawbacks once it came to building a career in Japan, such as needing to be equipped with a certain framework, or common understanding, shared by the members of Japanese learned society. Although not without dilemma, my academic beginnings were basically removed from Japanese learned society.

Studying abroad had non-academic merits as well. Normandy, where the University of Caen is, is very verdant, and remains one of my favorite places. Students over there would completely switch off on weekends. They cloistered themselves in the library from Monday to Friday, went to the movies on Saturday as if to get away from it all, went to the disco straight after the movie, spent the whole night having fun, and took the car out to the sea at dawn, where they might have bonfires. Student life was hectic, but great fun.

— France was where you met your future wife.

SATO: Yes, I met her when she was a fellow study-abroad student on a language course. We married and our first child was born after we returned to Japan, and when I was doing my doctoral course back at Waseda University Graduate School. My student life involved both babysitting and essay writing.

In 1979, when I was 32 or so, I was fortunate enough to get a job at a relatively young age. I became an associate professor of Western legal history at the faculty of law and economics at Aichi University (Toyohashi City). From 1984 I spent two years in Paris as an Aichi University overseas researcher.

My wife and two daughters accompanied me to Paris, where my daughters attended a local elementary school, although they didn't even know their ABCs when they started.

— During your time as an overseas researcher you visited many monasteries.

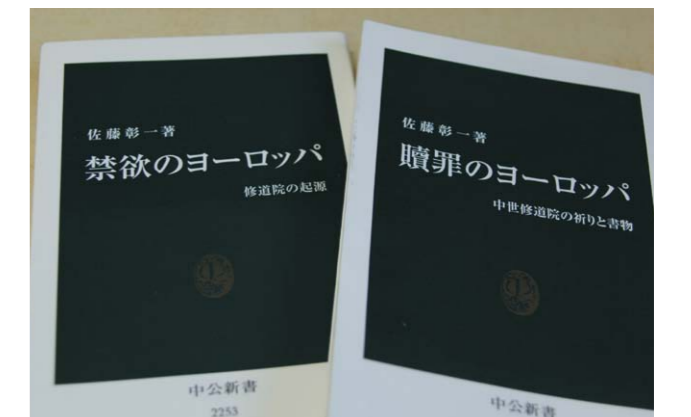
SATO: Whenever there were long holidays I took my family in an old, secondhand Audi to various parts of France, as well as Italy and Spain. We visited a lot of monasteries too, despite the grumbings of my wife and daughters. Early monasteries, from the 6th and 7th centuries, were often made of wood, which made surviving examples extremely rare. Many monasteries also lay in ruins after being abolished. Nothing remained of about half the monasteries we visited, which were just empty plots, to the great disappointment of my daughters. There were always plaques, though, or information boards for us to read, telling how the place was once the site of a certain monastery, and so on.

— You compiled your research on early medieval society into Shudojin to Nomin [Monasteries and Peasants] published by Nagoya University Press in 1997.

SATO: In or around the 9th century, many monasteries started keeping written accounts of the administration of their manors and tenants, and surviving examples of these records serve as invaluable historical sources today. The kind of manors described in these materials existed under a system known as bipartite manorialism. In Japanese scholarly circles, bipartite monor system had largely been viewed as a kind of slavery. However, I was not convinced by this view.

My attention was drawn to a series of accounting documents thought to have been made at the Abbey of St. Martin of Tours during the 7th century, or late Merovingian dynasty. The material is fragmented and very difficult to read, which was why it had largely escaped scholarly attention until then. I researched the material's provenance, and went on to decipher and analyze it largely with the advices from Pierre Gasnault and Jean Vezin who had published a transcription of the texts in 1975, for the first time. I consequently found that the material was a series of notes made by the local monastery when collecting tributes from its tenants. Some describe cases where tenants refused to settle outstanding amounts of tribute. Refusing payment is not an attitude commonly associated with slaves. This suggests that bipartite monor system was not a slavery-like system, and that tenants, though dependent on monasteries to an extent, maintained their personal freedom. This reaffirmed my belief that the idea of early medieval European society as rooted in slavery needed reviewing. I compiled this research into Shudojin to Nomin.

— In 2014 you published Kinyoku no Yoroppa [Asceticism in Europe], and in 2016 Shokuzai no Yoroppa [Atonement in Europe], both by Chuko Shinsho.



SATO: These were intended for a general readership, rather than as academic treatises. In Japan, studies of monasteries tend to be written or translated by Christian scholars. I am a Buddhist, not at all Christian. That could be a sort of hurdle, but I believe there are also viewpoints uniquely available to a person to whom the subject of investigation is not an object of worship. I wanted to base my historical overview of monastic systems on asceticism because the notion of asceticism is ever-present at the root of European monastic systems.

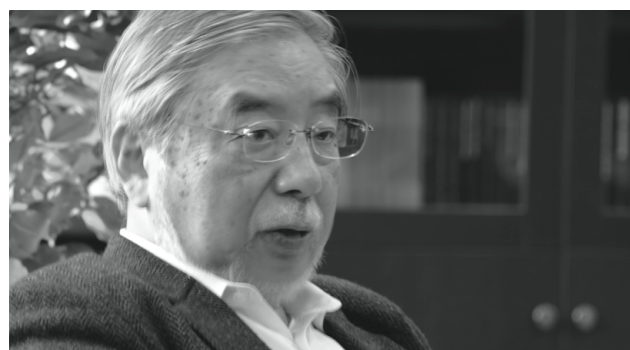
In December 2017 I published a sequel to the earlier books, *Ken to Seihin no Yoroppa* [The Sword and Honorable Poverty in Europe]. The book discusses military orders and mendicant orders from around the 12th to 15th centuries. Together the three books summarize my account of monastic orders from ancient to medieval times.

