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Pharmacogenetics of antipsychotic-induced metabolic disturbances: preliminary results for DRD2 rs1800497 and HTR2A rs6313 in Russians

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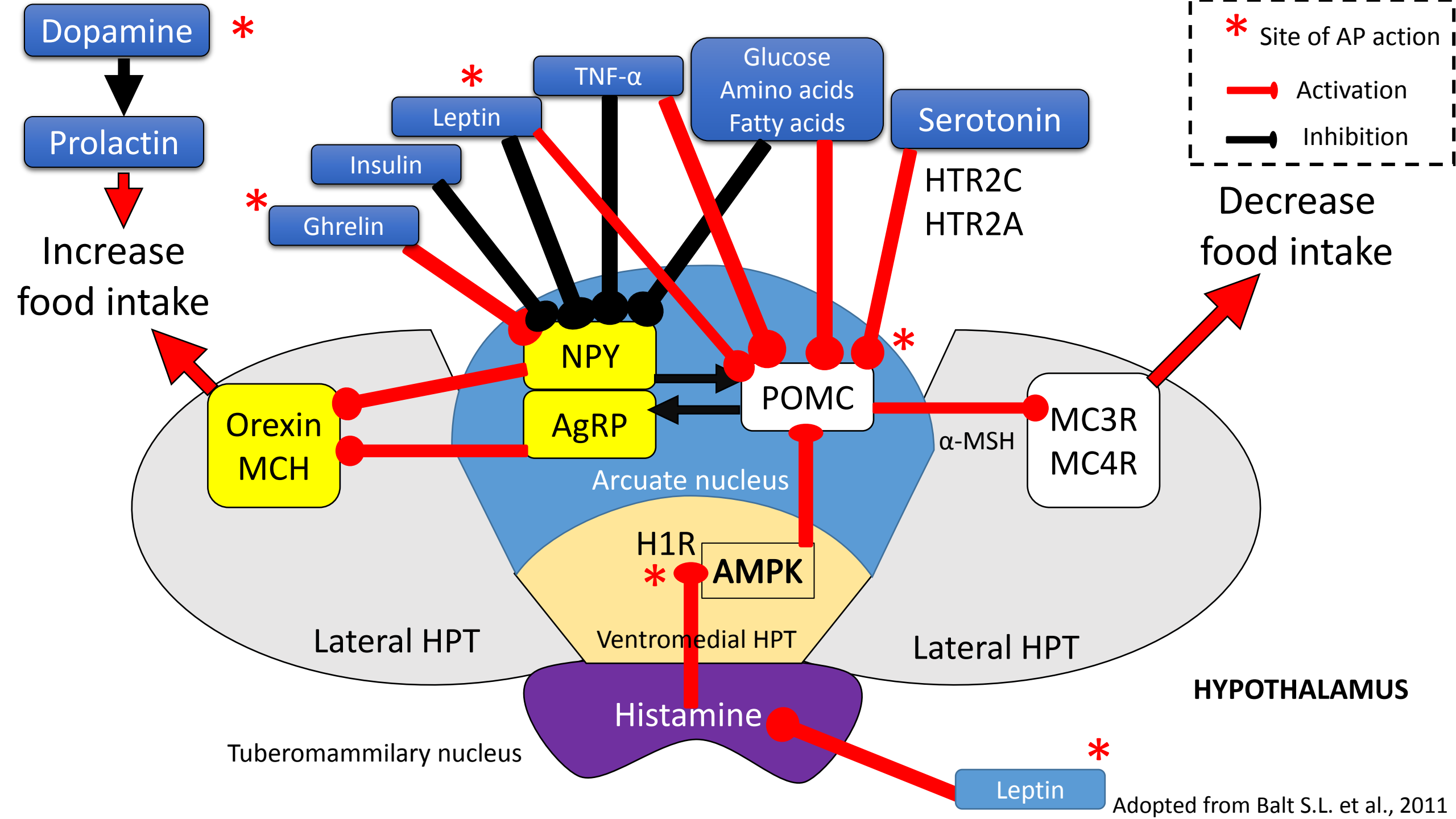
INTRODUCTION

Antipsychotics can increase weight gain and lead to other metabolical disturbances

