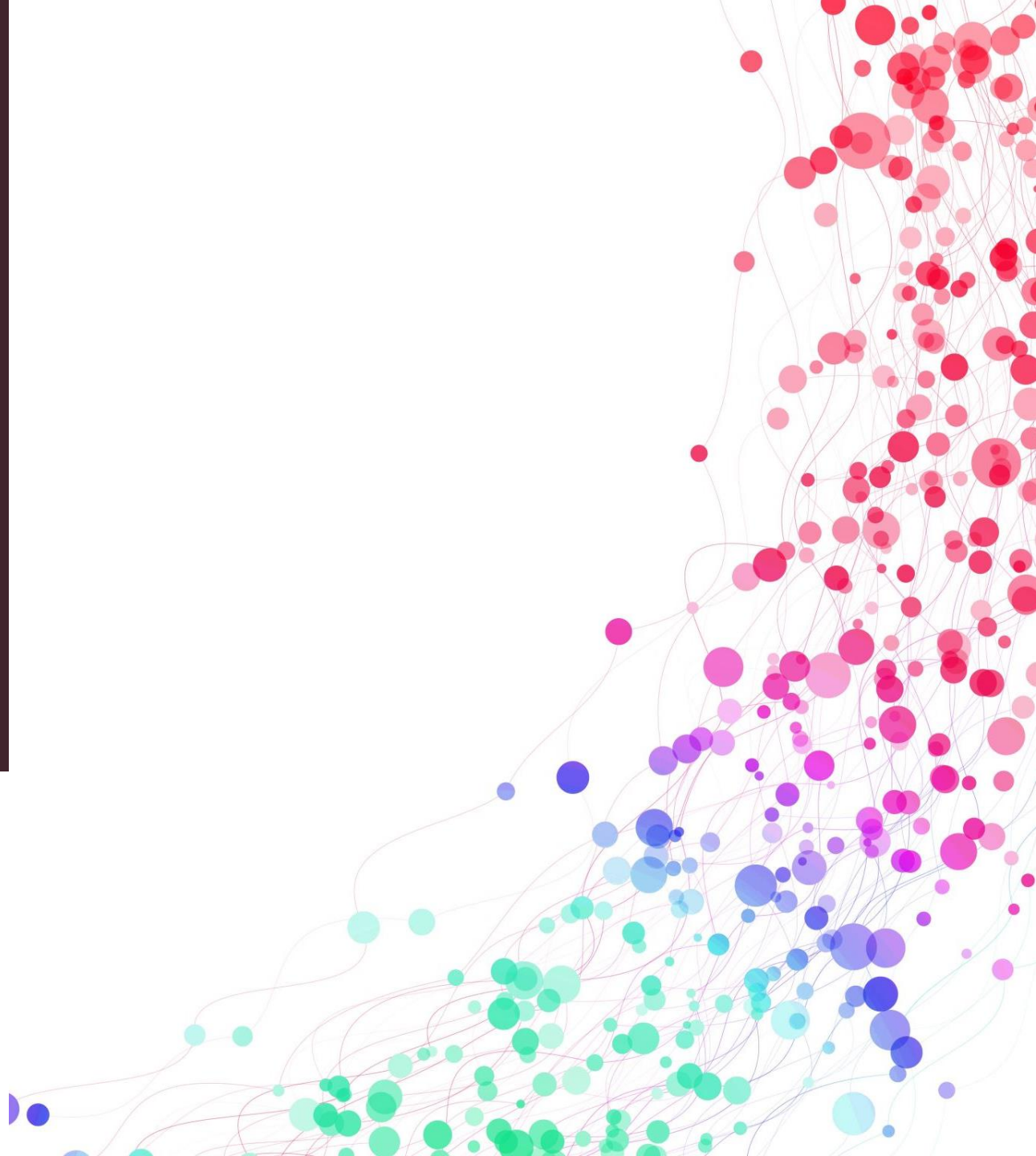
Analysis of the Relationship Between Oxytocin Receptor Mutations, Oxytocin Receptor Binding and Autism

Presented by: Ethan Dayley

Faculty Mentor: Dr. Sara Freeman

In consultation with: Dr. Jill Lundell



Why are we studying autism?

- An estimated 1 in 44 children have Autism Spectrum Disorder (ASD) in the US
- ASD has a huge range of symptom severity, which is why we now call it Autism Spectrum Disorder rather than just autism
- It has a really big impact on people's lives, and by understanding it better we might be able to help people with ASD live better, more fulfilled lives

If it's such a big deal, why haven't we solved this yet?

First off, ASD symptoms are complicated and tightly bound with a huge variety of factors

