Role of MCR-2 mutation in altered response to Olanzapine: A pharmacogenomic based Case Study

Vyas Trina*[1,2], Parab Mala*[2], Gupta Subodh[1], Gupta PramodKumar[2].

1. Lords Mark Microbiotech, Hyderabad India
2. School of Biotechnology and Bioinformatics, D. Y. Patil Deemed to be University, Navi-Mumbai India

Background / Case History

14yrs old boy born of non-consanguineous parents, was referred by his consultant for a pharmacogenomic evaluation, with interest to understand his poor response for specific Durg that was administered to him for his anxiety and depression.
Additionally he was diagnosed with Familial glucocorticoid deficiency in 2014 and Epilepsy confirmed in 2023.
Medication of concern in present case is Olanzapine 1.25mg.

Family History

No relevant medical family history recorded.

Birth History

FTLSCS, cried at birth, 2.5kgs, hyperpigmentation skin.

Developmental History

All milestone were attained timely.

Clinical History , General Investigation

2010 - 2012

Symptoms : Deeper skin tone, In contrast to parents and other family members, Recurrent Viral infections.

2013 - 2014

Symptoms : Hypoglycemia, convulsions, decreased hydrocortisol production, Adrenal glands are partially hypofunctional. Observed behavioural issues at school.
Test performed : Blood test measuring VLCFA to rule out Adreno Leuco Dystrophy.
Results : Negative.

2018

Symptoms : Second Incident of convulsions.

2022

Symptoms : Behavioural issues, Reduced sleep depth and duration, conduct issue.

2023

Symptoms : Convulsions, Anxiety, O.C.D.
Test performed : MRI and EEG for epilepsy.
Results : Confirmed the condition.

Drug Administered

Year	Condition	Drug
2013	Adrenal Insufficiency	Hydrocortisone
2023	Epilepsy	Valence 500
2023	Anxiety, O.C.D	OLET 1.25mg

Genetic Diagnosis and Results :

1. CES: Positive for a homozygous “pathogenic” variant, which was detected in exon 2 of the MC2R gene (2014).

(**Description :** Germline pathogenic variations in the MC2R gene have been shown to be associated with FGD1, which manifests as hypoglycaemia, failure to thrive, hyperpigmentation, seizures, learning difficulties and other neurological problems. MC2R gene encodes a member of the melanocortin receptor family, which plays a role in immune function, glucose metabolism and nerve cell signalling in the brain).

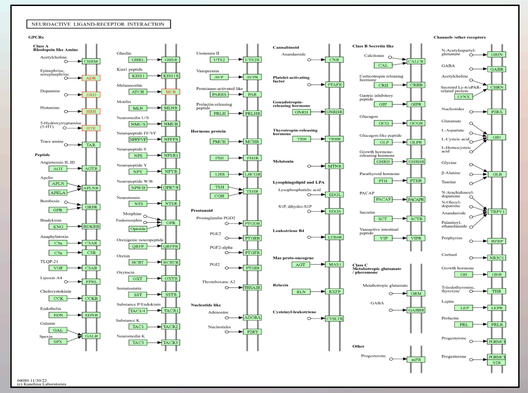
2. Pharmacogenomic test: Good metabolizer for the concerned drug (Olanzapine 1.25mg) (2023).

Gene : CYP2D6

(**Description :** Olanzapine is a second-generation antipsychotic, which acts as serotonin and dopamine antagonist. Dopamine activity is higher in individuals on atypical antipsychotics. Atypical antipsychotic drugs are associated with a lower risk for certain side effects, due to a slightly peculiar mechanism. This is because dopamine neurotransmission is not compromised, which reduces the probability of motor and cognitive impairment.)

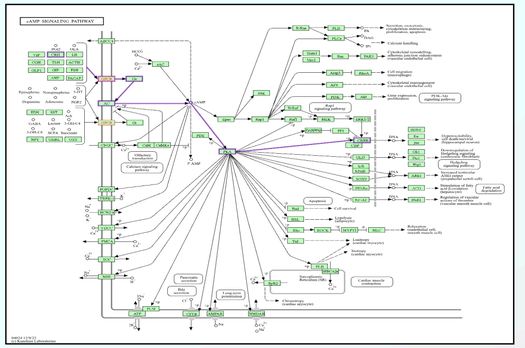
3. In-silico analysis: Preliminary *in-silico* screening revealed, mutations in MCR-2 can alter cellular drug response (2024).

(**Description :** It is postulated in present case study that, altered gene may alter molecular dynamics of the drug-gene interactions, as both cAMP signaling pathway and Neuroactive ligand-receptor interactions as both are mediated by MCR-2 and DRD-1 gene.)

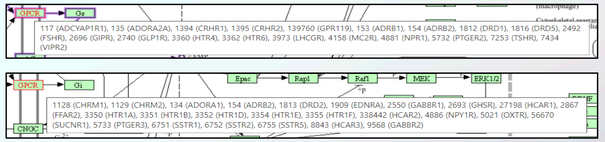


Neuroactive Ligand-Receptor interaction all the targets, ligand and MC2R (Red color highlight) are involved. ADR, DRD, HRH, HTR, MCR are identified.

Olanzapine involvement was found in neuroactive ligand-receptor, serotonergic synapse and dopaminergic synapse pathways.



cAMP signalling pathway GPCR is involved with DRD1, MC2R. This has potential effect on interaction between all the protein involved in the system / cascade and hence affects the drug interaction.



Conclusion

Drug binding to a nonspecific sites prohibits the drug from binding to the required receptor and thus inactivates the drug, provides altered response or reduces its effect. In this case the drug is potentially binding to ligand-receptor due to MC2R mutation that is providing a reduced response which is not beneficial for the patient.

Genetic Counselling

PGx report was explained to the consultant and parents, conversing that the patient is a good metabolizer for Olanzapine, however the presence of the altered gene is resulting in non-specific binding leading to reduced response of the drug. Consultant made the decision to continue with Olanzapine according to the report and Additionally established a new regime by adding Fluvoxamine. Fluvoxamine may significantly increase the blood levels of Olanzapineapine this lead to an increase in therapeutic effect and reduces adverse effects with a lower dosage for the patient.

Overview

This case highlights how, determining who will react positively to a given treatment for a condition or who won't respond at all, and who may experience adverse drug responses or serious side effects can be difficult at times. Conventional medicine frequently ignores individual genetic variations in favour of clinical trials and population averages. With assistance of pharmaco-genomic and genetic counselling we could collectively avoid trial and error and provide accurate medicine according to individual genotype. This approach benefited the patients by helping them reduce treatment duration and side effects with right drug and dose.