



RĪGAS STRADIŅA
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GENETIC ASPECTS OF AUTISM SPECTRUM DISORDER

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ASD etiology

- ASD is a complex disorder whose etiology can simultaneously be involved in the environmental and genetic factors at the **same time** (Bettelheim 1967, Rutter and Schopler 1987, Courchesne et al, 2003; Gillberg, 2006; Gardener et al, 2011)
- A distinction in syndromic ASD, which occur in 15% of the population in the case of all ASD and 85% of cases of idiopathic non-syndromic ASD, is that the cause remains unknown (Gillberg and Coleman 1996; Lint and Persico, 2009)

ASD in Latvia

- At the conducted study, the involved group of ASD patients does not represent all Latvian ASD population
- It could be the limiting factor of the population due to which ASD prevalence parameters have not been calculated because a representative ASD sample has not been created in which all ASD cases diagnosed in Latvia would be collected

Aim of the Study

To find the development of the genetic risk factors in non-syndromic autism, as well as to examine the clinical data, anthropometric measurements, molecular genetics data analysis, the characteristic phenotype of the patients and to evaluate drug therapy options with the pharmacogenetics method

The Study

This study was conducted from 2006 to 2013 in four phases:

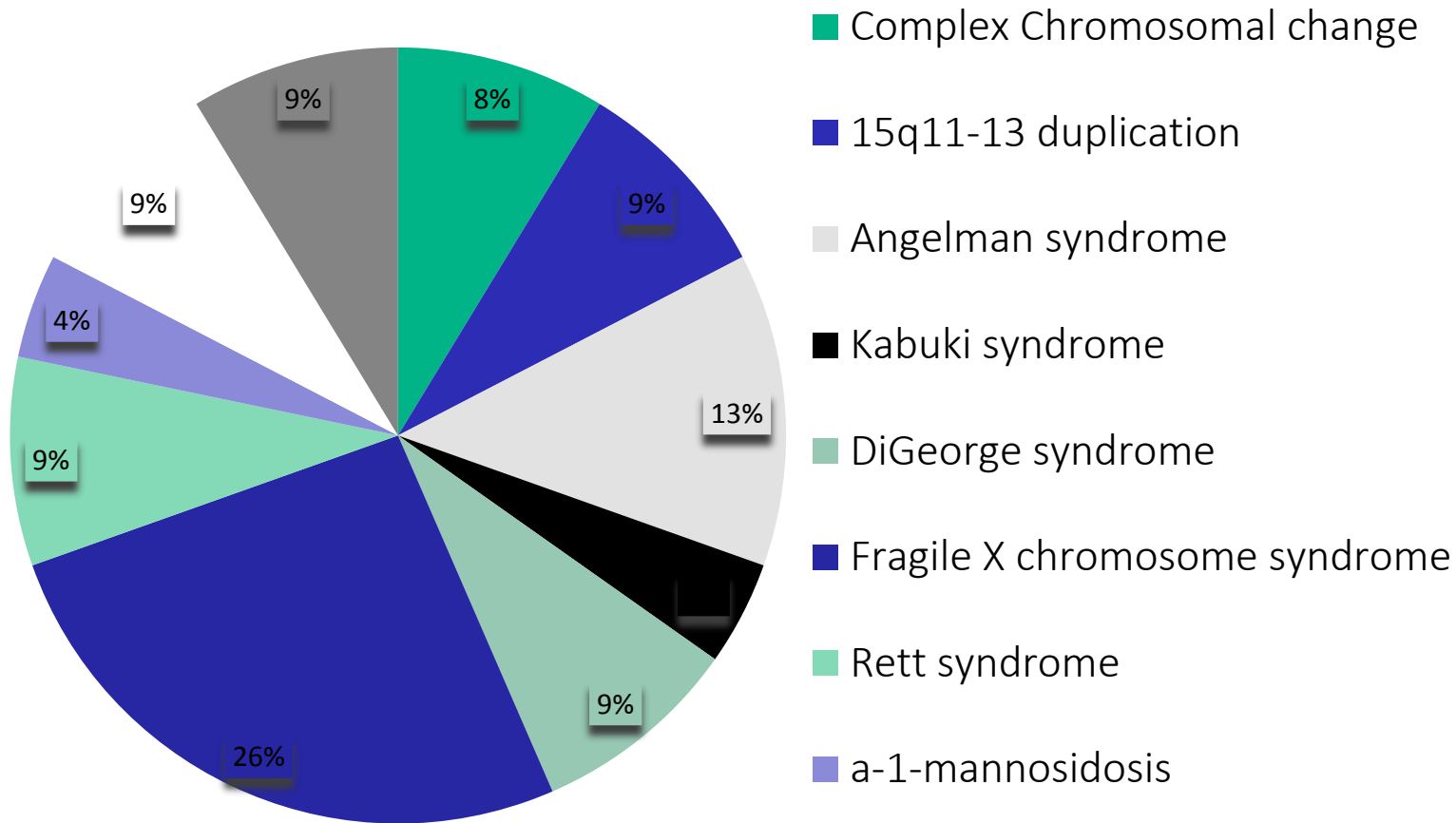
1. Were compared ASD anthropometric measurements and co-morbid disorders
2. Case – control association study of ASD potential candidate genes
3. Case – control association study of pharmacogenetic markers
4. Full exome sequencing family with Asperger syndrome