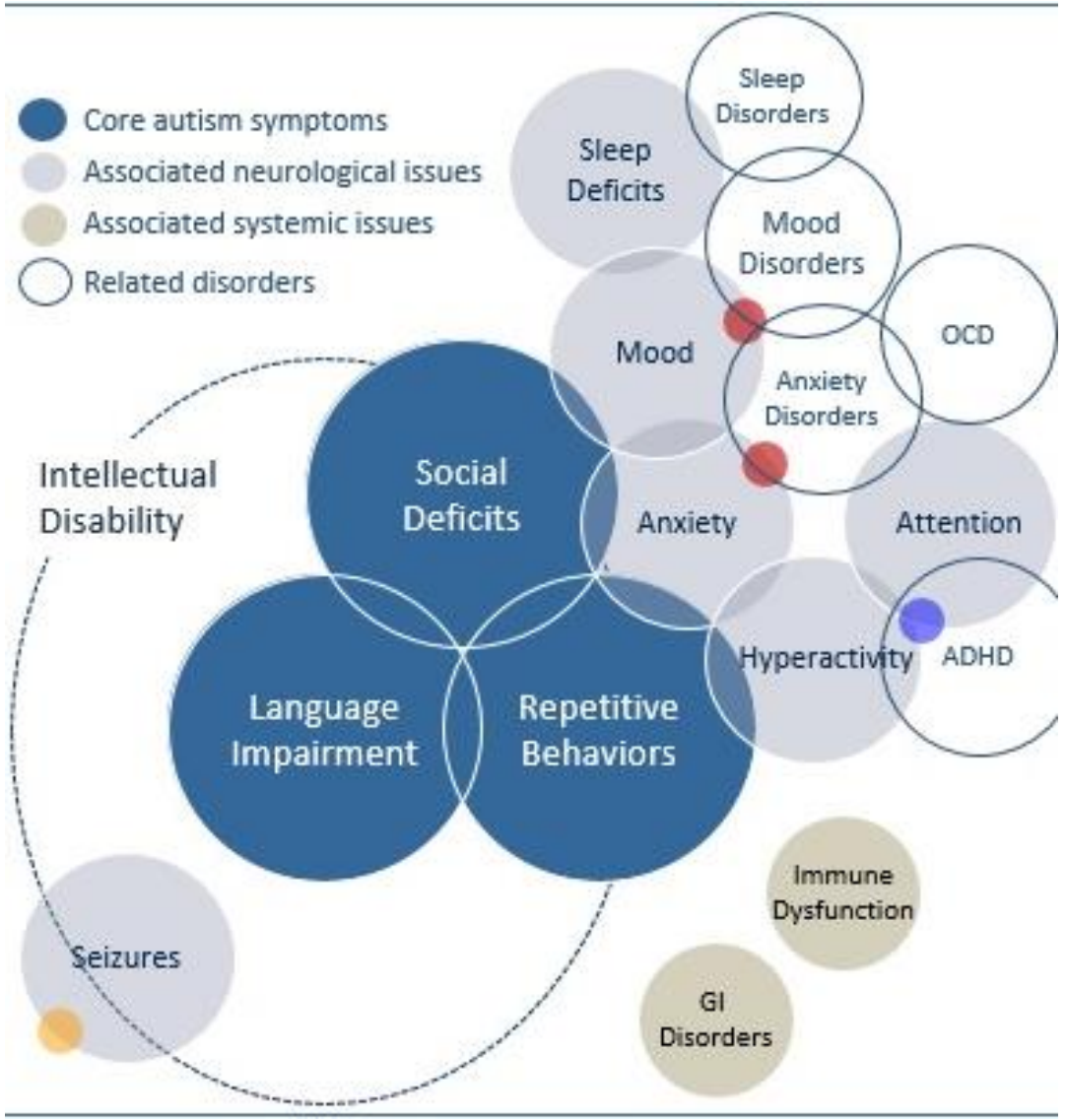


Image showing symptoms of autism

Do their brains look any different?

Interestingly, ASD doesn't seem to cause any obvious differences in macro brain structure.

Image comparing ASD and NT brains
See Haar, et al. (2016)

Well, ok, what about a smaller scale? Are there any likely causes?

The oxytocin hormone is closely linked to social interactions

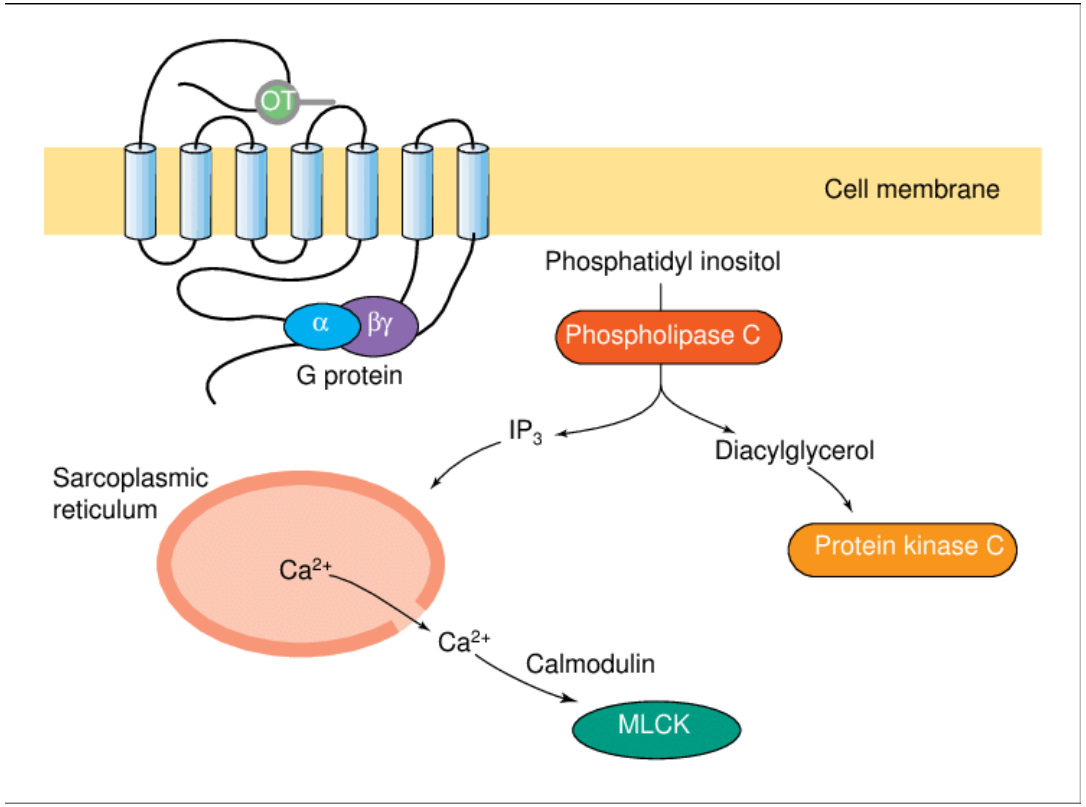


Diagram of oxytocin interacting with an oxytocin receptor
See: Mitchel et al. (1998)

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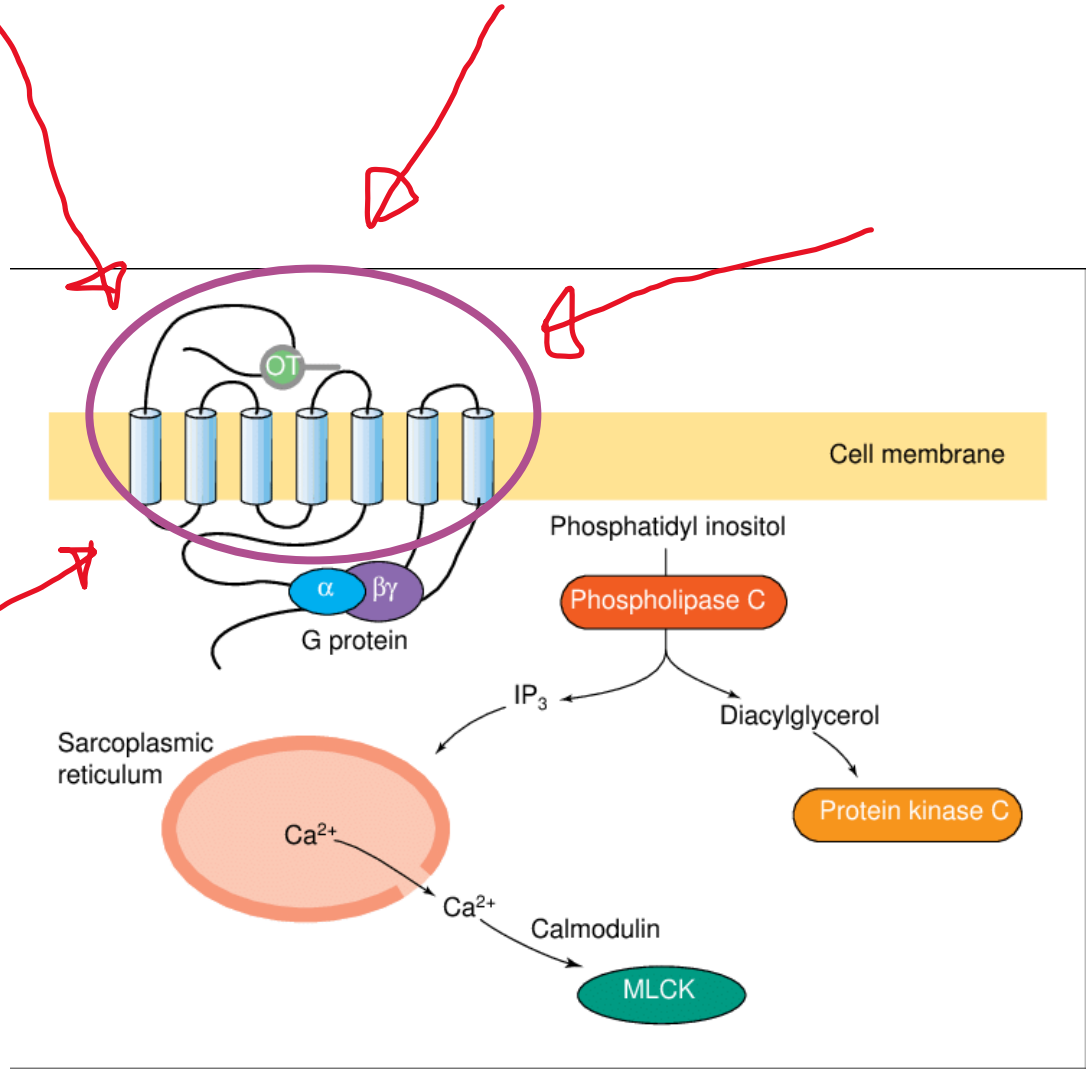


