Programa de Ayudas del GHEP-ISFG para Intercambios de Formación

Title: "A Mathematical Framework for Genetic Relatedness Analyses Involving X Chromosome Aneuploidies with Linked X-STRs"
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Purpose of the trip:
The main objective of this internship was to extend the mathematical framework established to evaluate the DNA evidence of independent markers, in pairwise kinship analyses where one of the individuals has an X chromosome aneuploidy (Trisomy X, Klinefelter and Turner syndrome) (Faustino et al., 2025). The goal was to consider the dependency between closely located markers within pedigrees (linkage) and across the population (linkage disequilibrium). Linkage needs to be accounted, as research has shown that markers between clusters/linkage groups are not completely independently transmitted (Nothnagel et al., 2012), since the recombination rate between some clusters is below 50%. Furthermore, we aimed to allow the evaluation of all 12 X-STRs from the Investigator® Argus X-12 Kit - the most used commercial kit, also considering dependencies within linkage groups. Argus X-12 markers are divided into four clusters/linkage groups, each containing three tightly linked markers, which are transmitted in block/haplotype. Since some haplotypes are more prevalent in the population than others due to linkage disequilibrium, it is necessary to use haplotype frequencies instead of allele frequencies. By considering both linked and linkage disequilibrium, we can attain a higher statistical power of the results when compared to using unliked markers alone, since more markers will be considered (twelve instead of the maximum of four unliked markers) they have a higher number of haplotypic possibilities.

Main results of the exchange:
During my stay at the Rättsmedicinalverket, I collaborated with my co-supervisor, Dr Daniel Kling, to adapt the version of the Lander-Green algorithm for linked markers, developed for euploid individuals (Kling et al., 2014), to accommodate those with a Trisomy X. This was implemented in a R program to calculate the likelihood of the DNA evidence given a certain hypothesis. The program considers the probability of each inheritance pattern and the corresponding transition between them, using recombination rates. Additionally, we began developing another program to consider also linkage disequilibrium where haplotypic frequencies are used instead of allelic ones, to "simplify" we assumed that recombination doesn't occur within clusters. This internship allowed me to start developing programs in R that will allow the scientific community to evaluate the weight of the DNA evidence in kinship analyses when one individual has Trisomy X considering linked X-STRs that may be in linkage disequilibrium. We will now adapt it to consider individuals with the Klinefelter or the Turner syndrome. The theoretical framework and the correspondent informatics tools will be freely available and announced through a peer-reviewed publication.

Bibliography:

Faustino, M., Gusmão, L., Amorim, A., Kling, D., & Pinto, N. (2025). A mathematical framework for genetic relatedness analysis involving X chromosome aneuploidies. *Forensic Science International: Genetics*, *74*, 103128. https://doi.org/10.1016/j.fsigen.2024.103128

Kling, D., Tillmar, A., Egeland, T., & Mostad, P. (2014). A general model for likelihood computations of genetic marker data accounting for linkage, linkage disequilibrium, and mutations. *International Journal of Legal Medicine 2014 129:5*, *129*(5), 943–954. https://doi.org/10.1007/S00414-014-1117-7

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