UNIVERSITÉ DE TUNIS EL MANAR

IPT Institut Pasteur de Tunis

INTERNATIONAL COMMISSION ON THE CLINICAL USE OF HUMAN GERMLINE GENOME EDITING

NATIONAL ACADEMY OF MEDICINE AND NATIONAL ACADEMY OF SCIENCES

THE ROYAL SOCIETY

A North African perspectives on the commission's work

Sonia Abdelhak, PhD
Head of Research Laboratory
Biomedical Genomics and Oncogenetics

General Secretary
Research in Action Association

Public “debate” and genomics in North Africa

Tunis January 14th, 2011

Inauguration of the space “DNA for All”, CST, April 25th, 2018

http://www.cst.rnu.tn/

ASSOCIATION
LA RECHERCHE
EN ACTION

http://react.org.tn

Prenatal diagnosis and IVF in North Africa

- IVF available (Public/Private sectors)
- Prenatal diagnosis available (Public/Private)
- Cultural and religious acceptability: allowed anytime during pregnancy but more easily accepted if <12 weeks.

Original Paper

Public Health Genomics

Public Health Genomics 2013;16:251–254
DOI: 10.1159/000354584

Received: April 15, 2013
Accepted after revision: July 24, 2013
Published online: September 7, 2013

The Experience of a Tunisian Referral Centre in Prenatal Diagnosis of *Xeroderma pigmentosum*

From a legal point of view, we expected to have more families to investigate. Indeed, in Tunisia, abortion has been allowed since 1973 (Act No. 73-2 of September 26, 1973). Tunisia is one of the few Arab countries that imposes no legal abortion during the statutory period (excluding time and medical staff), which makes the country one of the exceptions of the African continent and among Arab countries. After the 12th week of pregnancy, certain conditions must be met for an abortion. From a religious point of view, contrary to common belief, Islam does not prohibit abortion. It is permitted if the pregnancy is aged less than 120 days and only in cases where the medical staff states that the foetus will suffer from a severely disabling and life-threatening disease. Nevertheless, many families choose not to have an abortion even if they know that the foetus will suffer from a severe disease. If the diagnosis is established after the period of 120 days of pregnancy (4 lunar months: when the soul has been 'breathed into the foetus'), then abortion is not allowed, unless the mother's life is in danger (from Ahkaam al-Janeen fi'l-Fiqh al-Islami, by 'Umar ibn Muhammad ibn Ibraaheem Ghaanim).

Original Paper

Public Health Genomics

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The prenatal genetic counselling was done without specific mention to religion. Each couple was informed about the risk of having an affected child and being confronted with the decision to terminate pregnancy, if prenatal molecular diagnosis shows that the foetus is homozygous for the mutation. In case the parents did not accept to abort the affected foetus, PND was not chosen because of the low benefit for the couple and to avoid the risk of miscarriages associated to foetal cell sampling. The counselling geneticist should be neutral without having sociocultural or religious implications.

Pre-implantation Genetic Diagnosis in North Africa

Available in the private sector for a limited set of diseases

Les maladies monogéniques

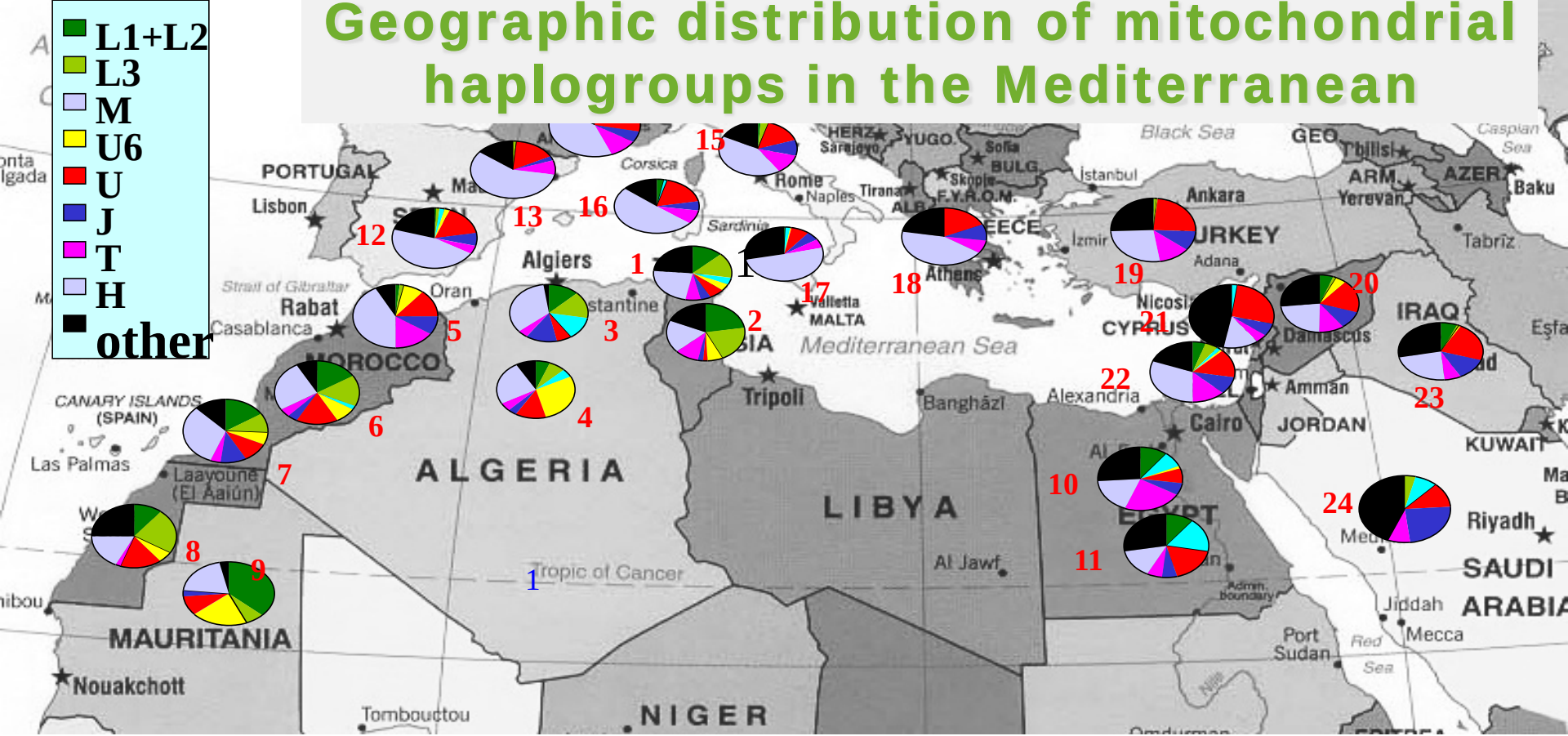
- Myopathie
- Mucoviscidose
- Neurofibromatose
- Béta-thalassémie
- Rétinite pigmentaire
- Dystrophie musculaire de Becker
- Hémophilie
- Maladie de Huntington