Diagram of oxytocin interacting with an oxytocin receptor
See: Mitchel et al. (1998)

That's… great. Have you actually found anything?

As it turns out, yes!

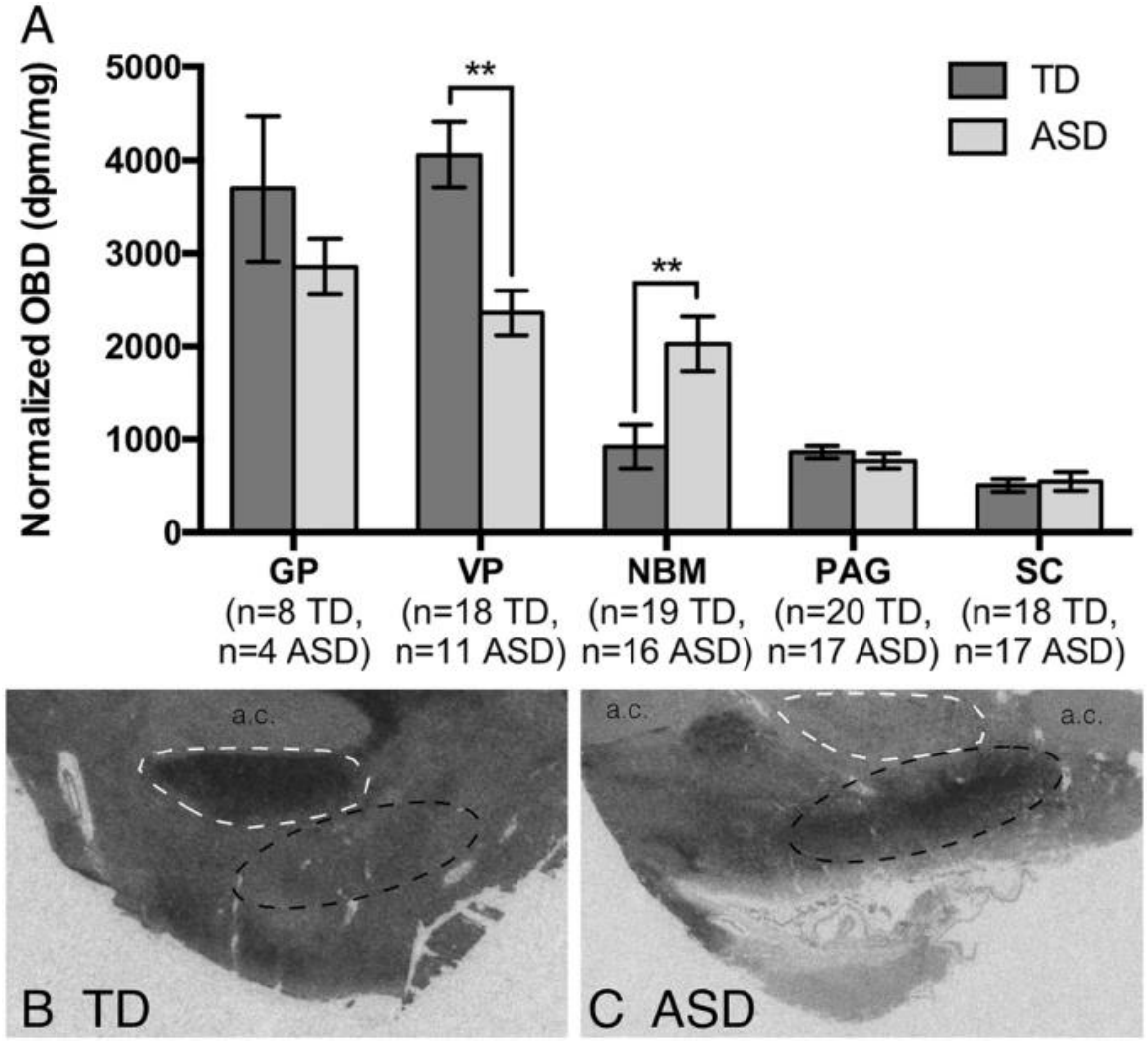


Figure comparing ventral pallidum (VP) and Nucleus Basalis of Meynert (NBM) OXTR binding levels
See Freeman et al. (2018)

Cool, but why just those places?

They’re important for some specific aspects of ASD.

Let’s start with the nucleus basalis.

