

# Uncovering the genetics behind autism spectrum disorder

Thermo Fisher Scientific recently spoke with Dr. Kristiina Tammimies about her work on autism spectrum disorder (ASD).

**Thermo Fisher Scientific:** Can you provide a brief history of the discovery of genetic links to ASD?

**Tammimies:** The first work was published in the 1970s, when research on twins revealed that there was a higher concordance of ASD in monozygotic (identical) twins than in dizygotic (fraternal) ones. These were the first indications that genetic factors played a major role in the etiology of ASD. Later, the identification of the genes responsible for rare genetic disorders such as Fragile X and Rett syndromes, known to have high comorbidity with ASD, gave the first indications of precise genetic associations in ASD. Thereafter, researchers, such as those led by Professor Scherer in Toronto, also discovered that rare copy number variants (structural variation in the genome) are very important in ASD. The second major contribution to the field of the genetics of autism happened when whole-exome sequencing (WES) showed the relevance of nucleotide-level *de novo* mutations in ASD. Now, with the help of WES and genome sequencing, many more genes and variants are being linked to ASD.

**Thermo Fisher Scientific:** How long have you been involved in the study of ASD?

**Tammimies:** For my doctoral thesis, I studied the biological basis of dyslexia, another neurodevelopmental disorder. In 2012, I moved to Toronto where I worked at the Hospital for Sick Children and began learning about genetics and ASD. I began to focus my work on ASD and am now building my own group at Karolinska Institutet to continue to investigate the genomics of ASD and other neurodevelopmental disorders.



Kristiina Tammimies, PhD, is a senior scientist and genomics group leader at the Center of Neurodevelopmental Disorders (part of the Department of Women's and Children's Health) at Karolinska Institutet (KIND), Stockholm, Sweden. She completed her postdoctoral training at the Centre of Applied Genomics at the Hospital

for Sick Children in Toronto, Canada, where she began her focus on neurodevelopmental disorders in children, including autism spectrum disorder. Dr. Tammimies and her colleagues recently published a paper in *The Journal of the American Medical Association (JAMA)* titled, "Molecular diagnostic yield of chromosomal microarray analysis and whole-exome sequencing in children with autism spectrum disorder."

**Thermo Fisher Scientific:** How is genetic analysis currently being applied in ASD research, diagnosis, and treatment?

**Tammimies:** The goal of my work is to better understand the genetic factors that are driving the symptoms of ASD and why children develop this disorder. At the same time, we are working to demonstrate through basic research that genetic testing could ultimately be a helpful part of the diagnosis and could help physicians tailor their treatments. Additionally, we study the genetic differences between children who respond to various treatments and those who do not.

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Currently, ASD is diagnosed through clinical investigation—observance of how the child interacts with other children and adults—and parent interviews. It is a behavioral assessment. The two main tests are the Autism Diagnostic Interview™-Revised (ADI™-R) and the Autism Diagnostic Observation Schedule™, Second Edition (ADOS™-2). The clinical presentations of children with ASD vary widely, and in addition to variability in the core autistic features, many children with ASD have physical anomalies along with medical, cognitive, and mental health comorbidities. Once a child is diagnosed with ASD, the first-tier genetic testing is done with chromosomal microarray analysis (CMA). If the child presents with additional features of ASD, targeted sequencing is the next step. The genetic tests help us get a more precise molecular diagnosis. In some cases, it may be possible to tailor the treatment based on these tests and to do follow-up medical assessments based on the findings.

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**Thermo Fisher Scientific:** Can you describe your work that was published in *JAMA*?

**Tammimies:** We set out to study and compare the diagnostic yields of the two genetic testing technologies that are most widely used today—chromosomal microarrays and WES—in a population-based sample of ASD children. Although CMA is the first-tier molecular diagnostic test for children with ASD, sequencing is becoming more and more popular in the clinic. With our study, we wanted to examine the benefit of bringing WES into the clinical genetics pipeline for ASD diagnosis and treatment.

The children in the study were recruited between 2008 and 2013 in Newfoundland and Labrador, Canada. At the outset, we divided our 258 study patients into 3 groups based on the complexity of their condition. Our study showed that the yields for CMA and WES are about the same; CMA analysis produced a 9.3% diagnostic yield, whereas the yield from WES was 8.4%. We observed a 15.8% combined molecular diagnostic yield when both tests were used together, and some children were diagnosed with both platforms. The combined diagnostic yield was 37.5% within the group of ASD children with more complex morphological phenotypes. The takeaway is that both CMA and WES are valuable when establishing a molecular diagnosis of ASD.

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**Thermo Fisher Scientific:** What will it take to further increase the diagnostic yield?

**Tammimies:** This is already happening all the time. We are finding more and more genes in the field as a whole, so it will just be a matter of time before the diagnostic yield increases. In our study, there were many findings we labeled “variants of unknown significance” and we did not calculate those in our reports. As we get more evidence, some of these variants will be classified as pathogenic. Technology is improving and so is our evidence of the phenotype, which will increase the yield as well.

My genetics group is connected with the clinical side and we have multiple studies going. The connection between the research group and the clinic is very exciting and necessary in order to truly translate the research findings into clinical practice.

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**Thermo Fisher Scientific:** Are you hoping there will ultimately be a standard of care using these tools to test all ASD patients?

**Tammimies:** Yes, it would be very beneficial to their clinical care, especially if we can look at genetic findings earlier on. I think it would be good if the clinical assessment included a whole genome-wide analysis. Also, most of the families want to know if there is a molecular cause for ASD. Although we are still in the early stages of discovering how the genetic testing can aid all individuals, in the future if we can identify the genetic cause of the ASD, patients can be enrolled faster in new clinical trials based on molecular testing.

**Thermo Fisher Scientific:** How long have you been working with Applied Biosystems™ microarrays?

**Tammimies:** Early on in my doctoral studies I used Applied Biosystems™ gene expression arrays, so I've been familiar with the technology for a long time. When we began looking for copy number variants, I was introduced to different Applied Biosystems™ platforms. For the biggest studies, we are using the Applied Biosystems™ CytoScan™ HD Suite of products.

The Applied Biosystems microarray platform is used in the first line of screening because we know now that many loci in the genome are affected by copy number variants. With this microarray, we can get results fast, uncovering what is of clinical significance. The speed is important because it helps us plan the next step in our studies.

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**Thermo Fisher Scientific:** What is the next step in your research?

**Tammimies:** We are currently using microarrays as the first step, then based on those findings and also on phenotype information, we are prioritizing patients for WES/WGS. We have a number of studies going on, relating to many types of neurodevelopmental disorders. One of them focuses on investigating genetic determinants of intervention response in 300 high-functioning children with ASD who have participated in a randomized clinical trial on social skills training. We are also working on a twin cohort study of about 150 twin pairs, focusing on ASD-discordant monozygotic twins to better understand the contributions of genetic and environmental factors using twin design.

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