Also in the pipeline, though I haven't written it yet, is a work dealing with the Society of Jesus. The Jesuits were different from monastic orders that were born in the Middle Ages. And importantly, the Jesuits affected Japan. The history of Christianity's spread during Japan's Sengoku and early Edo periods (from the end of the 16th to 17th centuries) is studied today by young scholars in Europe, leading to fresh findings. They analyze historical sources archived in Portugal and other locations associated with the Jesuits, which had hardly been seen in Japan before, and I am greatly looking forward to discovering what they reveal.

And to finish off my series, I intend to write a fifth book dealing with the 17th century and beyond. In the 17th century, after monasticism in its original sense had lost the clout it enjoyed in the Middle Ages, monastic orders survived as academic institutions. The foundation of history as a discipline was built by members of such monastic orders. I want to complete my series with this topic, which I find interesting also from the point of history's evolution as a discipline. I want the five books to provide a sort of spiritual history of monasteries from their beginnings to the present day.

— You also conduct active research into the history of the Franks.

SATO: The history of the era of the Franks is where my scholarly roots are. The history of the Franks is slightly tricky. The noun "Frank" is originally an adjective meaning "bold" or "courageous." It is not associated with a place name like "Goths from Gothland" or "Nagoyaites from Nagoya." Franks are, in a sense, secondary groups resulting from the integration of various small and medium-size tribes. Identifying their ancestry is not easy given the lack of records. Their roots date back to the pre-era, late Bronze Age or early Iron Age, the



study of which involves the use of prehistoric archaeological, rather than historical, materials.

The ancestors of the Franks could be found in the north, in the North Sea and Baltic Sea areas, making their living primarily from selling amber to the Romans. Before gemstones like diamonds and opals, amber was a jewel in its own right. Excavations of ancient Egyptian and ancient Syrian tombs often yield amber, which when analyzed, invariably show that they were brought from the Baltic Sea area. This supports the idea of a "world-system" in history, which is increasingly believed to have existed from about 3,000 years ago.

Recent advancements made by archaeology are truly impressive. For example, excavations have managed to track down to a certain degree of accuracy that trade existed between the Baltic Sea and Black Sea areas as early as 2000 BCE. I think going back that far in time, informed by archaeological findings, is absolutely necessary in order to reveal the origins of the Frank people. I would like to give the title "In Search of the Land of Origins" to the first part of my work.

— Going as far back as pre-Greek prehistoric times is a novel approach for the study of Frankish history, isn't it?

SATO: Absolutely. I don't think anyone has done it yet, which is why it is innovative, and at the same time, susceptible to attracting suspicion. Ancient Greek folklore and knowledge include many aspects that suggest links with peoples of the north. I want to take my investigations that far.

Cutting-edge research trends in the West makes me want to destroy conventional frameworks in one way or another. I want to be bold in my approach.

— How would you justify the fascination, or meaningfulness, of learning about history, including that of the Franks?

SATO: Just imagine how tragic it would be for a person to have no memory. Translate this situation to a group of people—a community. Whether a single country or the entire world, humans desire to know what actually happened, in other words, "history." Living is otherwise not possible. And I think the discipline of history is about investigating what really happened, or what is most likely to have happened.

The era of the Franks has absolutely nothing to do with the Japanese; it is totally unrelated. However, by researching the subject, a picture emerges of how people lived in a certain region at a certain time. The people mentioned in the above accounting records kept at the Abbey of St. Martin of Tours were clearly peasants, who left no other trace in history. But when I, as a historian, read their names, understand the kinds of taxes they owed annually, and the kinds of activities they engaged in, someone who lived in the far past becomes a part of myself; it becomes possible for me to identify with that person, though we live in different eras. I think approaching history with this sense of identification with others enables us to better understand humanity.

— The recent tendency in Japan is to scale down undergraduate bunkei (social sciences and humanities)

programs at universities, including history programs. There are arguments for making bunkei subjects available only at top universities, and turning the rest into vocational institutions serving the needs of industry, because unlike rikei (science) subjects, bunkei subjects of study do not directly contribute to the country's economic development. What is your view on this?

SATO: This is clearly a wrong idea. Although the term "bunkei" encompasses diverse disciplines, at the core of all bunkei subjects is the desire to understand humanity.

In today's society, people who have completed undergraduate bunkei courses of study could be working, for instance as company employees, or perhaps they are raising children at home. The experiences of studying disciplines for understanding human beings must surely have significant effects on the ordinary, day-to-day lives of these people. The idea of doing away with such experiences is to deny the development of a more mature society.

I cannot understand why we need to gauge, at this point, the [economic] efficiency of the output of bunkei disciplines, which is to understand humans. I feel that it is a shortsighted idea held by a handful of industry players.

— You have spent many years in France. How do you feel about the education system in France?

SATO: My two daughters attended local schools in France, so education was a very pertinent issue. From my experience as a parent, French education spares no effort in cultivating the ability to think.

High school students take the baccalauréat exams before graduation, which are pretty grueling. For a philosophy exam, for example, because philosophy is among the subjects taught in high school, students sit exams lasting up to three or four hours writing a ten-A4-page essay on a fairly subjective topic, for instance pertaining to Kant. And although the exam is taken by hundreds of thousands of students, markers rank each and every essay as 1st, 2nd and so on. I don't think such subjective exams would be feasible unless the markers were fairly confident in their own ability to build intellectual arguments, judge and analyze, yet the French baccalauréat exam somehow manages to do it. I think French education cultivates that kind of intellectual tenacity. The same can be said about individual scholars, whom I feel are outstanding in their tenacity of thought.

— In Europe, Britain is now in negotiations to leave the EU. What do you think lies in store for Europe?

SATO: France is arguably the country fearing any EU dissolution the most. The idea of the EU itself historically originates in France's longtime wish to have Germany under control, so as not to repeat the tragedy of the two world wars. French international policy over the recent two hundred years has been based on how to avoid confrontation with Germany, and maintain a good relationship. For this reason, France wants to avoid any EU dissolution at all costs. After Brexit, French President Emmanuel Macron will probably try to carry on maintaining the EU as best as he can through coordinated efforts with German Chancellor Angela Merkel.



— In 2016 you gave a lecture in the presence of the Japanese Emperor and Empress.