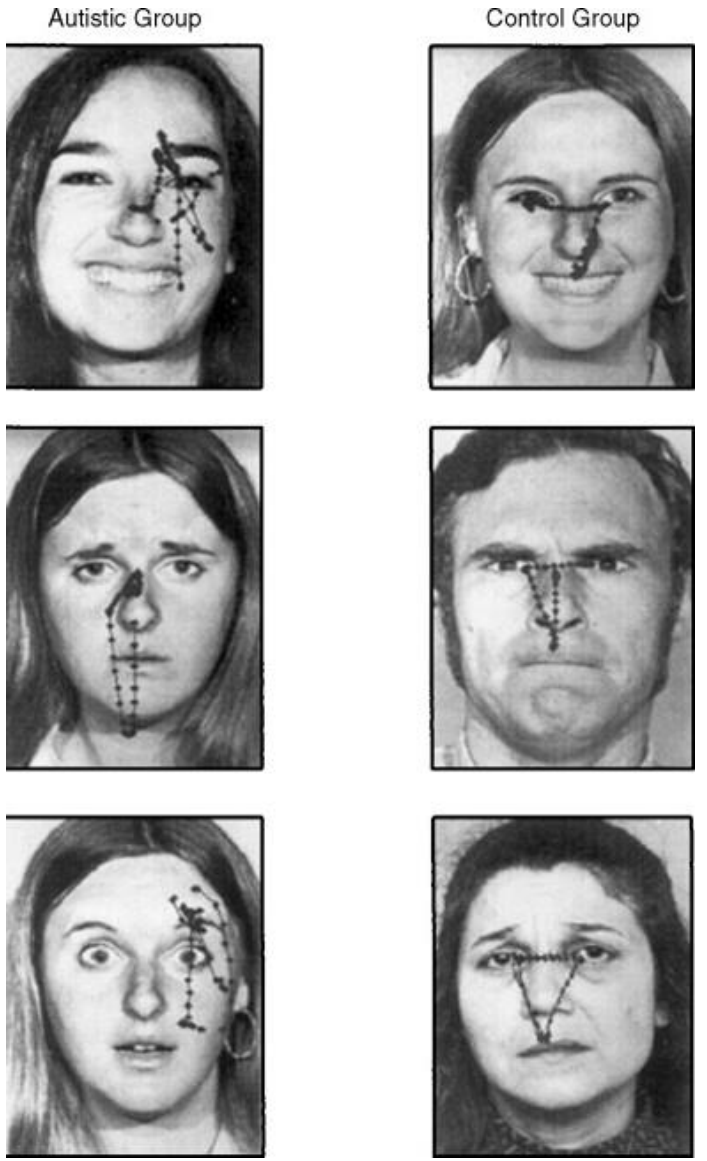


Figure showing differences in gaze between ASD and NT subjects.
See Senju and Johnson (2009)

Ok, but what about the ventral pallidum?

Turns out it also has close ties to ASD behaviors

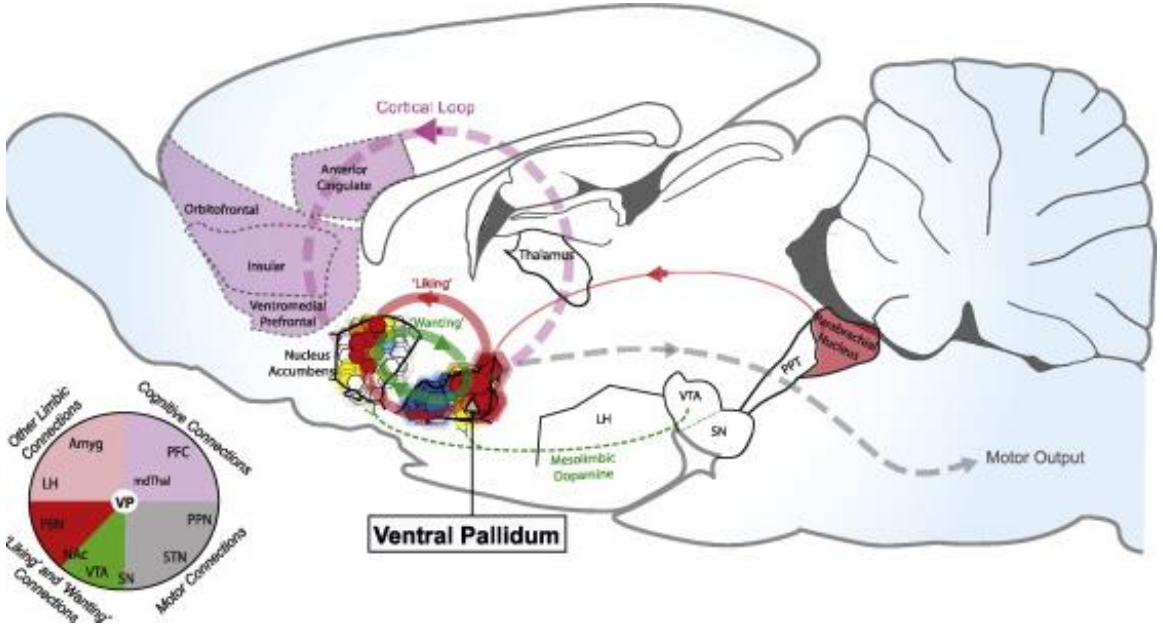
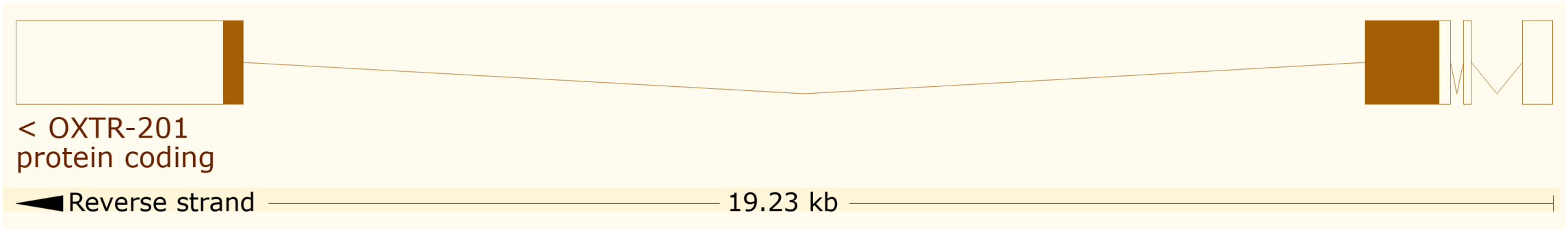


Figure showing ventral pallidum's role in reward pathway.
See Smith et al. (2009).

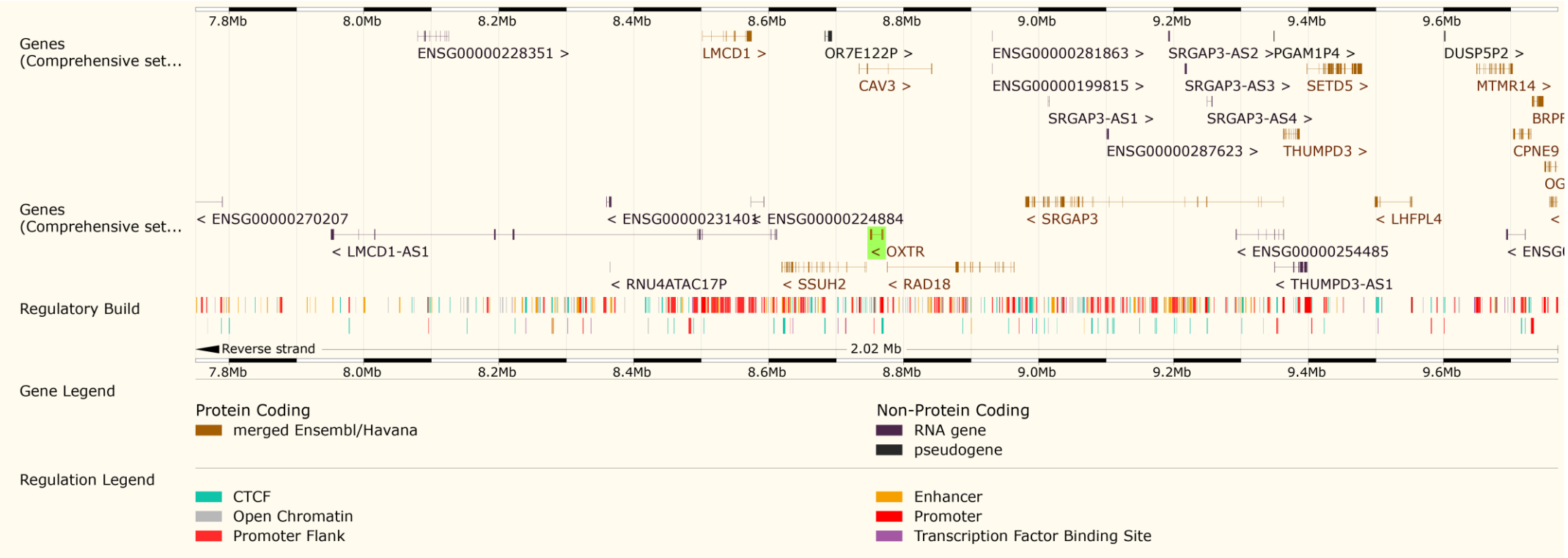
Time out!
Why is this happening?

