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A Insilco Study on Human Mitochondrial DNA of Different Ethnic Population Identifying the Polymorphisms, Haplogroup and Evolutionary Relationship

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Abstract

Mitochondria are small energy-producing organelles found in cells. Mitochondria have their own DNA molecules, entirely separate from our nuclear DNA with independent function. Human mtDNA consist of 16,569 base pairs with 37 genes, 13 proteins (polypeptides), 22 transfer RNA (tRNAs) and two ribosomal RNAs (rRNAs) and has been completely sequenced by Anderson et al., 1981. This insilico study was focused on identifying the polymorphism, haplogroup and evolutionary relationship among the different ethnic population and the polymorphisms were identified among them, haplogroup were grouped and the Phylogenetic analysis were performed in identifying the evolutionary relationship. Conclusion: Among the selected 40 different ethnic population 4 different population were effected with a mtDNA gene polymorphism which are responsible for causing the hereditary diseases.

Introduction

In July 1997, the first successful extraction of Neandertal DNA was set by team of German and American researchers led by Svante Pääbo (Krings et al., 1997). They have extracted mitochondrial DNA (mtDNA) from a piece of bone cut from the upper

arm of the first recognised Neandertal fossil, the individual found at the Feldhofer grotto in the Neander Valley in Germany in 1856 (Kahn and Gibbons 1997, Ward and Stringer 1997).

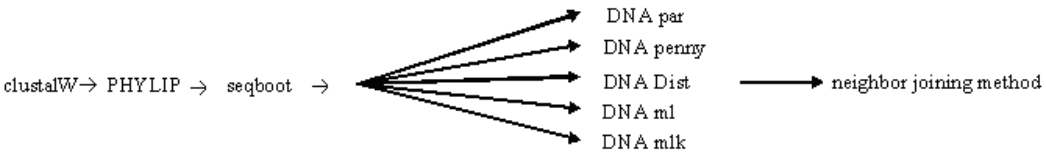
Mitochondria are small energy-producing organelles with their own DNA molecules, found entirely separate from our nuclear DNA with independent function (Grivell LA 1983). Most of these cells contain nearly 500 to 1000 copies of the mtDNA molecule, which makes it more easier to find and extract than the nuclear DNA does. Human mtDNA genome consists about100-10,000 copies per cell, with each circular molecule consisting of 16,569 base pairs with 37 genes, 13 proteins (polypeptides), 22 transfer RNA (tRNAs) and two ribosomal RNAs (rRNAs) and has been completely sequenced by Anderson et al., (1981). Degenerative diseases (Yen et al., 1989; Cooper et al., 1992; Bowling et al., 1993; Brandon et al., 2005) involving the central nervous system, heart, muscle, endocrine system, kidney, liver and cancer have been associated with systemic mtDNA mutations, by either base substitutions or insertion-deletions (Feng et al., 2009, Tan et al., 2002; Lee et al., 2004; Sangkhathat et al., 2005; Dimauro and Davidzon 2005). Diseases resulting from base substitutions are generally maternally transmitted, consistent with the maternal inheritance of the mtDNA (Giles et al 1980). Insertion-deletion mutations can be spontaneous maternally inherited or mendelianly inherited due to predisposing nuclear mutations (Brandon et al., 2005), the genome accumulates mutations at a linear rate over time, the polymorphisms represent a sort of molecular clock: the more polymorphisms that differ between two person's mtDNA, the longer ago in the past they shared a common ancestor compared to with the revised Cambridge Reference Sequence, (rCRS) (http://www.cagetti.com/Genetics/reportmtdna.pdf).

Y Chromosomes Consortium (2002) determined the haplogroups are genetic population groups that identify the Y-DNA or mtDNA tree of humanity emerges as a major branch from the family tree of Homo sapiens. Y-DNA haplogroup is defined as all of the males and mtDNA haplogroup is defined as all of the females descendants of the single person who first showed a particular polymorphism. These haplogroup branches characterize the early migrations of population groups (Underhill and Kivisild., 2007).

Methodology

The sequences were retrieved from the website Genpat - mtDB - Human Mitochondrial Genome Database (http://www.genpat.uu.se/mtDB/). This web site consists of the whole sequence of human mtDNA of different population of different regions with the reference and GenBank accession number.