There are genes which associated with antipsychotic-induced weight gain

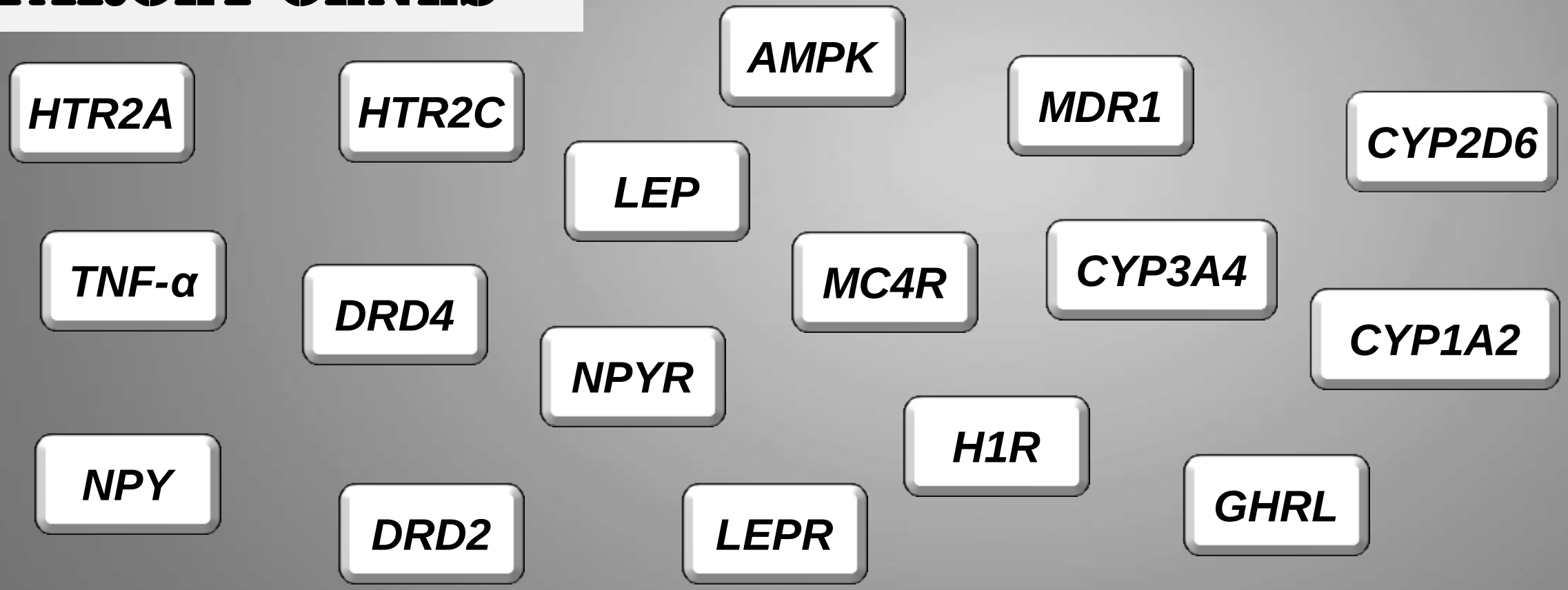
Pharmacogenetic approach allows doctor to choose the most effective and tolerable drug

Ma X. et al., 2014; Kao A.C. et al., 2013


Dopamine
Prolactin
Increase food intake
Leptin
TNF-α
Glucose
Amino acids
Fatty acids
Serotonin
Insulin
Ghrelin
HTR2C
HTR2A
Decrease food intake
NPY
AgRP
POMC
Orexin
MCH
α-MSH
MC3R
MC4R
Arcuate nucleus
H1R
AMPK
Lateral HPT
Ventromedial HPT
Lateral HPT
HYPOTHALAMUS
Histamine
Tuberomammilary nucleus
Leptin
Site of AP action
Activation
Inhibition
Adopted from Balt S.L. et al., 2011