Let's talk about those SNPs for a second…



OXTR gene diagram
Source: ensembl database, April 2022

…. and the stuff around them



OXTR gene regulation diagram
Source: ensembl database, April 2022

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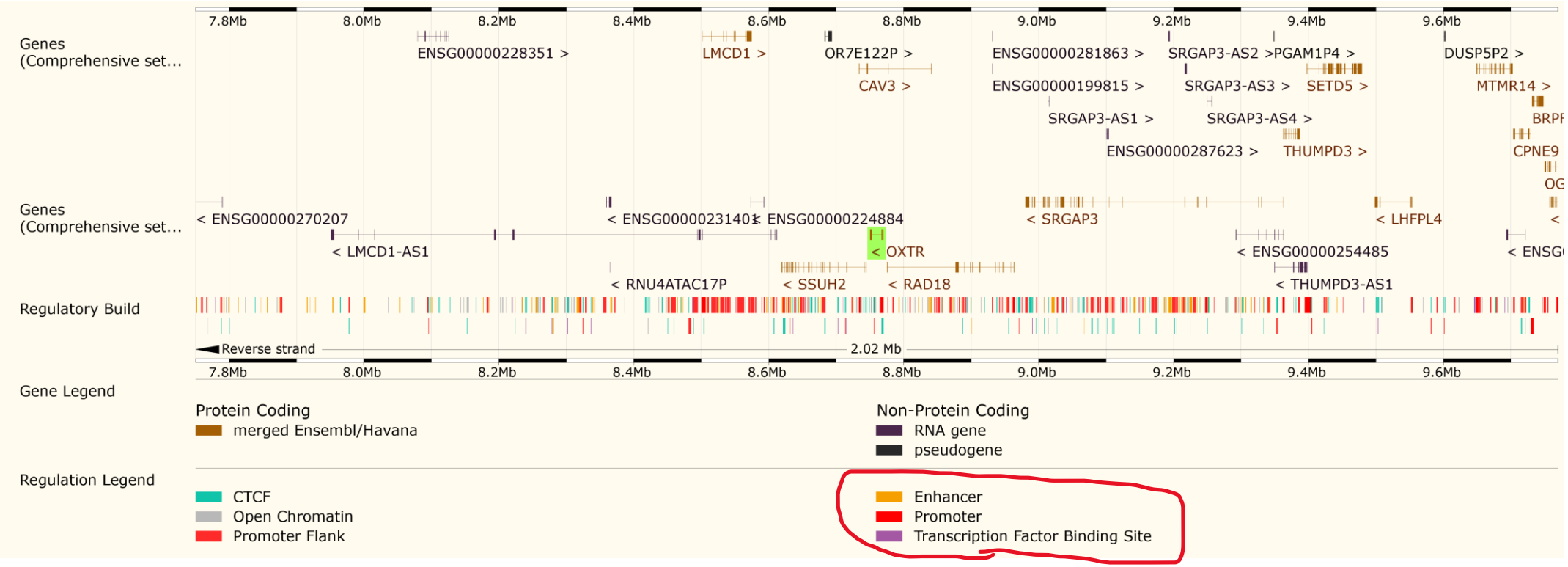


OXTR gene regulation diagram
Source: ensembl database, April 2022

OK, what did you do?

We figured out what SNPs they had!

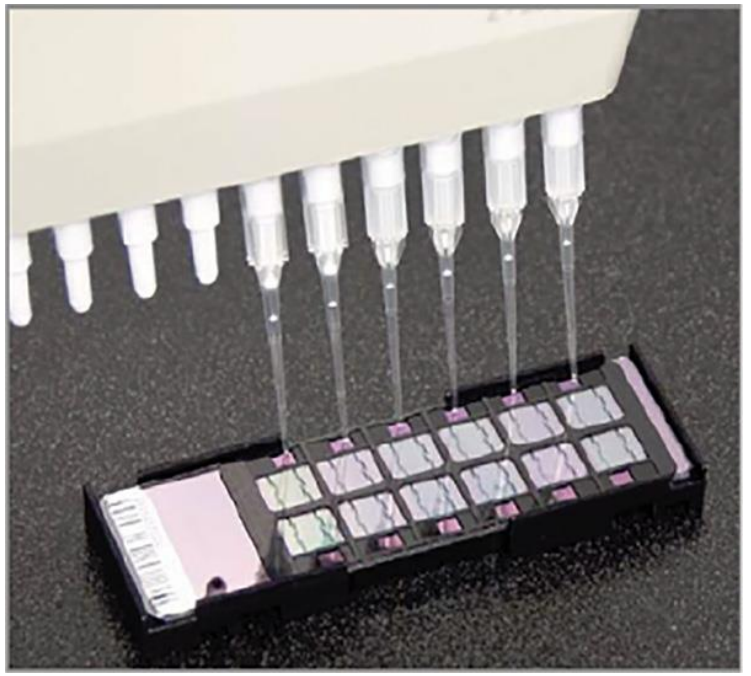
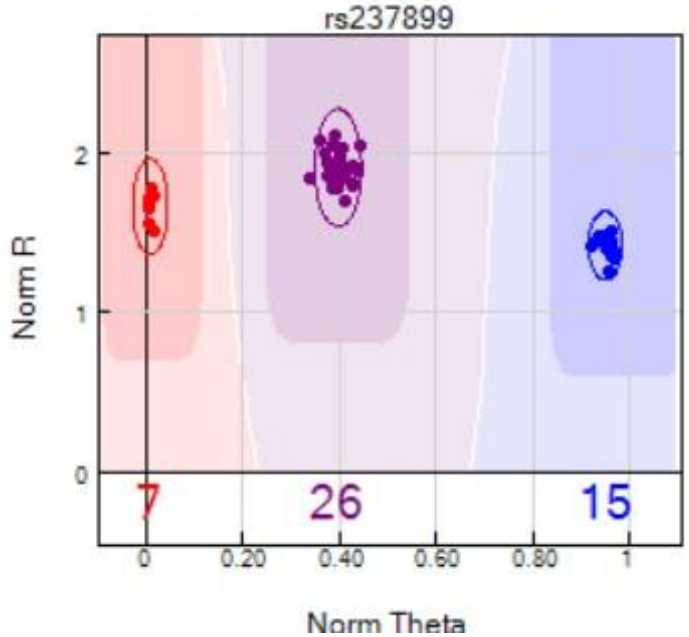
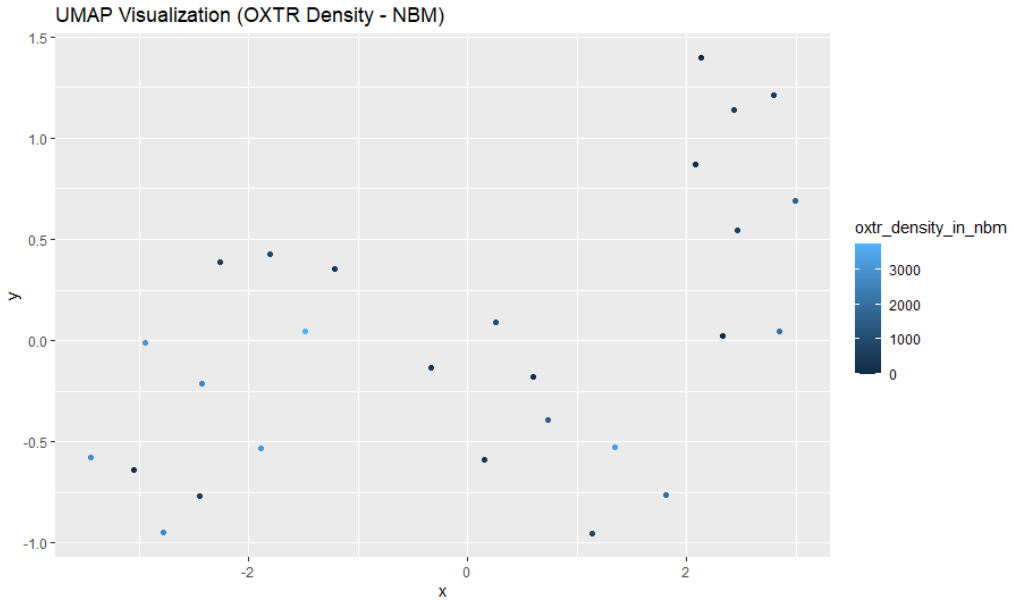


