A Study of any Possible Relationships Between 7-DHCR and Hemochromatosis

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Smith Lemin-Optiz Syndrome (SLO) is a recessive autosomal linked genetic disorder (Smith, 1964 #1). It arises due to mutations in the 7-dehydrocholesterol reductase gene located on chromosome eleven. (Wassil, 2005 #4) When both alleles are mutated the result is SLO syndrome which causes an inability in the affected individual to biosynthesize cholesterol. This lack of cholesterol leads to varying symptoms depending on the severity of the case. Not all SLO patients lose the ability to biosynthesize cholesterol entirely, the severity of the SLO is typically diagnosed as SLO type I or II type II being more severe and most often fatal. (Peneden, 1997 #5) (Porter, 2003 #6) Symptoms most often include various physical and/or mental retardations including but not limited to cleft palate, malformation of extremities and genitalia and a general failure to thrive often resulting in early death. Recent studies have lead to the development of prenatal diagnosis and treatment of the syndrome. (Nowaczyk, 2001 #8) One can help compensate for the lack of natural cholesterol by increasing the amount of dietary cholesterol consumed by the individual which has lead to improvement in the condition of the patients.

An aspect of the 7-DHCR mutations that is of particular interest from a genetic standpoint is that the mutation is believed to exist quite prevalent in the general population through heterozygote carriers, with an estimated 3% of all alleles being mutant. This leads us to question whether or not an evolutionary advantage exists in being a heterozygote carrier of SLO similar to the noted resistance to malaria seen in individuals who are heterozygote carriers for mutations that can cause sickle cell anemia. (Luzzatto, 1970 #7)

These suspicions have lead to a detailed phenotype study of individuals known to be heterozygote for 7-DHCR mutations. This study was conducted here at the University of Utah in the Eccles Institute of Human Genetics building by various staff including the faculty sponsor for this project Dr. James E Metherall. The study noted one consistent abnormality amongst test individuals - abnormally elevated levels of iron in their blood. (unpublished results)

These studies lay the foundation for my project, an investigation into a possible link between being a heterozygote carrier for SLO and severity of hemochromatosis symptoms. The project involves replicating, cleaning, and sequencing 7-DHCR genes from individuals diagnosed with hemochromatosis, a disease in which the body’s ability to regulate iron levels in the blood is compromised, resulting in extremely elevated levels of iron. (Curtori, 1950 #9) Should mutations be found, the sequencing of this DNA will hopefully illustrate any existing links between the two disorders. For example, if the 7-DHCR mutations are found in patients with especially severe hemochromatosis symptoms, this would suggest that the 7-DHCR mutations contribute to the severity of the hemochromatosis symptoms. Discoveries made here may lead to subsequent studies leading to possible treatments for these disorders similar to the prenatal treatments that have been developed. It is conceivable that, if indeed being a carrier of SLO exacerbates hemochromatosis symptoms, treating for SLO as well as hemochromatosis, may help relieve the symptoms of the patients.

At this time no decisive information exists to strongly suggest the effect or lack of effect that being a SLO carrier has on hemochromatosis symptoms so therefore no informed hypothesis can be proposed at this point. This is an investigative experiment which will hopefully reveal a link between these mutations. Should such a link present itself through this project, then specific hypotheses can be offered and tested. Enclosed are the experimental procedures followed in the reactions of this project. All primers for both PCR and sequencing were purchased from IDT laboratories and the reagents for sequencing were purchased from ABI laboratories. The DNA used in this project was obtained from Dr. Kushner in the hematology department at the University of Utah hospital.