PHARMACOGENTICS OF ANTIPSYCHOTIC-INDUCED WEIGHT GAIN

TARGET GENES



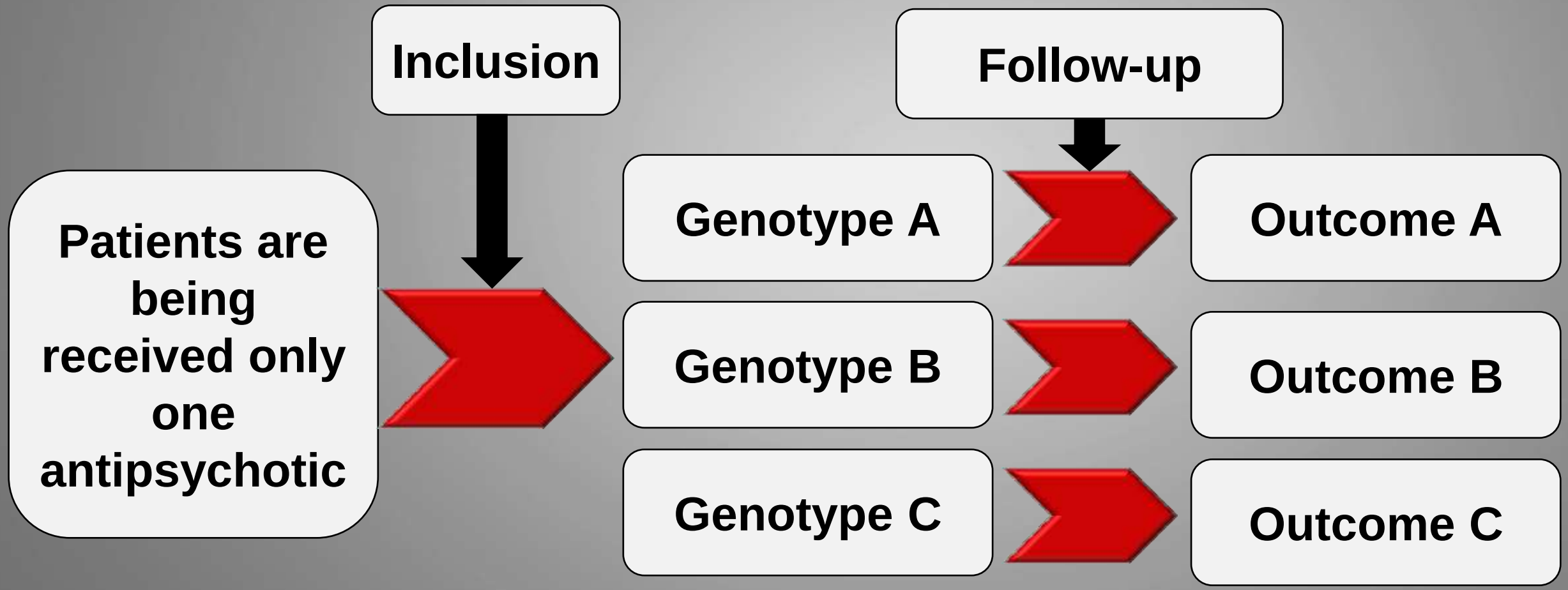
RUSSIAN STUDIES

Antipsyhotics' efficacy:
***BDNF* (Gareeva A.E. et al., 2015),**
***GRIN2B* (Gareeva A.E. et al., 2013)**

Antipsychotics safety, focus on tardive dyskinesia:
CYP1A2 (Ivanova S.A. et al., 2015),
NMDA (Ivanova S.A. et al., 2012),
PIP5K2A (Fedorenko O.Y. et al., 2014),
A2A, DRD2 (Ivanova S.A. et al., 2012)

There are still no pharmacogenetics studies of antipsychotic-induced metabolic disturbances in Russians

STUDY DESIGN



MATERIALS AND METHODS

Inclusion criteria:

- Diagnosis from F2**** group of ICD-10;
- Monotherapy by antipsychotic;
- Age 18 – 55;
- Signed informed consent of participant.

Non-inclusion criteria:

- Concurrent psychopharmacotherapy;
- Verified cerebral disease;
- Diabetus mellitus;
- Hepatic or renal failure;
- Thyroid diseases
- Renouncement from participation in study.

Screening = 78

-23

Included = 55

-10

Completed = 48

Discontinuation's reasons:

Adverse effects – 2;

Additional psychopharmacotherapy was needed – 2;

Withdraw from follow-up – 6.