Subjects

- **150** ASD patients were selected from the Children's University Hospital, Children's Psychiatry and Medical Genetics clinics
- Control group consisted of **190** randomly selected, potentially healthy, mutually unrelated people who did not have a history of ASD or other psychiatric disorders in the family

Results

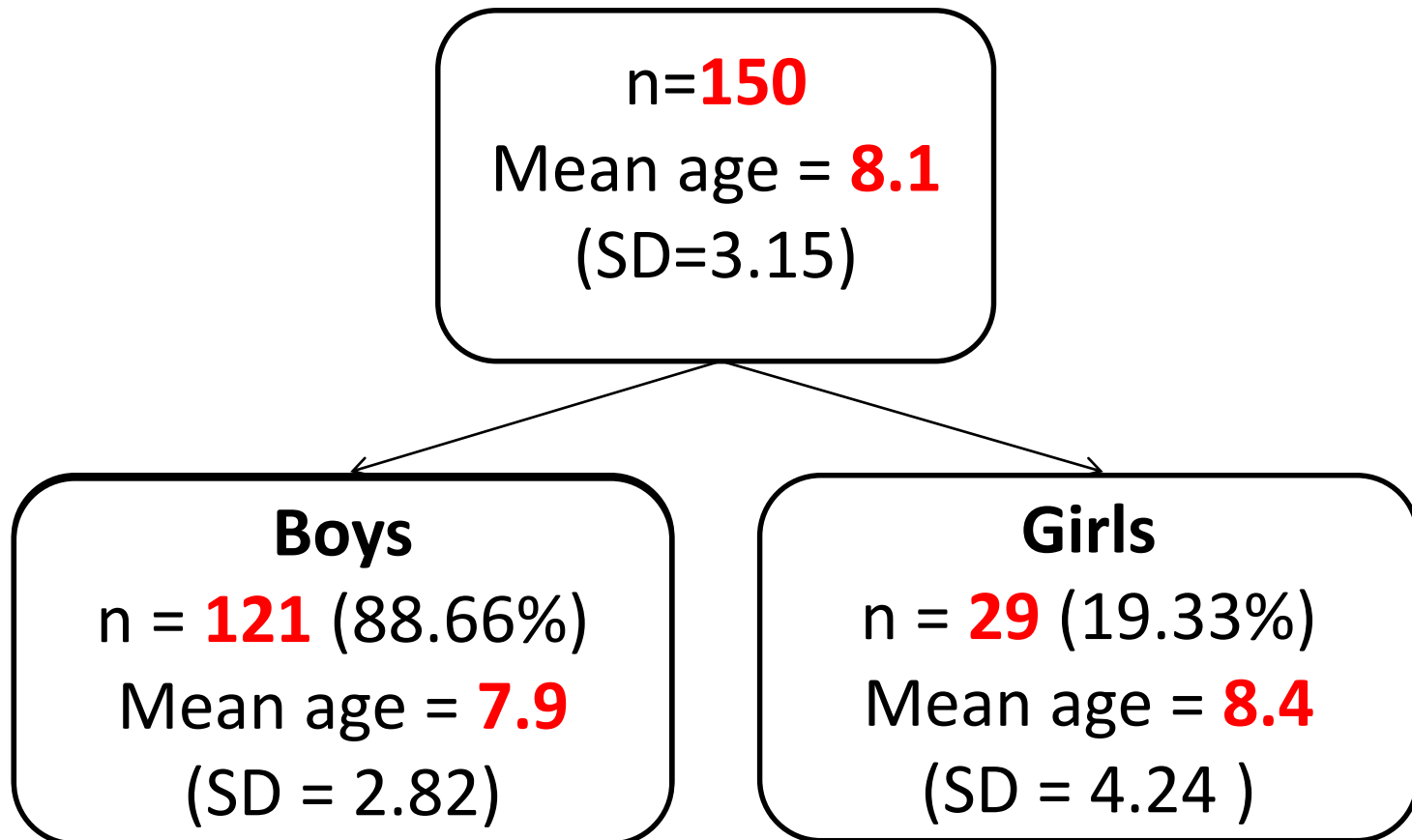
Syndromic ASD patients (13,29%)



