

***In silico* mapping of a Charcot-Marie-Tooth Disease gene in a Pedigree of**

Hong Kong Chinese

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Abstract Submission

Nowadays high throughput biotechnologies and biological data-mining methods are greatly facilitating identification of human disease genes. Compared with traditional disease gene mapping strategy, a combination of high throughput genotyping technology and data mining method can dramatically reduce the cost of research in terms of time and money.

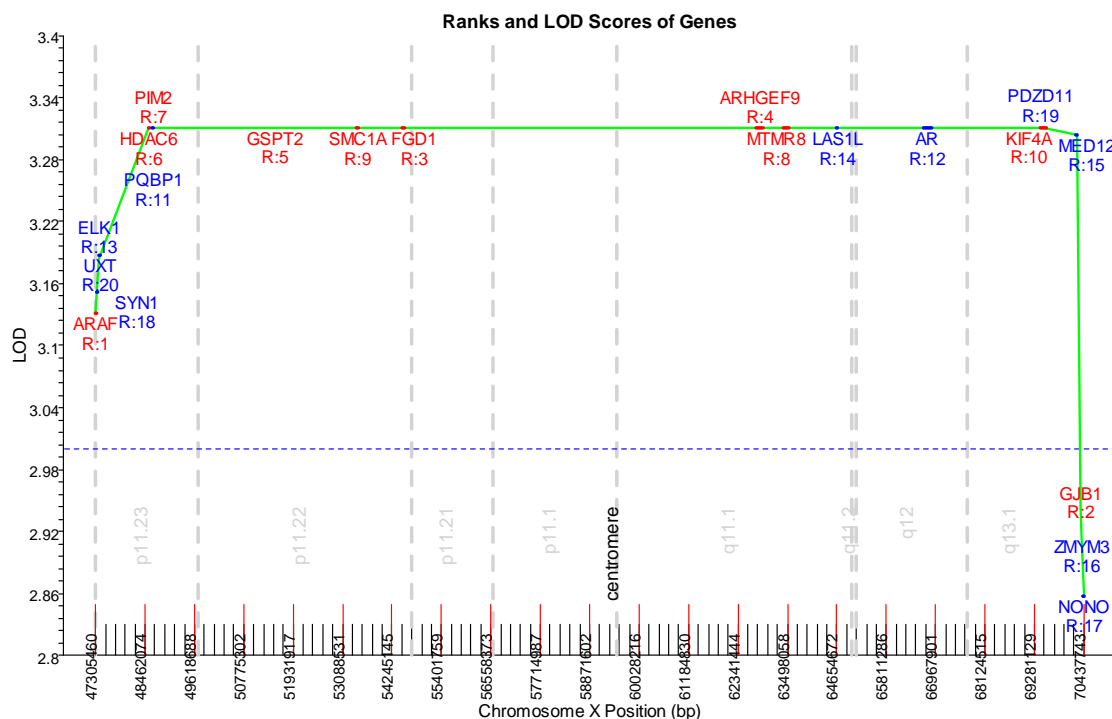
In order to unravel an underlying Charcot-Marie-Tooth (CMT, an inherited degenerative disorder of the peripheral nervous system with large clinical and genetic heterogeneity) disease gene (Hentati *et al*, 1992; Huttner *et al*, 2006) in a median-sized pedigree of Hong Kong, GeneChips with dense SNP markers were used for a genome-wide multipoint linkage scan. The gene chips including 7 Illumina Human Linkage IVb Panels (<http://www.illumina.com>), 3 Affymetrix 50k Xba and 8 Affymetrix 250K Nsp GeneChips (<http://www.affymetrix.com>). Genotypes from these GeneChips and HapMap datasets (<http://www.hapmap.org/>) were integrated by our newly-developed software package, named IGG (<http://bioinfo.hku.hk/iggweb/>) for a comprehensive analysis. The linkage scan was performed by Merlin (Abecasis *et al*, 2002). Based on the linkage scan, ENDEAVOUR, a tool to prioritize disease genes through genomic data fusion (Aerts *et al*, 2006) from 10 sources such as BIND protein interactions, KEGG pathways and Transcription factor binding sites (TFBS), was utilized to select genes for further functional mutation detection after trained by 33 known CMT genes.

In the genome-wide linkage results, a ~12-centiMorgan region on chromosome X with logarithm of the odds (LOD) score over 3 was detected, indicating a X-linked dominant CMT disease model (Spray and Dermietzel, 1995). In this region 191 genes were prioritized by ENDEAVOUR and GJB1, a well-studied CMTX gene (Kleopa and Scherer, 2006), was at second place of the prioritized list. Most likely the gene is the underlying causative gene for this pedigree, subjecting to the verification by sequencing. Figure 1 shows the top 20 prioritized genes. This insightful prioritization will be of great benefit to a subsequent sequencing work, which is underway, to efficiently identify potential functional mutations in this pedigree.

This study combines available high throughput genotyping technologies, accumulated biological resources, and advanced data mining methods to speed up the process of disease gene identification. Once the disease gene is proven in the top-10 or even top-20 gene list soon, it will

be regarded as a successful pioneer in the identification of human disease genes in the post-genome era.

Figure 1: The top-20 prioritized gene generated by ENDEAVOUR and their LOD scores (green line) from Merlin. Genes are mapped in the human reference genome (build 36), their length corresponding to the length of segments in the plot. Their HGNC Symbols are shown, followed by the ranks (R:?). The top-10 genes are in red and the remainders are in blue.



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