At least 6-8 weeks

Visit 1

- Genotyping
- Anthropometry (weight, height, waist, thigh)
- Biochemical blood analysis
- PANSS
- CGI-S
- Depression in schizophrenia Calgary Scale

Visit 2

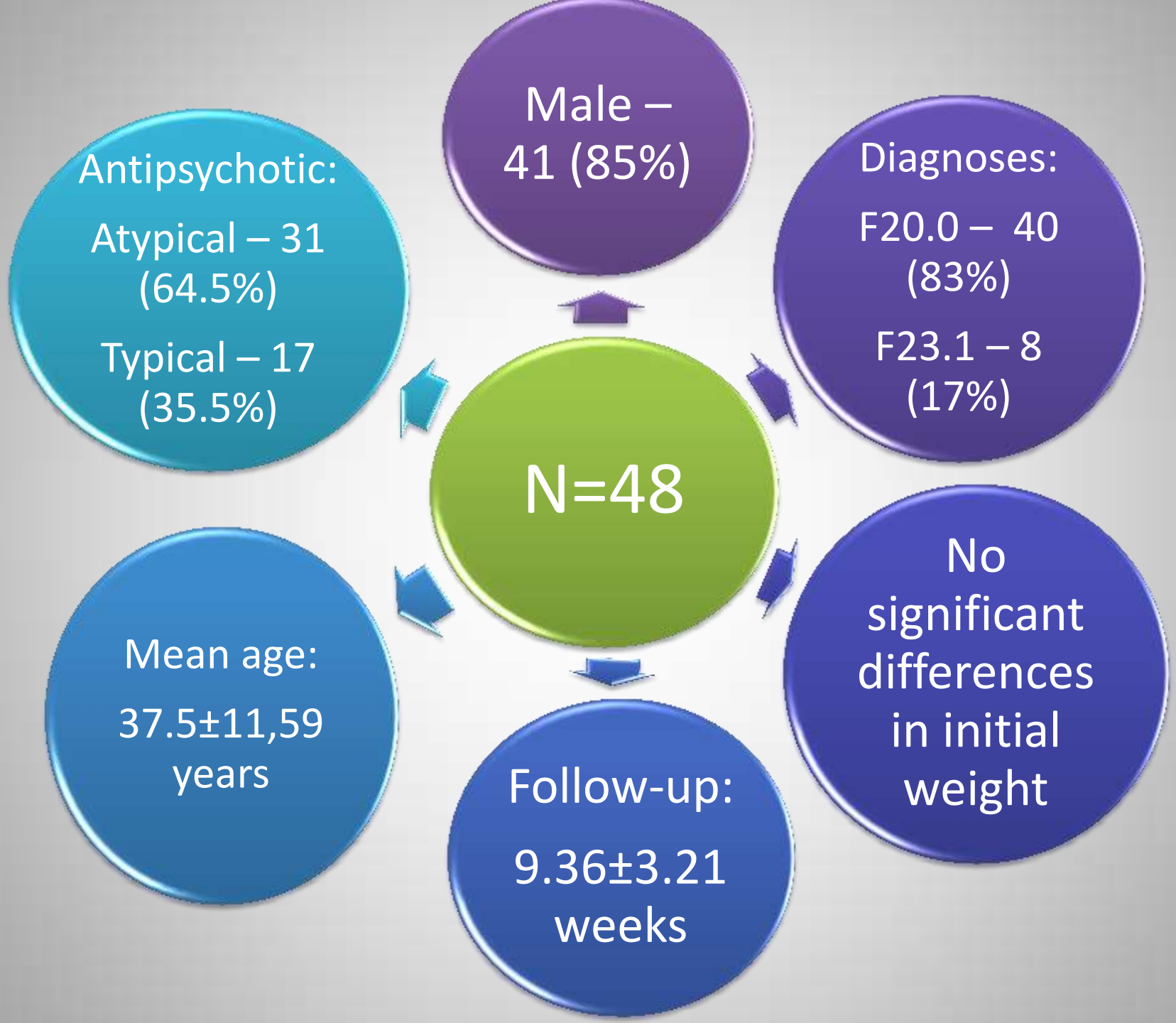
- Anthropometry (weight, height, waist, thigh)
- Biochemical blood analysis
- PANSS
- CGI-S
- CGI-I
- Depression in schizophrenia Calgary Scale