Multiple sequence alignment was done using ClustalW tool. Phylip is a phylogentic program used for finding the Phylogenetic analysis of the mt DNA of the different regions of the populations. And the tree file of different set of PHYLIP programs was viewed using a tree viewing tool PHYLODRAW



The polymorphism of the human mtDNA was identified by using an online software tool GenSNip, which accepted the fasta format of 40 human mtDNA sequences and compared with the rCRS (Cambridge reference sequence) and the results of the polymorphisms were observed. The Haplogroup was grouped using online tool GENPAT in the mtDNA of each population.

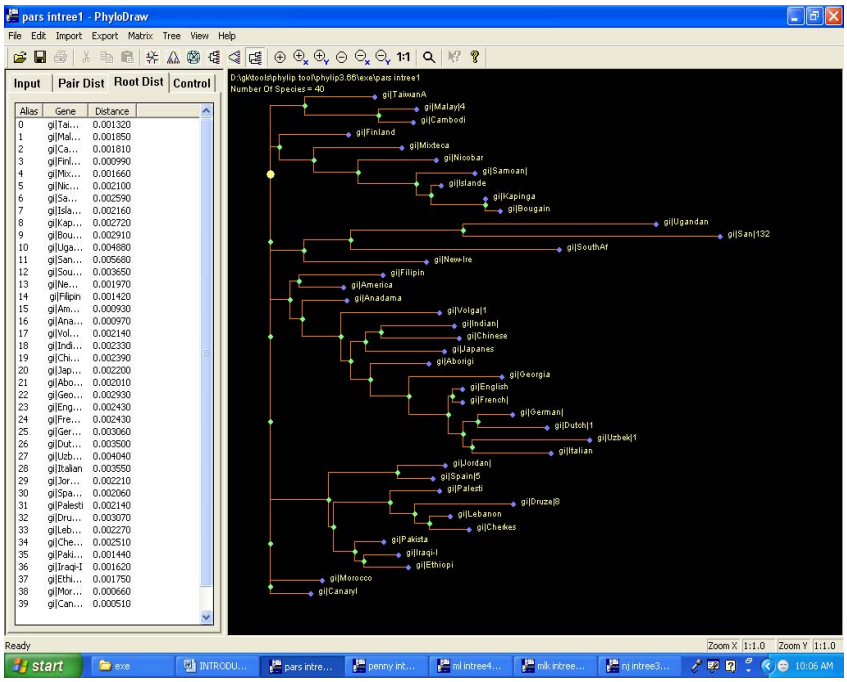
GenBank accession number

Region	Population	GenBank
African	Canary Island	Af381982
African	Ethiopia	AY882389
African	Morocco	AF381983
African	San	AF347008
African	South Africa	AY195766
African	Ugandan	AY963585
America (north)	Mixteca	AY195786
America (north)	Native American	AY195748
Asia	Cambodian	AY963572
Asia	Chinese	AF346972
Asia	Filipino	AF382012
Asia	Japanese	AF346989
Asia	Malay	AY195791
Asia	Taiwan Aborigine	AY289095
Asia	Uzbek	AF347011
Australia	Aborigine	AF346963
Europe	Cherkes	DQ301809
Europe	Dutch	AF346975
Europe	English	AF346978
Europe	Finland	AY195773
Europe	French	AF346981
Europe	Georgian	AF346982
Europe	German	AF346983
Europe	Italian	AF346988
Europe	Spain	AY882382
Europe	Volga	DQ902708
Melanesia	Bougainville	AY963574