SATO: Yes, a very memorable event. On January 12, 2016 I had the honor of giving a lecture titled "The Cultural Significance of Western Medieval Monasticism" in the presence of the Emperor, Empress and other members of the imperial family in the Matsu-no-ma grand hall at the Imperial Palace.

In the lecture I discussed the copying of texts by medieval monks. Without this activity, ancient Greek and Roman texts would not have survived to this day. Today, about 2,000 ancient text survive, including fragments and later copies which have been written down before the year 800. This is only a fraction considering that aristocratic residences of ancient Rome invariably had libraries housing huge collections of books. The small number survives because of the medieval monastic scribes. Without the copies they made, Aristotle and Socrates would be unknown to us. In view of this, we could risk depriving future generations of records of the present age if we converted everything published today into electronic media. These were some of the topics covered by the lecture.

The experience was immensely rewarding for me personally because I greatly admired the range of activities conducted by the Emperor and Empress after World War II. After seeing a photograph of me lecturing, a friend in Paris sent the compliment, "Like Alcuin lecturing to Charlemagne," which was very flattering.



Interview with Prof. SATO was done by Nagoya IAR faculties and C. Tsuboi (Chunichi Shimbin Co., Ltd.). This interview article was written by C. Tsuboi and translated to English under the responsibility of Nagoya IAR.

Genetic copy number variation (CNV) analysis of schizophrenia

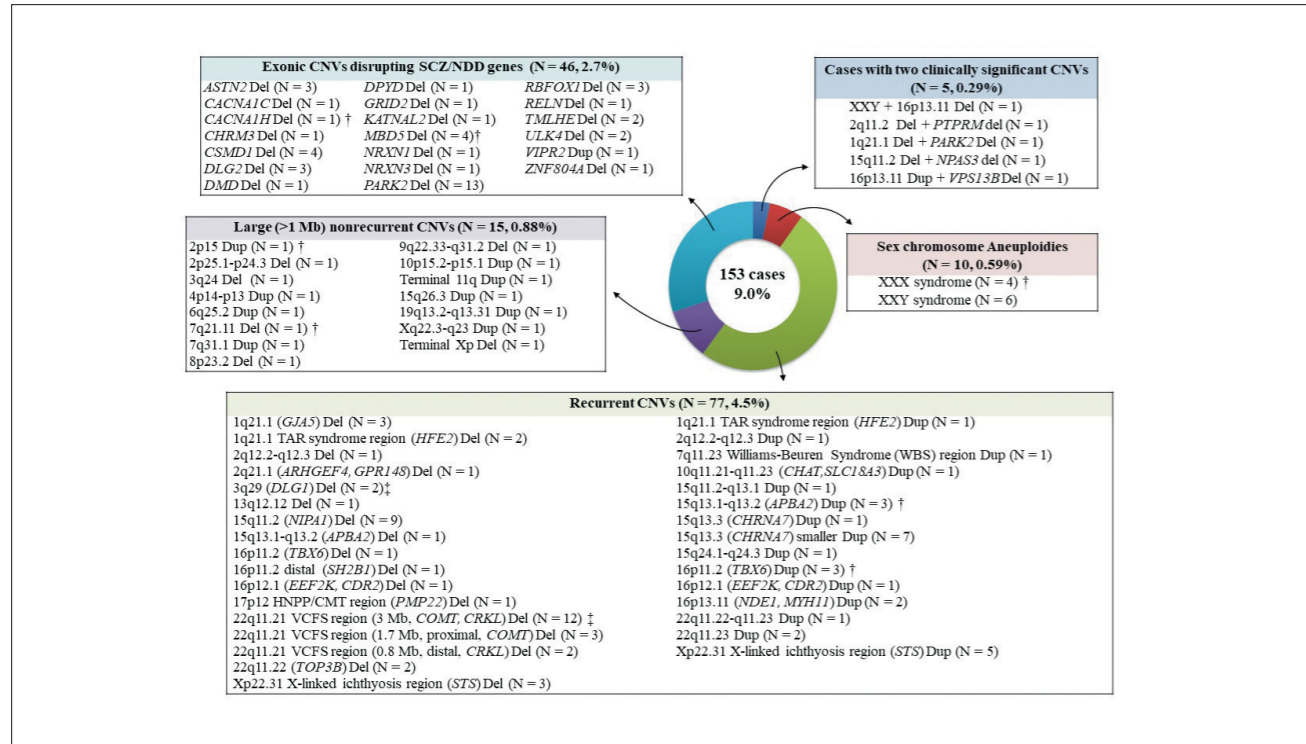


Figure shows clinically significant (or pathogenic) copy number variations (CNVs) identified in patients with schizophrenia. 158 CNVs were detected in 153 of 1699 patients (9.0%). Five patients had two clinically significant CNVs. The CNVs were classified into four categories: 1) sex chromosome aneuploidies, 2) recurrent CNVs, 3) large nonrecurrent CNVs, and 4) exonic CNV disrupting SCZ/NDD genes. Number and % frequency of each category are presented in parentheses. † indicates that de novo CNV was detected in one patient, and ‡ indicates that de novo CNV was detected in two patients. Abbreviations: Del: deletion; Dup: duplication; NDD: neurodevelopmental disorder; SCZ: schizophrenia



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Genetic copy number variation (CNV) contributes substantially to human evolution, normal phenotypic variation, and human disease. To date, thousands of different genomic duplications and deletions, each spanning hundreds to millions of base pairs, have been mapped genome-wide, and collectively account for a significant fraction of human genetic variation. The importance of several rare CNVs (<1% in population) in the risk of schizophrenia has been suggested in previous studies. We performed a high-resolution genome-wide CNV analysis of 1699 schizophrenia patients and 824 healthy controls. Our study revealed high genetic heterogeneity of schizophrenia and its clinical features and raises the possibility that genomic instability is involved in its pathogenesis, which may be related to the increased burden of de novo CNVs and the variable expressivity of CNVs.