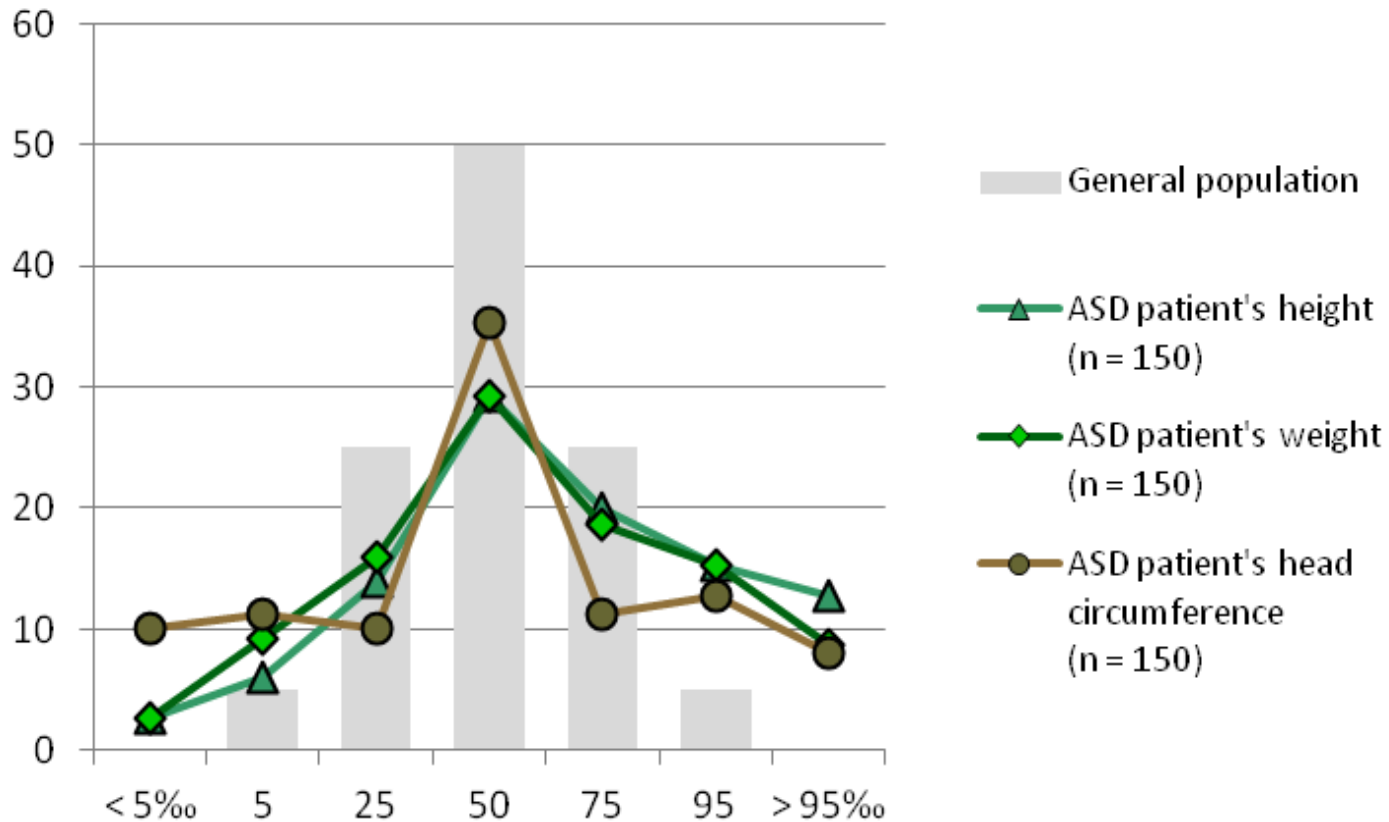
Syndromic autism number of patients and percentages for the selected patient group