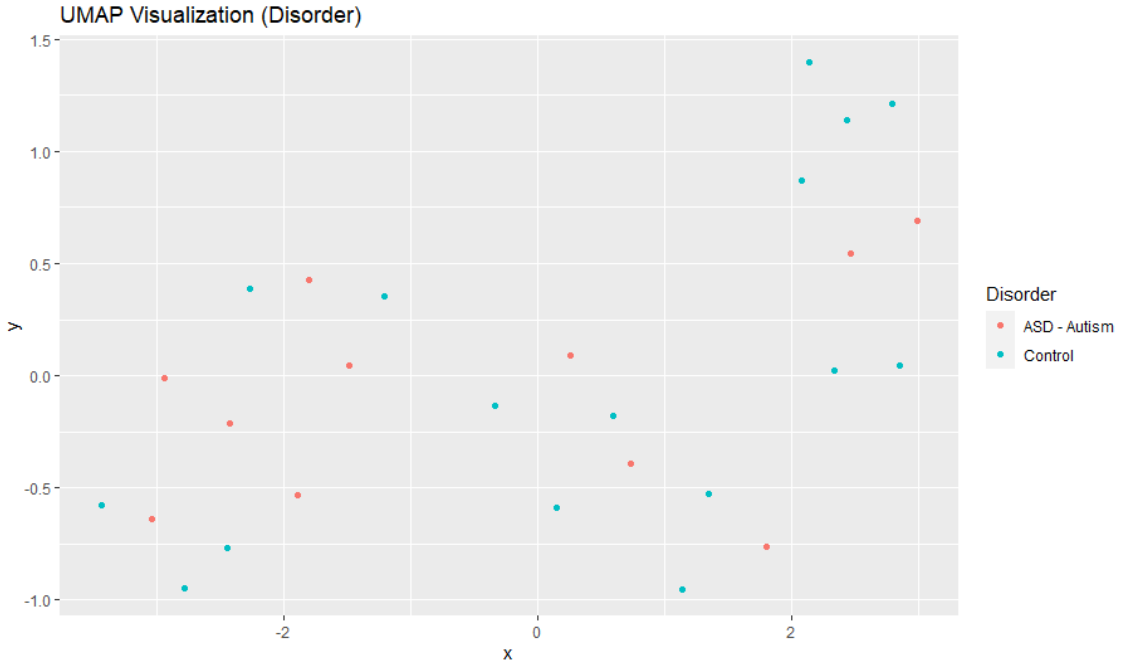
Image of Illumina Infinium Assay

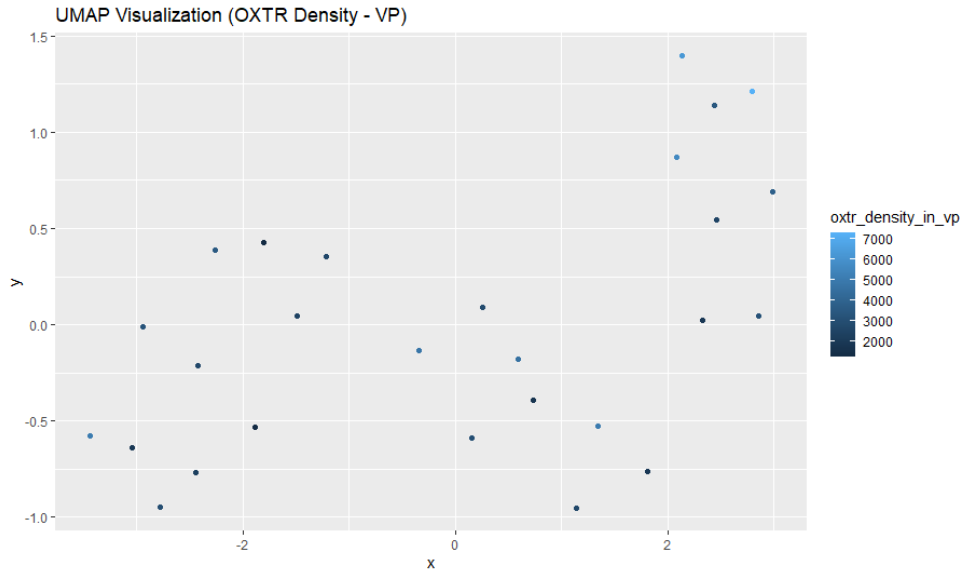
Image of genotype clustering

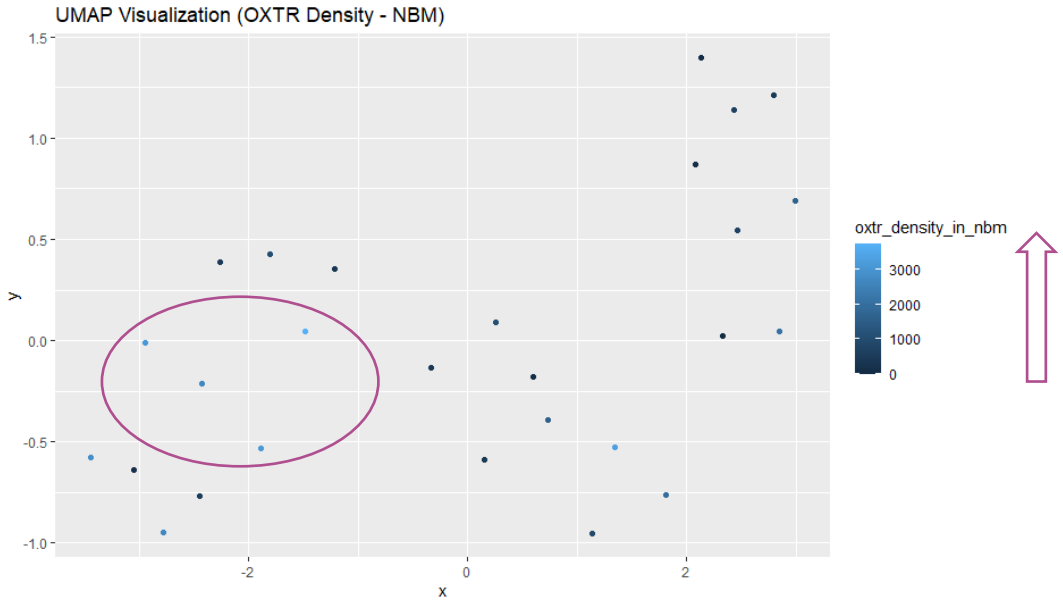


What did we find?


UMAP Visualization (OXTR Density - NBM)
oxtr_density_in_nbm
3000
2000
1000
0
x
y


UMAP Visualization (Disorder)
Disorder
ASD - Autism
Control
x
y


UMAP Visualization (OXTR Density - VP)
oxtr_density_in_vp
7000
6000
5000
4000
3000
2000
x