INTRODUCTION

Human genomes vary from one to another in many ways, and the totality of this genetic variation underlies the heritability of human traits and genetic diseases. Recent genome studies have revealed that various types of genetic variations are present in the human genome. Among them, copy number variations (CNVs) are a particularly important component of genetic variations, affecting a greater fraction of the genome. CNVs are defined as copy number changes including deletions and duplications of genomic regions that range from

one kilobase (kb) to megabases (Mbs) in size. Recently, several rare CNVs (<1% in population) have been found to be associated with a risk of schizophrenia. Schizophrenia is a major psychiatric disorder that affects about 1% of the population. This disorder is characterized by psychotic symptoms (delusions and hallucinations), negative symptoms (social withdrawal and blunted affect), and cognitive impairments. Although the precise pathogenesis of schizophrenia remains largely unclear, epidemiological studies have shown that genetic factors have an important role in the risk of this disorder, with heritability estimated at

70–90%. Eleven large rare CNVs have been reported to be associated with the risk of schizophrenia with odds ratios (ORs) of 2 to over 50. Such CNVs included deletions at 1q21.1, NRXN1, 3q29, 15q11.2, 15q13.3, and 22q11.2 and duplications at 1q21.1, 7q11.23, 15q11.2-q13.1, 16p13.1 and 16p11.2. These CNVs were also implicated in the risk for other neurodevelopmental and psychiatric disorders (variable expressivity of CNVs). Despite the progress, small CNVs (<100 kb) have not been fully studied in schizophrenia. Furthermore, the pathogenesis of this disorder has not been elucidated. Thus, we performed a high-resolution genome-wide CNV analysis to address these issues.

CNV analysis

Using a microarray technology called array comparative genomic hybridization, we performed a high-resolution genome-wide CNV analysis of 1699 schizophrenia patients and 824 healthy controls (1). This was the largest CNV study for a psychiatric disorder in Japan. Overall, we identified 7066 rare (<1%) CNVs and 70.0% of them were small (<100 kb). These small CNVs were difficult to detect in previous studies. We examined the genome-wide CNV burden in schizophrenia and confirmed the previous findings that patients with schizophrenia had a greater genome-wide burden of rare exonic CNV than healthy controls.

We then looked into clinically significant (or pathogenic) CNVs, which were previously associated with the risk of neurodevelopmental or psychiatric disorders (e.g., intellectual disability, autism spectrum disorder, attention deficit hyperactivity disorder, bipolar disorder). Such CNVs were identified in 9.0% (153/1699) of patients (Figure) and 3.2% (26/824) of healthy controls. The excess of these CNVs in patients was statistically significant (odds ratio = 3.04, $P = 9.3 \times 10^{-9}$), supporting the pathogenicity of such CNVs in schizophrenia. This result also indicated that schizophrenia is a genetically heterogeneous disorder and that genetic risk factors are shared among different neurodevelopmental and psychiatric disorders. For individual CNVs, we obtained evidence for a significant association of X-chromosome aneuploidies (XXX/XXY) and 22q11.2 deletions with schizophrenia. The 22q11.2 deletions have been reported as the most important genetic risk factor for schizophrenia in previous studies.

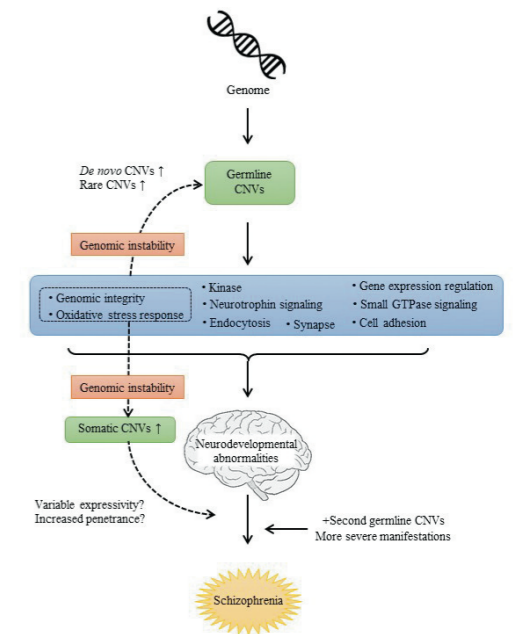
Phenotypic analysis

To characterize clinical features of patients with clinically significant CNVs, we examined their clinical information in detail. As a result, 41.7% of patients with such CNVs had a history of congenital phenotypes (e.g., congenital heart defects) or premorbid developmental problems (e.g., intellectual disability). In addition, the rate of treatment resistance to antipsychotics (primary medication for schizophrenia) was significantly higher in patients with these CNVs than in those without them (36.1% vs 16.9%, odds ratio = 2.79, $P = 0.0036$). This indicated that CNV findings may be useful in predicting the response to antipsychotics in patients with schizophrenia. We also found more severe clinical manifestations in patients with two clinically significant CNVs.

Biological pathways

Identification of biological pathways is critical for understanding its pathogenesis and development of novel treatment. For that purpose, we performed bioinformatic analysis (i.e., gene set analysis) using our CNV datasets. As a result, we identified multiple biological pathways implicated in the pathogenesis of this disorder: oxidative stress response, genomic integrity, gene expression regulation, cell adhesion, neurotrophin signaling, kinase, synapse, small GTPase signaling and endocytosis. The importance of synapse, cell adhesion, and small GTPase signaling in schizophrenia were strongly supported by previous genetic studies. Novel biological pathways included oxidative stress response and genomic integrity. Oxidative stress, which is an imbalance between reactive oxygen species and the antioxidant defense system, induces DNA damage such as double-strand breaks.

