Hi, I'm Thomas Rolland from Institut Pasteur Paris, and I will introduce our paper published in Nature Medicine in June 2023.

- **What is the publication about?**

There are hundreds of genes associated with autism identified through the sequencing of the DNA of autistic people and their families. These genes can carry genetic variants that include replacement of one single base of the DNA that disrupt the function of the underlying protein. Most of these genes have been identified by focusing on autistic people, but there is very little information about the presence of genetic variants in these genes in non-autistic people.

In this context, the story of this publication started a few years ago, when we discussed about the fact that genetic variants in these genes strongly associated with autism, were recurrently found in non-autistic people, leading to confusion among clinicians on how to interpret these variants.

- **What methodology did you choose and why?**

We took a radical approach and, conversely to what has been done in the past, we decided to focus on both autistic and non-autistic people who seemed resilient to the presence of these variants.

So, we first identified rare genetic variants impacting the function of 185 genes robustly associated with autism among more than 10 thousand autistic individuals and 200 thousand individuals not diagnosed with autism. This was particularly challenging because we had to analyze an extremely large amount of DNA sequences from very different sources.

We then measured the strength of the association of each gene with autism. For this, we had to develop a method to calculate the frequency of each variant among autistic and undiagnosed people. We ran this method 10,000 times in subsets of autistic and undiagnosed people to extract the most robust estimate of the association for each gene with autism.

Finally, we wanted to test the association of genetic variants with virtually any trait from the general population and to study whether such variants were associated with specific autism-related traits in autistic individuals, and with any cognitive or socioeconomic trait in non-autistic individuals. For the association in the general population, we tested more than 18,000 traits from medical records to socioeconomic status.

- **What are the key results and impacts for the different target groups?**

We identified genetic variants in autism-associated genes in 4% of autistic individuals. While the enrichment was very significant, we still observed similar variants in approximately 1% of individuals not diagnosed with autism.

We identified some genes for which we couldn't find any variants among the 200,000 individuals undiagnosed with autism, suggesting that these genetic variants that disrupt the function of genes such as SCN2A or CHD8 always lead to autism. However, for the majority of the genes, we found carriers of genetic variants in at least one undiagnosed individual, indicating what geneticists name "incomplete penetrance": You carry the genetic variant but you don't have the condition.

Among the autistic individuals, we observed that the variants were not associated with more severe autistic traits, but with reduced cognitive performance and later age of developmental milestones such as the age of first words or delayed walking.

When we tested the association of the variants with 18,000 traits among the individuals from the general population, we observed that the strongest associations were with reduced cognitive performance, income, and qualification level, and with increased material deprivation measured by the unemployment, non-car and non-home ownership and house overcrowding.

Our results suggest that rare genetic variants in some autism-associated genes are not necessarily associated with autism but could influence the global functioning of the people carrying these variants. However, our results do not represent causal relationships since some individuals carrying a variant show little differences in socioeconomic metrics while some others are very impacted. These difficulties could be for example due to their environment, neglecting their neurodivergence, and not only due to their genome. Further research is warranted to identify the genetic, environmental, and societal factors that allow some individuals to flourish.