MATERIALS AND METHODS

ALL INCLUDED PATIENTS WERE GENOTYPED FOR:

HTR2A rs6313

DRD2 rs1800497 (Taq1A)


Male – 41 (85%)
Diagnoses:
F20.0 – 40 (83%)
F23.1 – 8 (17%)
No significant differences in initial weight
Follow-up:
9.36±3.21 weeks
Mean age:
37.5±11,59 years
Antipsychotic:
Atypical – 31 (64.5%)
Typical – 17 (35.5%)
N=48

RESULTS

DRD2 rs1800497 (Taq1A)		Frequency	%
Genotypes	**CC**	32	66.0
	CT	14	29.8
	TT	2	4.3
Overall		48	100
Alleles	**C**	78	81
	T	18	19

Hardy-Weinberg equilibrium p = 0.72

RESULTS

5HTR2A rs6313 (T102C)		Frequency	%
Genotypes	**CC**	16	33.3
	CT	25	52.1
	TT	7	14.6
Overall		48	100
Alleles	**C**	57	59
	T	39	41

Hardy-Weinberg equilibrium p = 0.46

RESULTS

		Visit 1	SD	Dynamics	Visit 2	SD	p
Weight (kg)	Typical AP	77.18	17.57	0.38±4.26 (1%)	77.56	16.19	0.72
	Atypical AP	**78.45***	20.50	1.33±3.55 (2%)	**79.78***	19.77	**0.067**
Waist (sm)	Typical AP	91.6	16.57	-0.6±4.32 (0.6%)	91.0	16.44	0.56
	Atypical AP	91.96	17.07	1.15±5.31 (1.5%)	93.12	16.28	0.25
Thigh (sm)	Typical AP	48.86	8.26	1.8±4.7 (2.3%)	50.66	8.44	0.16
	Atypical AP	48.55	9.09	0.22±3.05 (1.1%)	48.77	7.74	0.49
BMI	Typical AP	25.9	7.08	0.11±1.33 (6%)	26.03	6.83	0.73
	Atypical AP	26.1	6.04	0.28±1,54 (6.4%)	26.38	6.02	0.33