Although increased oxidative stress has been reported in these patients, its role in the pathogenesis remained unclear until now. Genomic integrity is essential for neuronal survival and normal neuronal function. This pathway included 'DNA repair', 'DNA replication' and 'DNA recombination', errors which are involved in the major mechanisms of CNV formation. Therefore, CNVs in patients which affect the oxidative stress response or genomic integrity may promote genomic instability that underlies high de novo CNV rates and a greater burden of rare CNVs in schizophrenia. In addition, genomic instability may influence the genome of somatic cells (neurons) and increase somatic mutations. Consistent with this, an increased copy number of L1 retrotransposon in neurons has been recently reported in schizophrenia. Somatic mutations (mosaicism) are also implicated in variable expressivity of CNVs. Finally, a genetic model of schizophrenia is provided in Figure.



A genetic model of schizophrenia

In pathogenesis of this disorder, nine pathways (oxidative stress response, genomic integrity, gene expression regulation, cell adhesion, neurotrophin signaling, kinase, synapse, small GTPase signaling, and endocytosis) are affected by CNVs. Disruption of genomic integrity and oxidative stress response induces genomic instability, which is involved in germline CNV formation and somatic CNV formation in neurons. The former account for an increased rate of de novo or rare CNVs and the latter for the variable expressivity of CNVs.

Research Summary

We revealed the high genetic heterogeneity of schizophrenia and clinical features of patients with pathogenic CNVs, and raised the possibility that genomic instability is involved in its pathogenesis, which may be related to the increased burden of de novo CNVs and the variable expressivity of CNVs.

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Categorical representation theory and its application to knot theory



Roman city ruins (Conímbriga in Portugal).



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We are studying knots, which are formed by closed strings in three-dimensional space. Because of the simple structure of the knot, our knot studies relate to fields such as string theory in mathematical physics and research into knots in DNA. In fact, the knot invariant defined by the author and the knot invariant calculated by string theory coincide, and new knot invariants using category theory are applied to the structure determination of DNA knots.

Knot theory

A knot is a closed string in three-dimensional space (Figure 1), and beautiful knots with high symmetry have been used as geometrical patterns from ancient times. When I was a postdoctoral researcher at Algarve University in Portugal, I visited Conímbriga, the ruins of a Roman city, and found lots of knots in the mosaic floors (Figure 2). In knot theory, we treat these geometric objects mathematically and we study the classification and structure of knots.

Before talking about knots, let us consider a polygon on a two-dimensional plane as a simple example. First, how many kinds of polygon exist? Their number is infinite. You all know them as triangles, squares, pentagons, etc. Another question: can we determine what kind of polygon a

given polygon is? Yes, we can find that by examining the structure of the polygon. We can find the answer by examining the number of edges, the number of corners or the sum of the interior angles. For instance, if the sum of the interior angles of a given polygon is 900 degree, then the polygon is a heptagon. So what about knots?



Figure 1: From the left: Trivial knot, Trefoil 1, Trefoil 2, Trefoil 3, Figure-eight knot



Figure 2: Trivial knots (geometrical pattern).

Knot invariant before 1999

First question: how many kinds of knot exist? We find that there is an infinite number of knots. As you can see from the first line in Figure 3, by gluing the top and bottom of two strings together, we obtain a knot that has two components that are not intertwined (left in Figure 3). If we twist the strings once and glue the top and bottom together again, we obtain a one-component knot that is topologically the same as the trivial knot in Figure 1 (middle in Figure 3). If we twist the strings twice and glue the top and bottom together, we get a two-component intertwined knot (right in Figure 3).

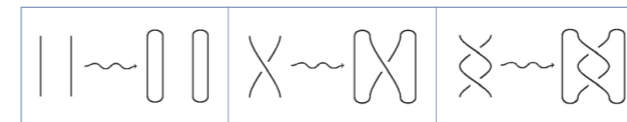


Figure 3: Knots by string closure

We can obtain more complex intertwined knots by twisting the string three or four times and gluing the top and bottom together. Using three strings and four strings, more complex knots can be made. Not all knots are made in this way; there are more complex knots. This does not prove that there is an infinite number of knots, but we can understand the fact intuitively from the above.

Second question: can we determine what kind of knot a given knot is? Unfortunately, we cannot always know what kind of knot a given knot is. For instance, Trefoil 2 and Trefoil 3 in Figure 1, which do not look the same at first glance, become the same knot if we use a continuous deformation without separating the knot components (please confirm this for yourself). In addition, Trefoil 1 will not change into Trefoil 2 using a deformation. However, if you work a little harder, Trefoil 1 might be made into Trefoil 2 (do not try too hard, because these are different). That is, we need to indicate that Trefoil 1 will not change into Trefoil 2. Knot invariants are effective in proving this.

Alexander polynomial and Jones polynomial

In extracting the structure of a knot, we need to define a knot invariant, which is a map from the set of knots to a well-known set, and classify all knots using the knot invariant. There are knot invariants such as the Alexander polynomial and the Jones polynomial, which are maps from the set of knots to the set of one variable polynomial. How to construct these polynomials is omitted here, but the evaluations for the knots in Figure 1 are summarized in Table 1.

From Table 1, the evaluations of the Alexander polynomial for the trefoil and the figure-eight knot are different and so the Alexander

polynomial tells us that these knots are different. However, although Trefoil 1 and Trefoil 2 (and 3) are different knots, the evaluations of their Alexander polynomials are equal. That is, the Alexander polynomial cannot always determine whether they are different or not. In general, the Alexander polynomial cannot distinguish knots that have a mirror image relationship like the relationship between Trefoil 1 and Trefoil 2.

On the other hand, Trefoil 1 and Trefoil 2 can be distinguished using the Jones polynomial (Table 1). The Jones polynomial tells us whether the knots listed in Figure 1 are equal or different. However, the Jones polynomial also does not classify all knots, because there are non-trivial knots whose evaluation of the Jones polynomial is the same as the trivial knot. Whether we can construct a knot invariant which classifies all knots is still an open problem in knot theory.

From set theory to category theory

Set theory deals with collections of mathematical objects. Category theory deals not only with collections of objects but also with the relationship, called a morphism, between the objects in a collection. Sometimes we explore deeper structures by dealing with objects and morphisms. Using category theory it succeeded to obtain new knot invariants.

