Impulsivity is a trait that is found as a symptom in various psychiatric disorders and neurodegenerative diseases and is associated with addictive behavior such as substance abuse [1,2]. The dopamine receptor D2 (DRD2), a G protein-coupled receptor, is hypothesized to be linked to impulse control. Studies in animal models have shown that DRD2 levels are inversely related to impulsive behavior [3]. In humans, various association studies have described correlations between different DRD2 alleles and impulsivity-related behavior like drug addiction [4] and smoking [5]. However, there are also association studies that report no significant correlations between DRD2 and impulsivity-related behavior. Conflicting results may possibly be due to complex regulatory mechanisms of DRD2. As an example, various polymorphisms in the DRD2 gene have been suggested to influence the severity of impulsivity-related behavior and antipsychotic treatment effectiveness [5,6]. Also, there are two major DRD2 isoforms, with a third isoform having been more recently identified in individuals who died with psychosis. This third isoform may possibly be due to abnormal splicing [7].

Because the molecular mechanisms related to the onset of impulsive behavior have not been extensively characterized, the **primary goal** is to elucidate how regulation of DRD2 at the transcript and protein level may lead to impulsive behavior. It is **hypothesized** that DRD2 regulation influences impulse control and responsiveness to certain compounds. The **long-term goal** is to be able to characterize the role of DRD2 in the context of psychiatric illnesses and neurodegeneration, which can help in the development of therapies to offset impulse control dysregulation that is characteristic of those illnesses.

**Specific Aim 1**: To study the prevalence of the third DRD2 variant.

Approach: Obtain mRNA from post-mortem brain tissue of individuals placed into three groups: One control group, one group of subjects with history of substance abuse, and one group of subjects with psychiatric illnesses. Then, perform RNA-Seq to quantify the abundance of the third DRD2 mRNA variant. The DRD2 isoforms can also be quantified by quantitative mass spectrometry.

Hypothesis: The third DRD2 variant is more prevalent in subjects with impulsivity-related behaviors and psychiatric illnesses compared to the control group.

**Specific Aim 2**: Identify novel proteins that may interact with DRD2.

Approach: Perform affinity purification mass spectrometry (AP-MS) on DRD2 protein samples to identify other proteins that interact with DRD2. The interacting proteins identified can be compared to STRING—a protein interaction database—to uncover novel interacting proteins.

Basis: Impulse control pathways are regulated by proteins that interact with DRD2.

**Specific Aim 3**: To study the relationship between gene polymorphisms and DRD2 protein affinity to specific compounds.

Approach: Perform genotyping on individuals with different *DRD2* gene polymorphisms. Then, create human cell lines expressing the different polymorphisms by editing their genomes with the CRISPR-Cas9 system based on the sequences obtained from the individuals. Isolate the DRD2 proteins expressed by the cell lines, and test their affinity for compounds known to interact with DRD2.

Hypothesis: Different *DRD2* gene polymorphisms result in DRD2 proteins that have varying levels of affinity to a compound.

Dopaminergic pathways are very complex, which makes it difficult to study multifactorial traits like impulsivity. This project aims to elucidate some aspects of DRD2 regulatory mechanisms, which include its different isoforms and interactions with other proteins and compounds. Although DRD2 is only a small part of the larger dopaminergic network, studying it will give insight to impulse-related behavior and ultimately, psychiatric disorders and neurodegenerative diseases that are associated with the trait.

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