y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oxtr_density_in_nbm
3000
2000
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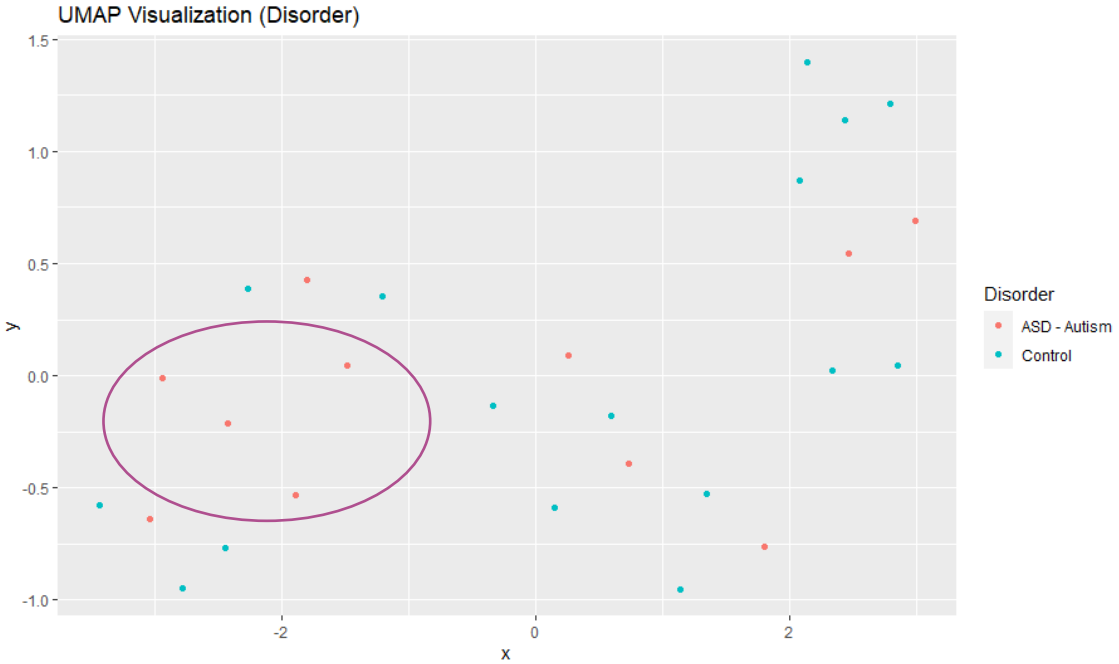
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Disorder
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x
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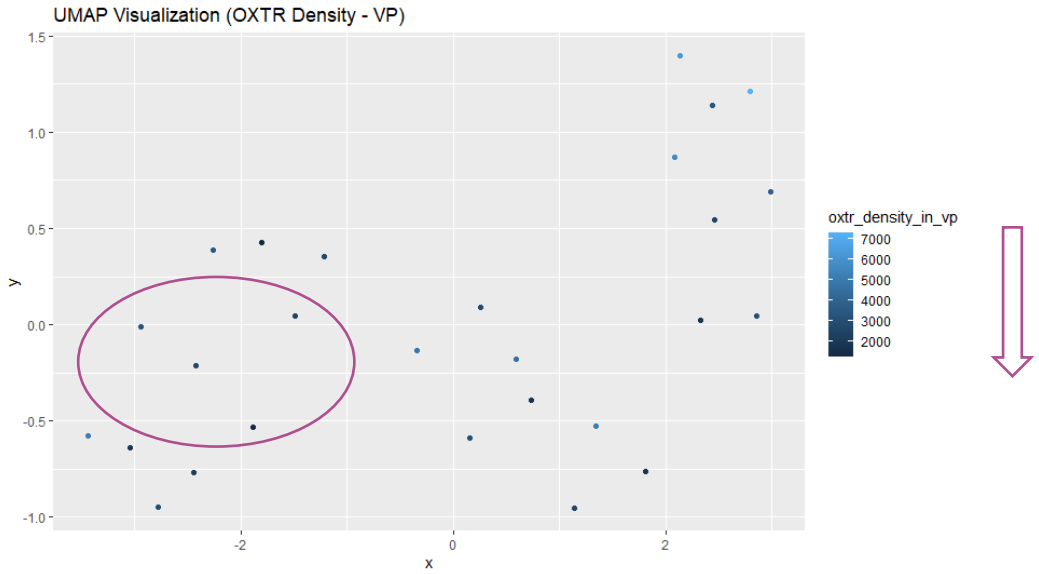
UMAP Visualization (OXTR Density - VP)
oxtr_density_in_vp
7000
6000
5000
4000
3000
2000
x
y