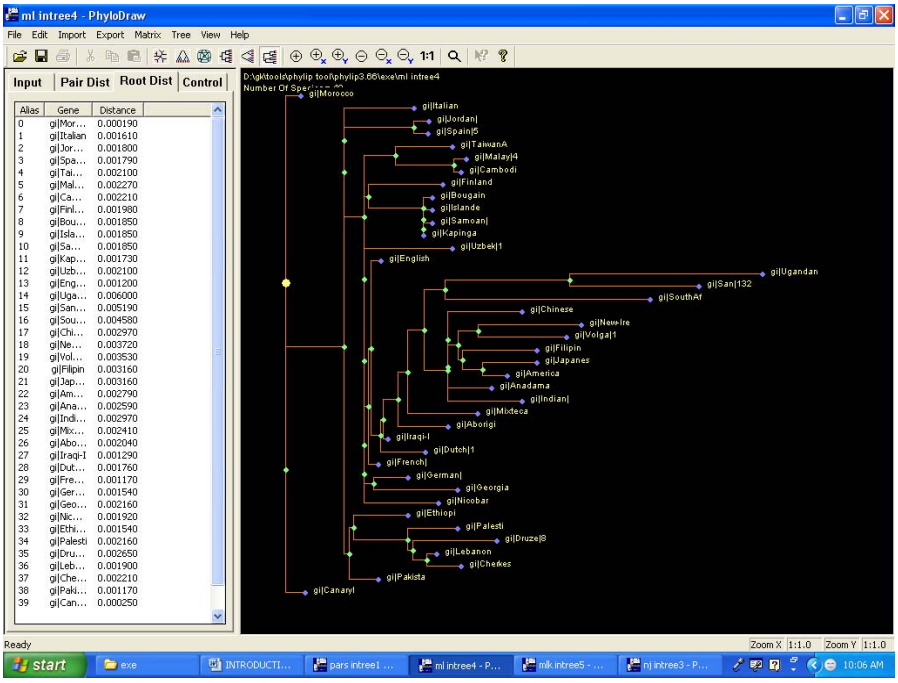
Melanesia	New-Ireland	AY956413
Micronesia	KapingamarangiAtoll	DQ372874
Middle East	Druze	DQ301792
Middle East	Iraqi-Israeli	AY195757
Middle East	Jordan	AF381995
Middle East	Lebanon	DQ301816
Middle East	Palestine	DQ301810
Polynesia	Cook Islander	AY289068
Polynesia	Samoan	AF347007
South Asia	Anadamanese	AY950296
South Asia	Indian	AF346966
South Asia	Nicobarese	AY950286
South Asia	Pakistan	AY882379

Results

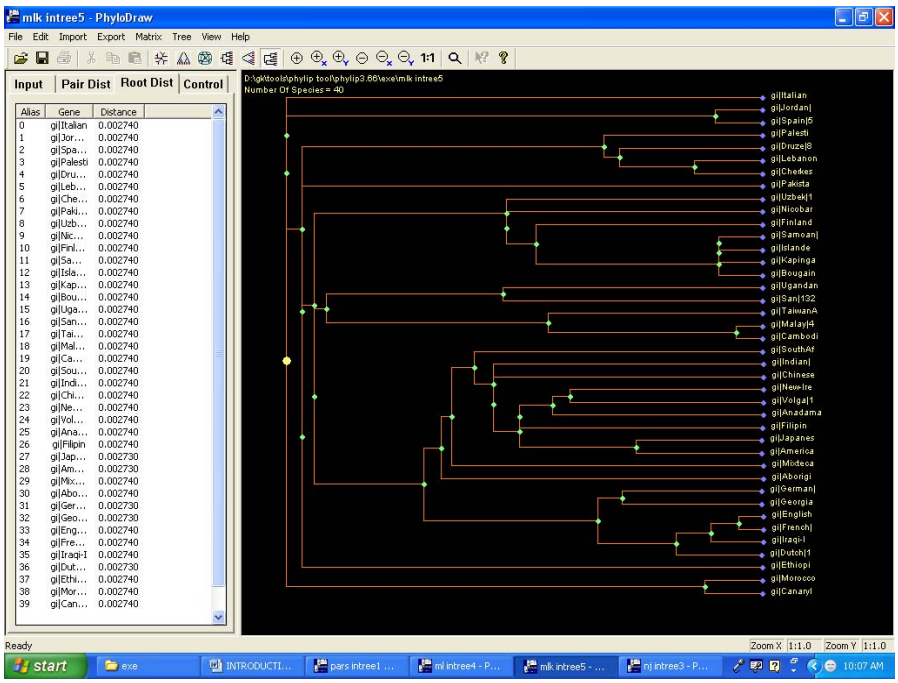
The Parsimony method takes the minimum number of evolutionary steps required to generate the observed variations in a set of sequences found by comparison of the number of steps in all possible phylogenetic trees. The phylogenetic tree is shown below represents the 40 sequences, using Maximum parsimony method.



In maximum likelihood method the most likely tree or alignment has given a probabilistic model of evolutionary change in DNA sequences. The below phylogenetic tree shows the divergence caused due to mutational changes.