Results

Non-syndromic ASD patients



Anthropometric measurements

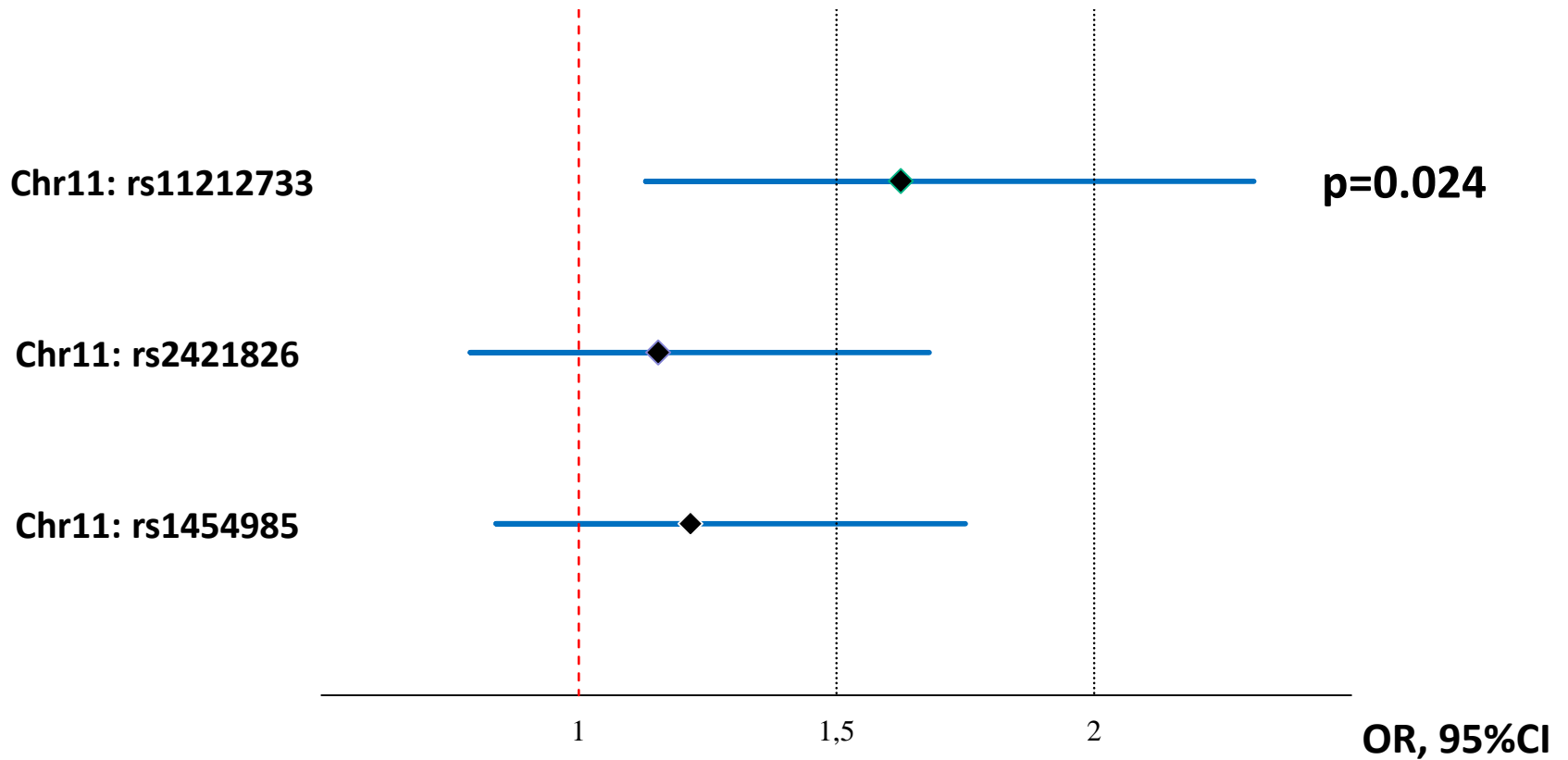


ASD patient and general population anthropometric measurements in terms of percentile

ASD co-morbid disorders

- Mental retardation (80.66%):
 - n = 29 (18.66%), normal intelligence (IQ > 70)
 - n = 77 (51.33%), mild (IQ 50 - 69)
 - n = 34 (22.66%), moderate (IQ 35 - 49)
 - n = 10 (6.66%), severe (IQ 24 - 30)
- 5.33% ASD patients had epileptic seizures which were more frequent in patients with severe mental retardation ($p = 0.009$)
- Expressive and receptive language disorders was 98.66%