Knot invariants after 1999

In 1999, M. Khovanov refined the Jones polynomial using a category. The refined polynomial is called the Khovanov polynomial. This is a knot invariant which is a map from a set of knots to a set of two variable polynomials. By specializing the parameter t in the Khovanov polynomial into -1 , the Jones polynomial is recovered.

From the evaluations of the Jones polynomial and the Khovanov polynomial in Table 1, the Jones polynomial is recovered from the Khovanov polynomial if the parameter t is specialized into -1 . Moreover, the number of terms in the Khovanov polynomial for the figure-eight knot is greater than the number of terms in the Jones polynomial. The Khovanov polynomial can thus capture the deeper structure of knots. In addition, the evaluation of the Khovanov polynomial for the trivial knot is different from for non-trivial knots. That is, the Khovanov polynomial can detect the trivial knot.

Developing Khovanov's research, we refined the generalization of the Jones polynomial using category theory. From its construction, it can be seen that our invariant is a generalization of the Khovanov polynomial. Moreover, our knot invariant relates to a knot invariant derived from the topological string theory method in mathematical physics.

Further research

Research into refining the knot polynomial using category theory so far has been limited to refinement of the knot invariant called type A. One problem for further research is how to construct a refinement of a knot polynomial which is not type A. We are also studying a refinement of representation theory of a quantum group, which is a concept for describing the symmetry of a physical phenomenon. We are hoping that our refinement of representation theory will induce a new knot invariant and the new knot invariant will help to classify knots.

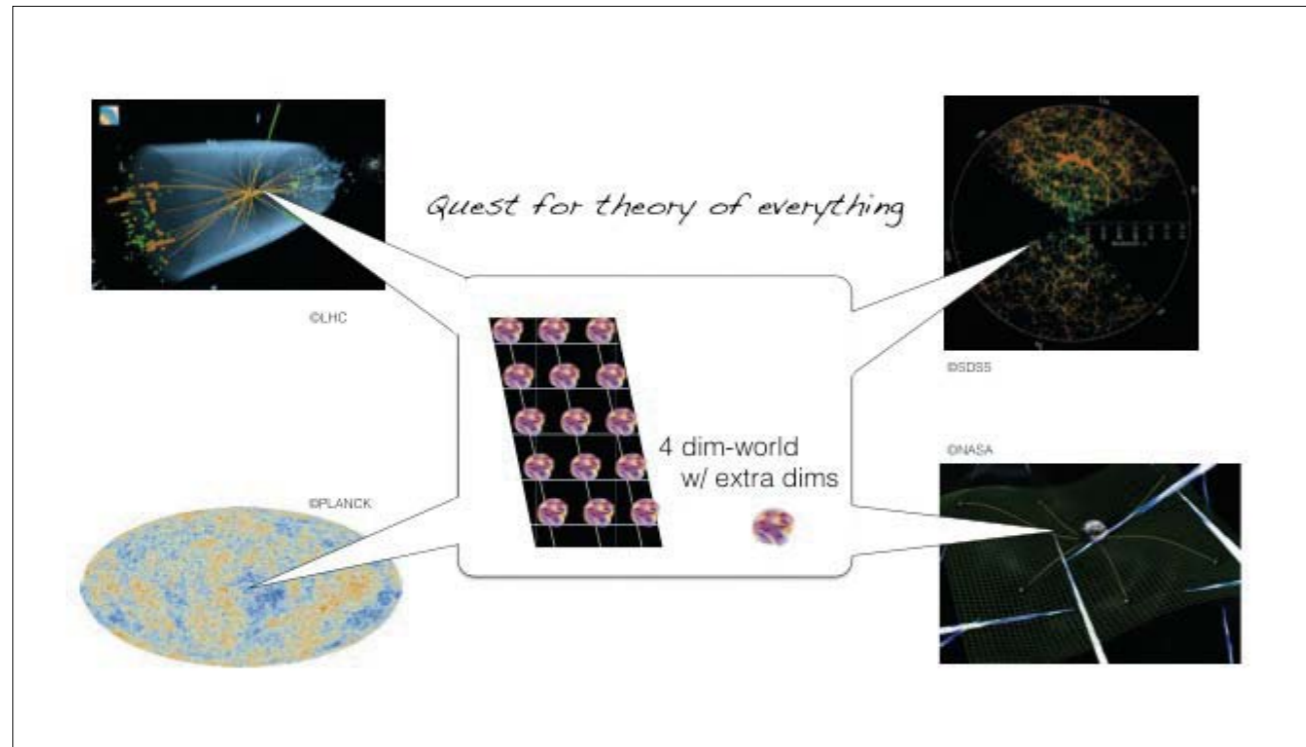
| Knot | Alexander poly. | Jones poly. | Khovanov poly. |
|--------------|-------------------|--------------------------------------|----------------------------------------------------------|
| Trivial | 1 | $q + q^{-1}$ | $q + q^{-1}$ |
| Trefoil 1 | $q - 1 + q^{-1}$ | $-q^{-9} + q^{-5} + q^{-3} + q^{-1}$ | $q^{-9}t^{-3} + q^{-5}t^{-2} + q^{-3} + q^{-1}$ |
| Trefoil 2, 3 | $q - 1 + q^{-1}$ | $-q^8 + q^6 + q^3 + q$ | $q^8t^3 + q^6t^2 + q^3 + q$ |
| 8 figure | $-q + 3 - q^{-1}$ | $q^{-5} + q^5$ | $q^{-5}t^{-2} + q^{-1}t^{-1} + q + q^{-1} + qt + q^5t^2$ |

Table 1: Alexander polynomial, Jones polynomial and Khovanov polynomial

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Exploring imprints of string theory from cosmological observations



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String theory is supposed to be the most promising candidate of “the theory of everything,” which unifies the four fundamental forces in nature. A striking prediction of string theory is the presence of the extra spatial dimensions that curl up so that we are not able to see them in our daily lives. Nevertheless, the “invisible” extra-dimensions indicate the presence of more degrees of freedom in addition to the elementary particles in the standard model. Among these degrees of freedom, axions can leave various imprints in the history of the universe, providing unique opportunities to explore the geometrical structure of the extra dimensions through cosmological observations. I am studying the imprints of axions predicted in string theory from the latest observations of the cosmic microwave background, the galaxy distribution, and in the near future, the gravitational wave background.