HTR2A CC

BMI

27.7

Waist

92.6 sm

Thigh

51.4 sm

81.3 kg

Weight

Visit 1

p>0.1

BMI

27.63

Waist

93.2 sm

Thigh

51.53 sm

82.4 kg

Weight

Visit 2

N=16

HTR2A CT+TT

BMI

25.2

Waist

91.48 sm

Thigh

47.2 sm

Visit 1

76.3 kg

Weight

N=32

p>0.1

BMI

25.5

Waist

91.94 sm

Thigh

48.3 sm

Visit 2

77.4 kg

Weight

DRD2 CC

BMI
26.12

Waist
93.17 sm

Thigh
48.6 sm

79.12 kg
Weight

Visit 1

N=32

p>0.1

BMI
26.33

Waist
93.8 sm

Thigh
49.0 sm

80.14 kg
Weight

Visit 2

DRD2 CT+TT

Visit 1

BMI
26.39

Waist
90.6 sm

Thigh
49.2 sm

77.4 kg
Weight

N=16

p>0.1

Visit 2

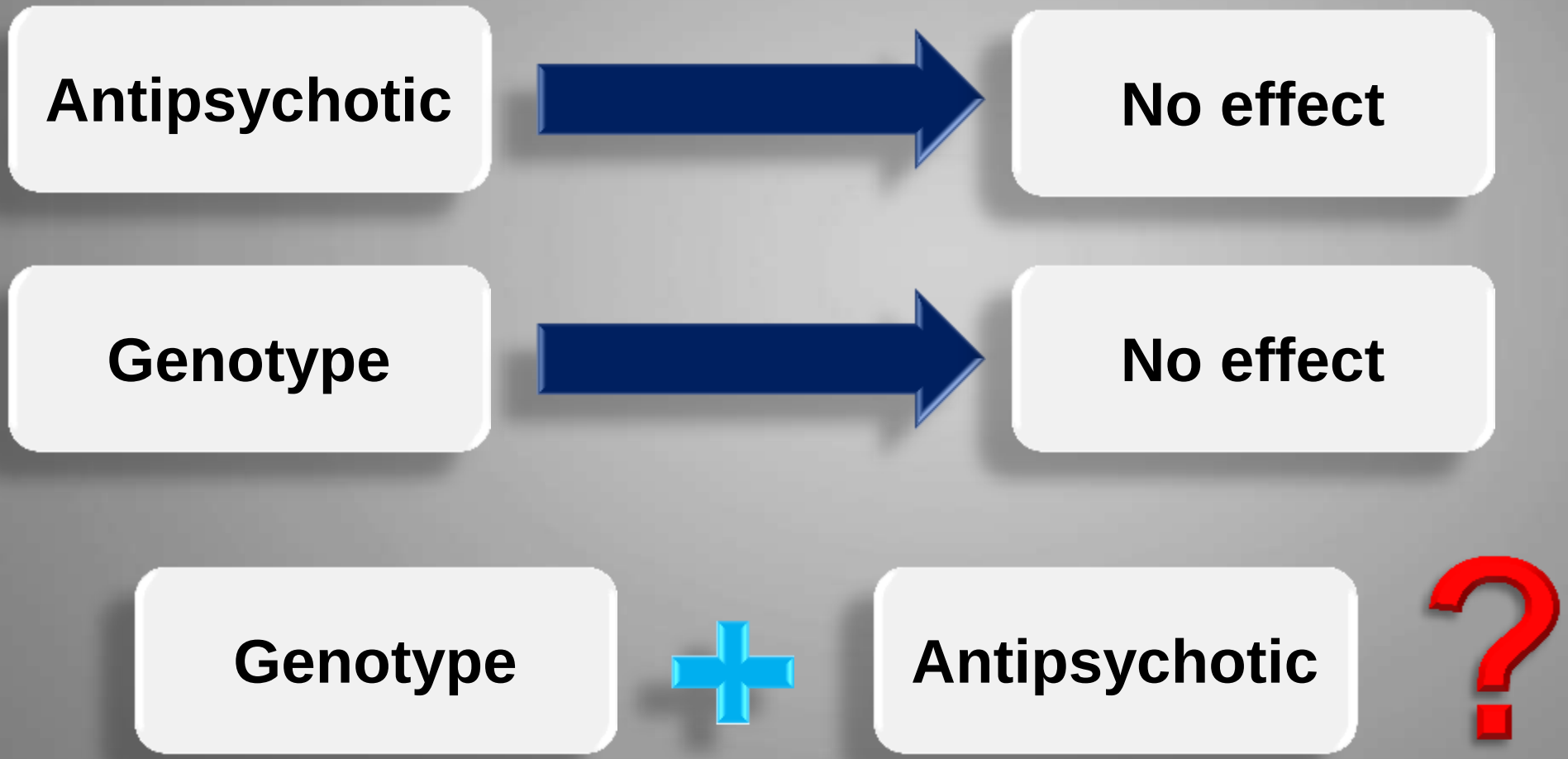
BMI
26.7

Waist
91.4 sm

Thigh
50.53 sm

78.6 kg
Weight

Does it exist effect on weight?