Case – Control Assotiation Study

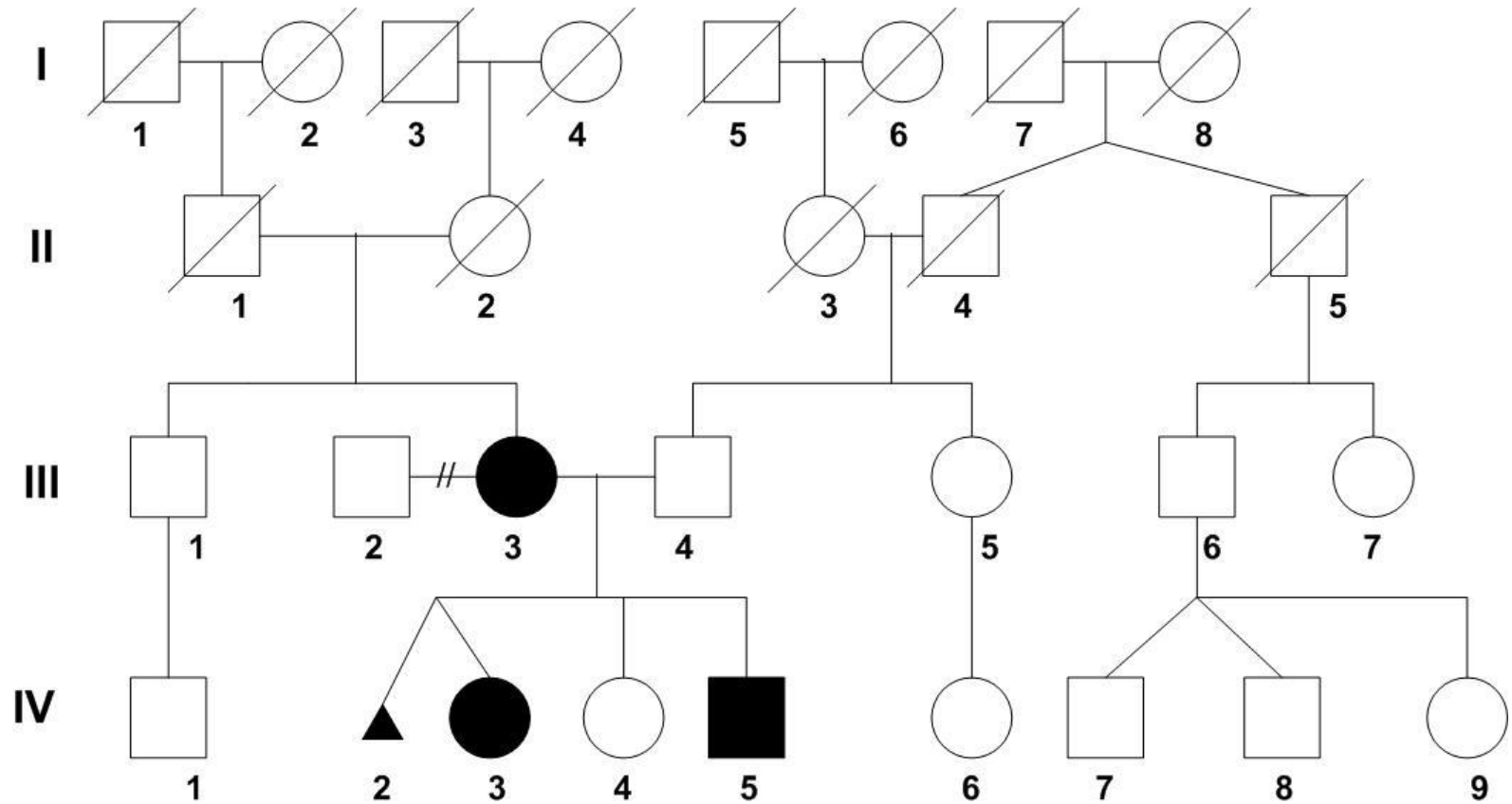


Statistically significant odds ratio for genetic polymorphism rs11212733 (11q2.3)

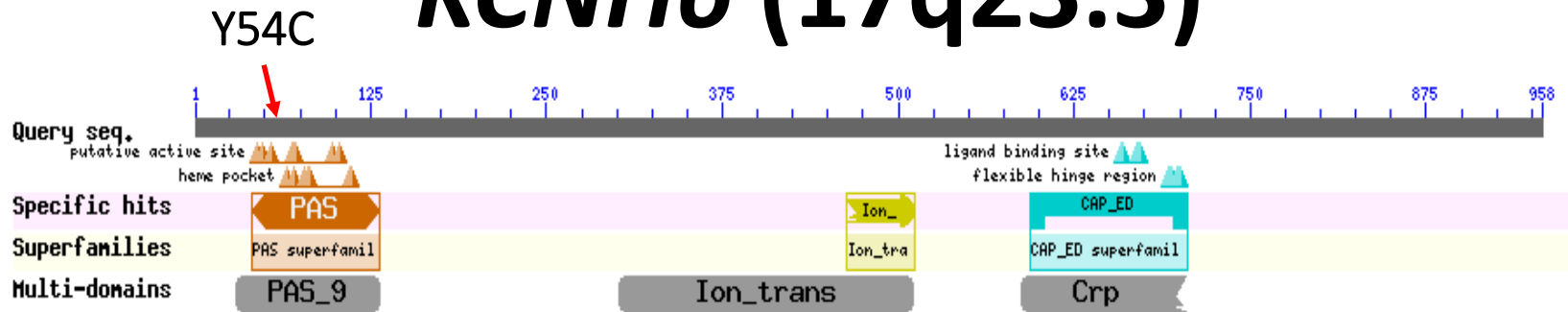
Pharmacogenetic

- A commercial pharmacogenetic test for evaluation of individual response for risperidone therapy is clinically available since 2012
- The selected pharmacogenetic markers were not associated with risperidone efficacy and adverse reactions