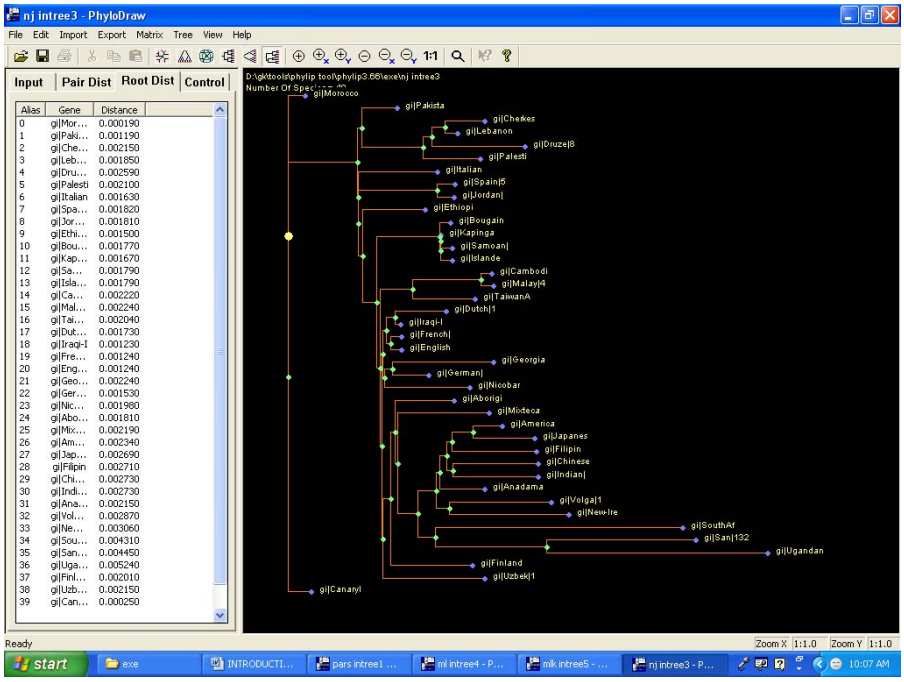


The maximum likelihood method represents the molecular clock hypothesis where the sequence changes at the same rate in the branch of an evolutionary tree.



Neighbor joining method clusters the alike pairs within a group of related gene with similar sequence to create a tree whose branches reflect the degrees of difference

among the gene. The below shown phylogenetic tree represents the distance calculated between 40 sequences.



Haplogroup of the populations

Region	Population	GenBank	Haplogroup
African	CanaryIsland	Af381982	U3
African	Ethiopia	AY882389	U
African	Morocco	AF381983	U3
African	San	AF347008	L1a
African	South Africa	AY195766	L2b
African	Ugandan	AY963585	L1a
America (north)	Mixteca	AY195786	A
America (north)	Native American	AY195748	D
Asia	Cambodian	AY963572	R
Asia	Chinese	AF346972	R
Asia	Filipino	AF382012	M
Asia	Japanese	AF346989	D
Asia	Malay	AY195791	R
Asia	Taiwan Aborigine	AY289095	R
Asia	Uzbek	AF347011	B
Australia	Aborigine	AF346963	N
Europe	Cherkes	DQ301809	K
Europe	Dutch	AF346975	R

Europe	English	AF346978	HV
Europe	Finland	AY195773	X
Europe	French	AF346981	R
Europe	Georgian	AF346982	T2
Europe	German	AF346983	J1
Europe	Italian	AF346988	U5B
Europe	Spain	AY882382	U
Europe	Volga	DQ902708	Z
Melanesia	Bougainville	AY963574	B
Melanesia	New-Ireland	AY956413	M
Micronesia	KapingamarangiAtoll	DQ372874	B
Middle East	Druze	DQ301792	K
Middle East	Iraqi-Israeli	AY195757	H
Middle East	Jordan	AF381995	U
Middle East	Lebanon	DQ301816	K
Middle East	Palestine	DQ301810	K
Polynesia	Cook Islander	AY289068	B
Polynesia	Samoan	AF347007	B
South Asia	Anadamanese	AY950296	R
South Asia	Indian	AF346966	G
South Asia	Nicobarese	AY950286	B
South Asia	Pakistan	AY882379	U

From the 40 retrieved sequences, the below shown populations were affected with Leber hereditary optic neuropathy (LHON) Disease caused due to the change in the mutational position.

Population	mtDNA mutation	Affected gene
Ugandan	G13708A	ND5
Native American	G14459A	ND6
Georgian	T4216C,A4917G	ND1,ND2
German	T4216C,G13708A	ND1,ND5

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