INTRODUCTION: String theory

General relativity, proposed by Albert Einstein, consistently predicts, e.g., a planetary motion and large scale structure formations in cosmology, which are predominantly governed by gravity. Recently, the prediction of general relativity was decisively verified by the detections of the gravitational waves from binary black holes. However, general relativity is a classical theory and it has to be modified when the quantum effects become important as in the early stage of the universe or at the final stage of the gravitational collapse. Since 1920's, a number of attempts have been made to reconcile general relativity and quantum mechanics. Among those, string theory has provided

the most promising answer, unifying the four fundamental forces in nature. In string theory, the fundamental building blocks are not volumeless point particles, but extensive strings. The properties of the elementary particles are described by the vibrating states of strings.

String theory and extra dimensions

The theoretical consistency of string theory requires six spatial dimensions in addition to our four dimensional world, which consists of one time dimension and three spatial dimensions. Here, the question arises as to where these extra dimensions are, since we are not aware of their presence. In

fact, to derive the laws of physics in our world, we need to compactify the additional six space dimensions such that they curl up and we do not see them. While we do not see the extra dimensions themselves, we can still find some imprints of their presence. It has been known that string theory (defined in certain six-dimensional compactified space) successfully predicts the elementary particles that we know to exist. In addition, more degrees of freedom appear, corresponding to the geometrical degrees of freedom for the extra six dimensions, which are called moduli fields and axion fields. Investigating the properties of the moduli fields and the axion fields is to probe the extra-dimensions, which are predicted by string theory. As we will see below, cosmology provides us with a unique opportunity to search for the extra dimensions.

Beyond standard model

Cosmological observations require us to consider additional ingredients, going beyond the standard model of the elementary particles. Thirty percent of the present universe is known to be filled with dark matter, which does not interact or only interacts very weakly with the standard model particles, but which plays a major role in the structure formation of the universe. Meanwhile, the large-scale fluctuation of the cosmic microwave background strongly suggests that the universe underwent the rapid acceleration just after the beginning of the universe, known as the inflation. All the structures of the universe are supposed to have been generated during inflation through the quantum fluctuation of the scalar field which drives inflation, the inflaton. In spite of the phenomenological success of inflation, the rapid expansion of inflation requires an element that has a negative pressure unlike the standard model particles.

String axiverse and cosmology

As has been argued above, string theory predicts a bunch of moduli fields and axion fields in the theory which describes our four dimensional world. To avoid conflict with the existing experiments and observations, moduli fields have to be stabilized at certain values. Depending on the values, axions can be in a wide mass range, which was dubbed as string axiverse (Arvanitaki et al., 2009). It is known that a light axion deserves to be a noble candidate of dark matter. One may expect a string axion also to be a candidate of the inflaton. Nevertheless, a difficulty for this to be possible has been known. In order to let an axion play the role of the inflaton, the axion has to take an excursion in a distance longer than the Planck scale (unless we accept a severe fine tuning or a contriving setup). However, it is known that a super-Planckian excursion leads to a string compactification out of control. In Ref. (1), we addressed this issue, focusing on modular invariance, which is a striking symmetry in string theory. We found that when the modular invariance is preserved, the super-Planckian excursion is hardly realized. This result is compatible with other studies which pointed out the difficulty of the super-Planckian excursion, and it has provided another perspective on this issue.

Exploring a new window of string axiverse

When the Hubble parameter, which gives the typical energy scale of the universe, becomes comparable to a mass of an axion predicted in string theory, the axion starts to oscillate coherently. In Ref. (2), we pointed out that the coherent oscillation of the axion can develop a highly inhomogeneous spatial configuration through the parametric instability, even if the spatial configuration of the axion at the onset of the oscillation is almost homogeneous. (To be precise, this instability becomes efficient, when a certain approximation is violated.) The axion in the time dependent and highly inhomogeneous configuration can emit gravitational waves. This opens up a new window to probe string axiverse. The frequency of the gravitational waves differs depending on the mass scale of the axion. We showed that the axions in interesting mass ranges can emit gravitational waves

which can be detected by pulsar timing arrays and gravitational wave interferometers. Meanwhile, the oscillating axion behaves as cold dark matter at least at cosmologically large scales. When the mass scale of the axion is much higher than 10-27eV, the axion already behaves as cold dark matter, when it starts to dominate the universe. Then, it may seem to be difficult to distinguish the axion dark matter from other candidates of cold dark matter. The resonance instability distinctively enhances the power spectrum at a specific scale and this may provide us with an opportunity to probe string axions from dark matter observations.

Being fancy; cosmological colliders

When the typical scale of string theory is high enough, it is very difficult to find a unique signal of string theory via phenomenological studies. However, when the typical scale of string theory is low enough and is comparable to the energy scale of inflation, we will find copious stringy corrections in the theory which governs the physics during inflation. In particular, string theory may suggest the presence of these higher spin particles. When such unknown higher spin particles are coupled with the inflaton, we may find a distinctive imprint of higher spin particles by observing the fluctuation of the inflaton. The figure below shows a schematical image of this study. The primordial fluctuation generated during inflation got stretched by the rapid expansion of the universe such that became much larger scale fluctuation than the size of the universe. Making use of the geometrical symmetry of the inflationary spacetime, Arkani-Hamed and Maldacena computed the non-Gaussian spectrum of the primordial fluctuation generated by the higher spin particles. The spectrum was evaluated at the time when the wavelength of the fluctuation became comparable to the size of the universe. Along this line, in Ref. (3), we computed the later time evolution to connect the prediction from high energy physics with detectable quantities in the cosmological observations. In more recent studies, we are addressing whether such imprints of higher spin particles can be detected through the observation of galaxy alignments.