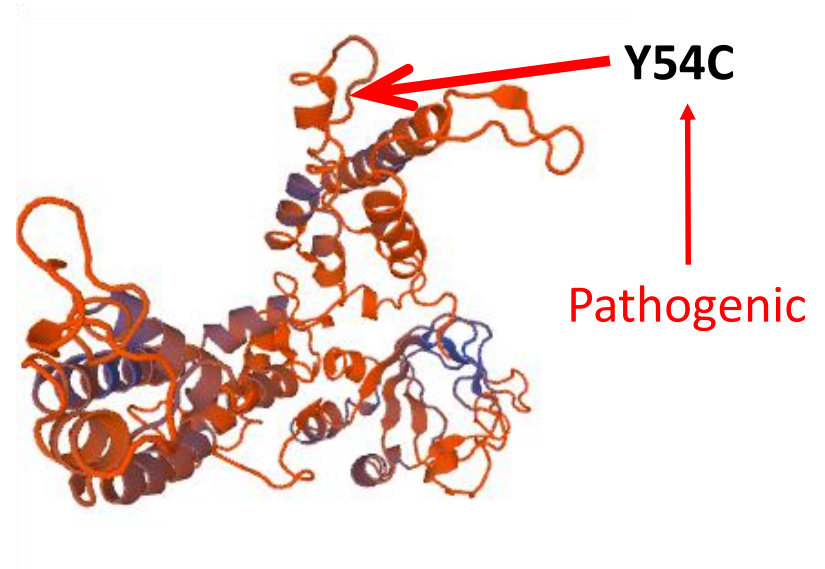
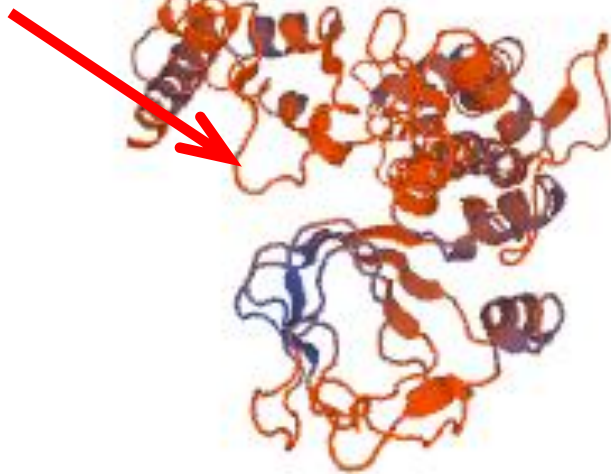
Family with Asperger syndrome



KCNH6 (17q23.3)



Norm



KCNH6 (*potassium voltage-gated channel, subfamily H (eag-related), member 6*). Its encoded protein had to do with ERG (*Ether-A-Go-Go-related gene 2*), which was defined by behavior

Conclusion

1. According to the anthropometric measurements taken and phenotypic features the mutual comparison of both presents a well-described sample of ASD, which includes data for this particular study on the questionnaire. It was found that the varying degrees of mental retardation rate were 80.66%, the frequency of seizures was 5.33%, and the percentage of language disorders was 98.66%. **Epileptic seizures were more frequent in patients with severe mental retardation ($p = 0.009$)**

Conclusion

2. As per the anthropometric measurements taken, ASD patients had a noticeably **larger head circumference and greater body weight** in comparison to the general population

Conclusion

3. **A statistically significant correlation was found between ASD and the SNP rs11212733 ($p = 0.024$), which was localized in the 11q22.3 locus between *DDX10* and *EXPH5* genes. These genes could quite possibly be ASD candidate genes**

Conclusion

4. In this study, cytochrome group (CYP) P450 *CYP2D6* marker alleles *CYP2D6*4* T, *CYP2D6*41* T frequency was not different for ASD patients when compared to the control group. Also, in ASD medication used in the treatment of second-generation antipsychotic, **a relationship was not found between risperidone adverse drug reactions and cytochrome group (CYP) P450 *CYP2D6* marker alleles of *CYP2D6*4* T, *CYP2D6*41* T, (studied markers were not informative)**

Conclusion

5. One family with Asperger's syndrome had a full exome sequencing done using the autosomal inheritance dominant model type. Several potential candidate genes were selected from which, (as per the Sanger sequencing model) **the pathogen *KCNH6* gene variant was identified**, which could possibly be an ASD candidate gene

Latvian ASD team



BMC



**Medical Genetic
Clinic**



**Latvian Autism
center**

Thank you for your attention!



Always

Unique

Totally

Interesting

Sometimes

Mysterious