Let's look at some numbers!

```
Call:
lm(formula = oxtr_density_in_nbm ~ . - oxtr_density_in_vp - Sample_ID -
    Disorder, data = red_data_tbl)

Residuals:
    Min      1Q  Median      3Q     Max
-1123.8  -144.4     0.0   130.2  1109.2

Coefficients:
                   Estimate Std. Error t value Pr(>|t|)
(Intercept)         3667.06    7718.11   0.475  0.64399
RaceAfrican American  1337.75    1114.23   1.201  0.25512
RaceCaucasian        725.66    1201.54   0.604  0.55813
RaceHispanic        2039.06    1946.55   1.048  0.31733
Age_yrs               99.61      30.75   3.239  0.00788 **
SexMale             -355.57     508.30  -0.700  0.49875
rs17365093          -539.42     562.25  -0.959  0.35798
rs78062775          -821.28     927.64  -0.885  0.39491
GSA.rs77943865      -683.20    1241.26  -0.550  0.59304
rs2268492            157.53     439.29   0.359  0.72669
rs2268495           -180.18     954.54  -0.189  0.85372
rs2268491           1106.92     635.73   1.741  0.10951
rs34992398          -677.38     758.61  -0.893  0.39101
rs1465386            666.92     668.62   0.997  0.33997
rs2324728            299.79     492.42   0.609  0.55502
rs918316             228.03     967.08   0.236  0.81792
rs34880121         -1337.24     526.54  -2.540  0.02750 *
rs237885            -844.27     701.14  -1.204  0.25381
rs237899            -355.64     684.08  -0.520  0.61345
rs53576              684.50     735.33   0.931  0.37190
rs237891            -442.00     497.63  -0.888  0.39344
GSA.rs61183828      2239.36    1274.38   1.757  0.10664
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 818.9 on 11 degrees of freedom
  (15 observations deleted due to missingness)
Multiple R-squared:  0.8205,    Adjusted R-squared:  0.4778
F-statistic: 2.394 on 21 and 11 DF,  p-value: 0.06848
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(Intercept)        -5211.58    8575.15  -0.608   0.5557
RaceAfrican American  1006.11    1237.96   0.813   0.4336
RaceCaucasian        1052.37    1334.97   0.788   0.4472
RaceHispanic         3236.89    2162.70   1.497   0.1626
Age_yrs               -21.80      34.17  -0.638   0.5366
SexMale              -808.64     564.75  -1.432   0.1800
rs17365093           1343.10     624.69   2.150   0.0546 .
rs78062775           1933.76    1030.65   1.876   0.0874 .
GSA.rs77943865      -3648.21    1379.09  -2.645   0.0228 *
rs2268492            1123.80     488.07   2.303   0.0418 *
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rs2268491            1387.84     706.32   1.965   0.0752 .
rs34992398            735.09     842.85   0.872   0.4018
rs1465386            -388.33     742.86  -0.523   0.6115
rs2324728            -429.51     547.10  -0.785   0.4490
rs918316             -145.04    1074.47  -0.135   0.8951
rs34880121            714.13     585.01   1.221   0.2477
rs237885             -581.93     778.99  -0.747   0.4707
rs237899             1180.25     760.04   1.553   0.1487
rs53576               -87.68     816.98  -0.107   0.9165
rs237891             -593.81     552.88  -1.074   0.3058
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```

So it's figured out then?

It's definitely a start, but let's make sure this makes sense!

Here's what we've found so far:

- There is some structure to the data, but it's not clear-cut
- Subject age and three different SNPs (genetic mutations) seem to be impacting OXTR binding levels
- We can explain about 50% of the OXTR binding variation with the factors we're looking at

What's next?

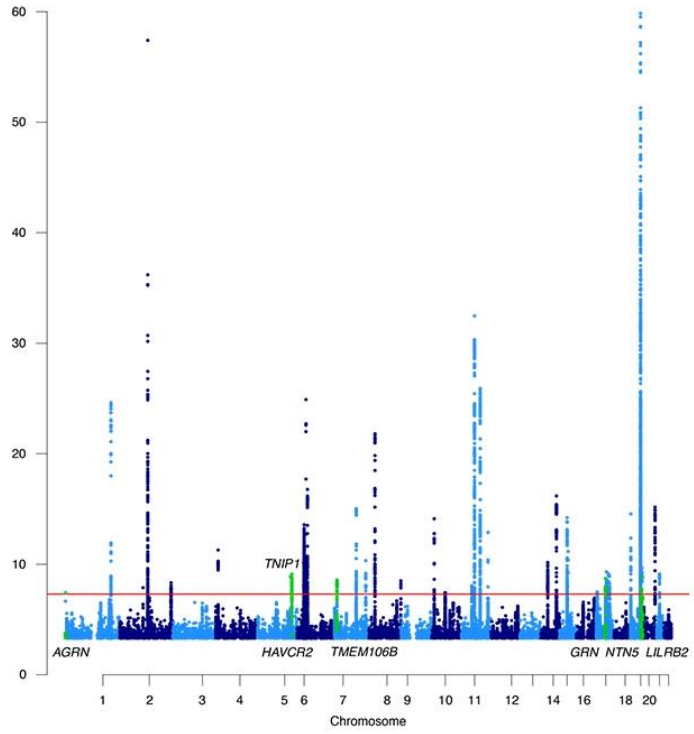

Image of GWAS study

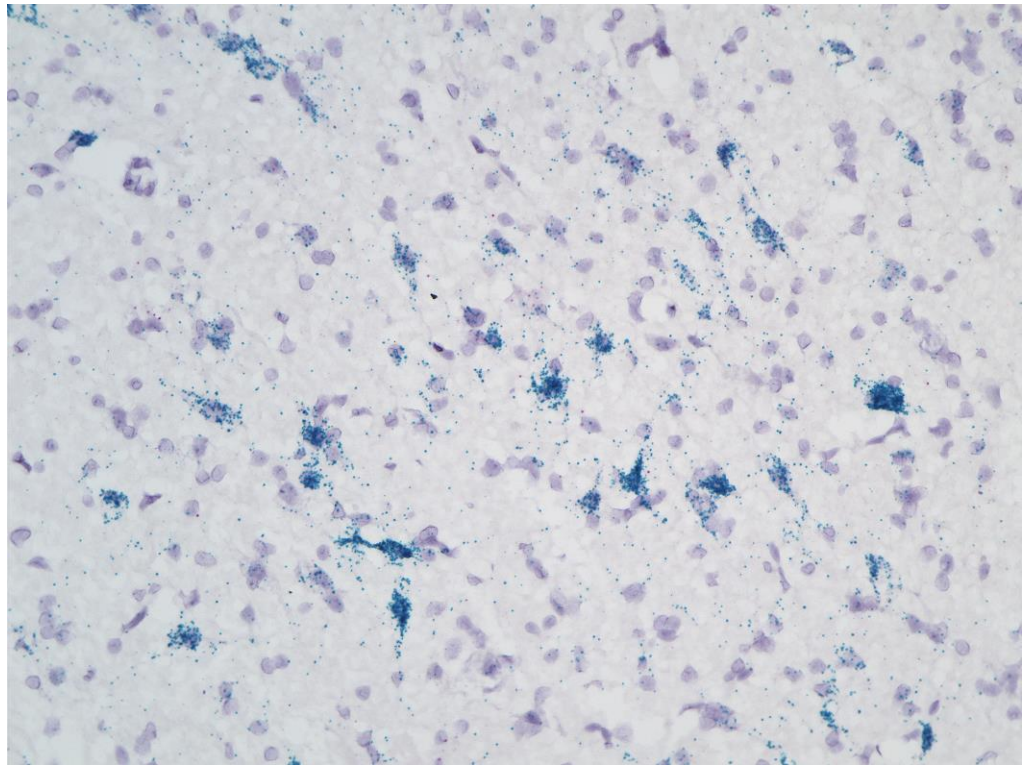

Image of in-situ hybridization conducted in Freeman lab

Citations

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Acknowledgements

- Without Dr. Freeman's support and guidance, none of this would have been possible
- Dr. Lundell provided substantial help with the statistical design of this research project and helped resolve many issues

Questions?

(You can ask me to go back to a slide)

Running out of time to ask your question?
Go ahead and shoot me an email at eedayley@gmail.com.