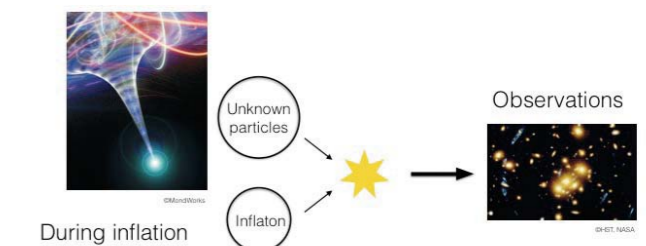


Figure : Image of Cosmological collider. The energy scale of inflation is expected to be much higher than the accessible energy scales by accelerators. Exploring the physics during inflation through cosmological observations provides us with a unique opportunity to probe unknown particles predicted in string theory.

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MAJOR WORKS

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MAJOR WORKS

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MAJOR WORKS

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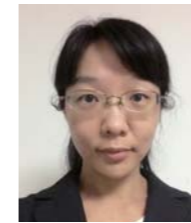
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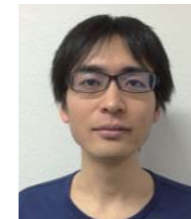
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MAJOR WORKS

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MAJOR WORKS

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Cyrus Tristan ROY

Young Leaders Cultivation Program Faculty (YLC)

Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Mathematics
Research Interests : Nonlinear dispersive equations, Long-time dynamics

MAJOR WORKS

"On control of Sobolev norms for some semilinear wave equations with localized data", T. Roy, *J. Funct. Anal.*, vol. 265, pp.2724-2752 (2013)
"Global existence of smooth solutions of a 3D log-log energy-supercritical wave equation", T. Roy, *Anal. PDE*, vol. 2, pp. 261-280 (2009)



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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Mathematics
Research Interests : Mathematical Physics

MAJOR WORKS

"A Quantum Affine Algebra for the Deformed Hubbard Chain", Niklas Beisert, Wellington Galleas, Takuya Matsumo, *J. Phys.A.*, vol. 45, no. 36, 365206 (2012)
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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Humanities
Research Interests : Mesoamerican Archaeology

MAJOR WORKS

"Reconsideración de la Cronología del valle de Zapotitán, Sureste Maya: Análisis tefrocronológicos y cerámicos", Ichikawa, Akira y Hiroaki Yagi, *América Antigua*, no.19, pp. 1-33 (2016)
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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Science
Research Interests : Molecular biology

MAJOR WORKS

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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Science
Research Interests : Cosmology with gravitational waves

MAJOR WORKS

"Implications of the B-mode Polarization Measurement for Direct Detection of Inflationary Gravitational Waves", S. Kuroyanagi, S. Tsujikawa, T. Chiba, N. Sugiyama, *Physical Review D*, vol. 90, pp. 063513 (2014)
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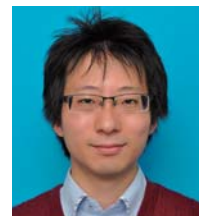


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Affiliation : Designated Assistant Professor at Nagoya IAR and Kobayashi-Maskawa Institute
Research Interests : elementary particle physics

MAJOR WORKS

"Lepton-Specific Two Higgs Doublet Model as a Solution of Muon $g-2$ Anomaly", Tomohiro Abe, Ryosuke Sato, Kei Yagyu., *Journal of High Energy Physics*, vol. 1507, pp. 64 (2015)
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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Science
Research Interests : Radio Astronomy, High-Energy Astrophysics

MAJOR WORKS

"A detailed study of non-thermal X-ray properties and interstellar gas toward the γ -ray supernova remnant RX J1713.7-3946" Sano, H., Tanaka, T., Torii, K. et al., *The Astrophysical Journal*, vol. 799, pp. 175-184 (2015)
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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate school of Engineering
Research Interests : Condensed matter physics (theory)

MAJOR WORKS

"Abe homotopy classification of topological excitations under the topological influence of vortices", Shingo Kobayashi, et al., *Nuclear Physics B*, vol. 856, pp. 577 (2012)
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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate School of Bioagricultural Sciences
Research Interests : Crop Production Science

MAJOR WORKS

"Root plasticity as the key root trait for adaptation to various intensities of drought stress water stresses in rice" Kano, M., Inukai, Y., Kitano, H. and Yamauchi, *Plant Soil*, vol. 342, pp. 117-128 (2011)
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"Root plasticity for maintenance of productivity under abiotic stressed soil environments in rice: Progress and prospects", Suralta, R.R., Kano-Nakata, M. et al., *Field Crops Res.*, In Press (2016)



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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate school of Engineering
Research Interests : Micro-nano manipulation

MAJOR WORKS

"Shape-controlled high cell-density microcapsules by electrodeposition", Z. Liu, M. Takeuchi, M. Nakajima et al., *Acta Biomaterialia*, vol. 37, pp. 93-100 (2016)
"On-chip Self-assembly of Cell Embedded Microstructures to Vascular-like Microtubes", T. Yue, M. Nakajima, M. Takeuchi et al., *Lab on a Chip*, vol. 14, pp. 1151-1161 (2014)
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Affiliation : Specially Appointed Assistant Professor at Nagoya IAR and Graduate School of Engineering
Research Interests : Organic Chemistry

MAJOR WORKS

"Stable And Versatile Gold(III) Catalysts by Oxidative Addition of a Strained Carbon-Carbon Bond", Chung-Yeh Wu", Takahiro Horibe", Christian B. Jacobsen, F. Dean Toste, *Nature*, vol. 517, pp. 449-454 (2015)
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Affiliation : Designated Assistant Professor at Nagoya IAR and Graduate school of Bioagricultural Sciences
Research Interests : Plant responses to nitrogen nutrition

MAJOR WORKS

"Interactions between nitrate and ammonium in their uptake, allocation, assimilation, and signaling in plants", Hachiya, T. and Sakakibara, H., *Journal of Experimental Botany*, doi.org/10.1093/jxb/ (2016)
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