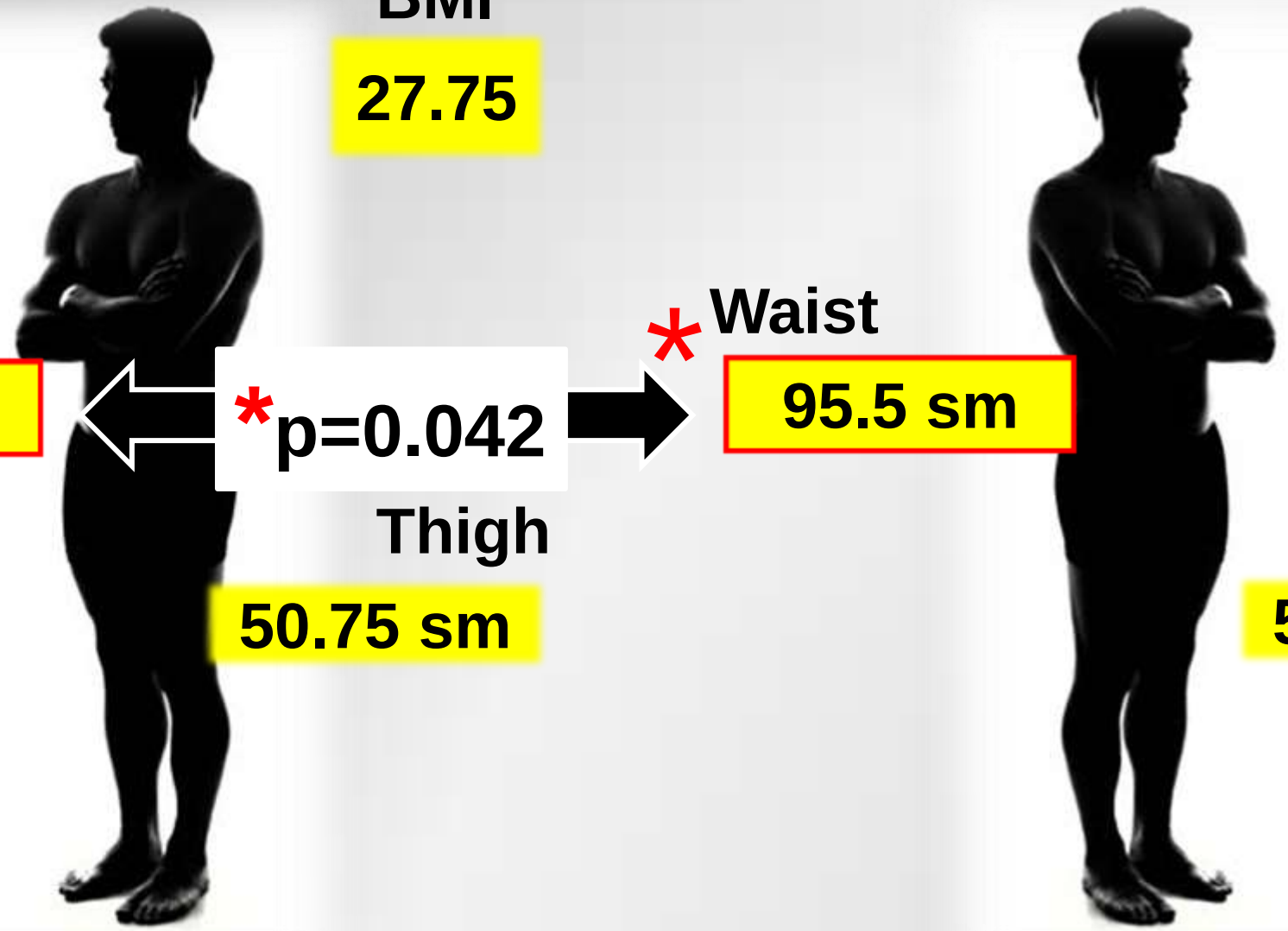


RESULTS

Genotype		Antipsychotic
DRD2 CC		Typical (FGA)
DRD2 CT+TT		Atypical (SGA)
HTR2A CC		
HTR2A CT+TT		

8 combinations

DRD2 CT+TT SGA



BMI
27.75

BMI
28.33

* Waist
92.25 sm

*p=0.042

* Waist
95.5 sm

Thigh
50.75 sm

Thigh
51.12 sm

Visit 1

Visit 2

78.02 kg
*

*p=0.035

80.26 kg
*

Weight

Weight

N=10

HTR2A
CC
SGA

BMI
26.36

Waist
87.44 sm

Thigh
50.66 sm

Visit 1

76.6 kg
Weight

*

*p=0.066

*

78.1 kg
Weight

BMI
26.0

Waist
89.0 sm

Thigh
50.77 sm

Visit 2

N=12

CONCLUSION

There is no effect of only genotype on metabolic side effects of antipsychotics

Patients which received atypical antipsychotics are more prone to weight gain

***DRD2* Taq1A CT+TT + SGA**

***HTR2A* rs6313 CC + SGA**

Are associated with antipsychotic-induced weight gain

ACKNOWLEDGEMENT

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THANK YOU!

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