Anomalie chromosomique

Le **DPI** peut être indiqué lorsque l'un des partenaires d'un couple est porteur d'une anomalie chromosomique de structure équilibrée chez lui, mais pouvant aboutir à un génotype déséquilibré pathogénique ou létal chez le fœtus (fausses couches):

- Translocation
- Inversion
- Dans d'autres cas, la sélection d'un embryon d'un sexe donné permet de garantir l'absence d'une maladie si cette dernière ne concerne qu'un seul sexe (**maladie liée au sexe**).

Geographic distribution of mitochondrial haplogroups in the Mediterranean

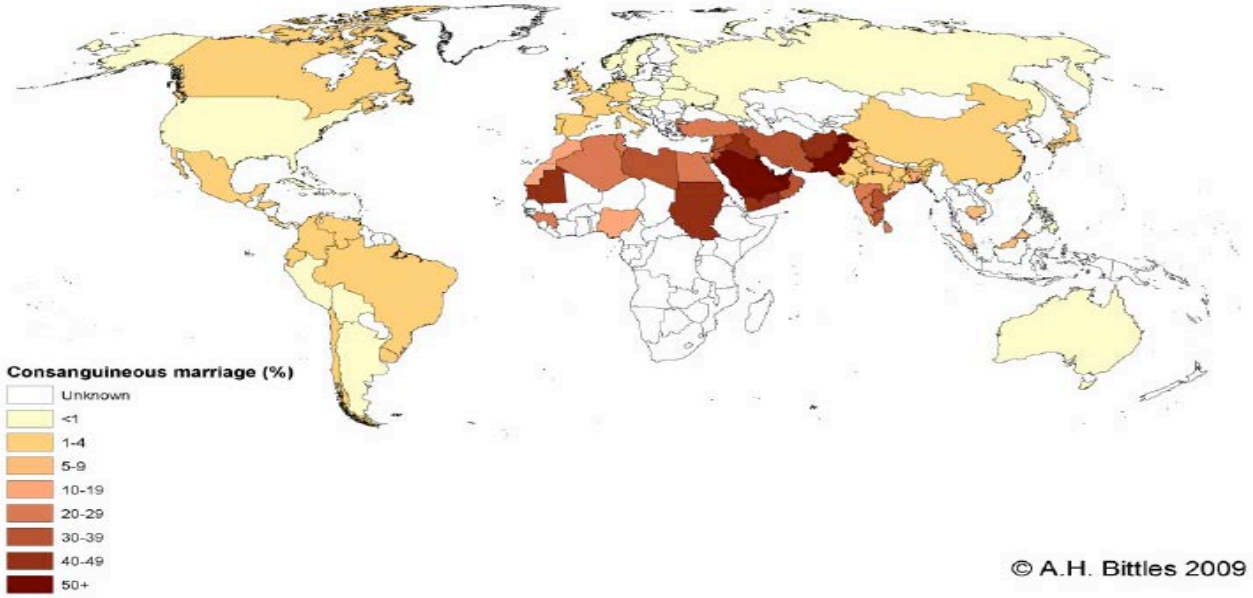


1:TUN, 2:MAK, 3: ALG, 4: MOZ, 5: MBN, 6: MAR, 7: SOU, 8: SAH, 9: MAU, 10: EGY, 11: GUR, 12: AND, 13: CAT, 14: FR, 15: ITA, 16: SAR, 17: SIC, 18: GRE, 19: TUR, 20: SYR, 21: DRU, 22: PAL, 23: IRA, 24: BED

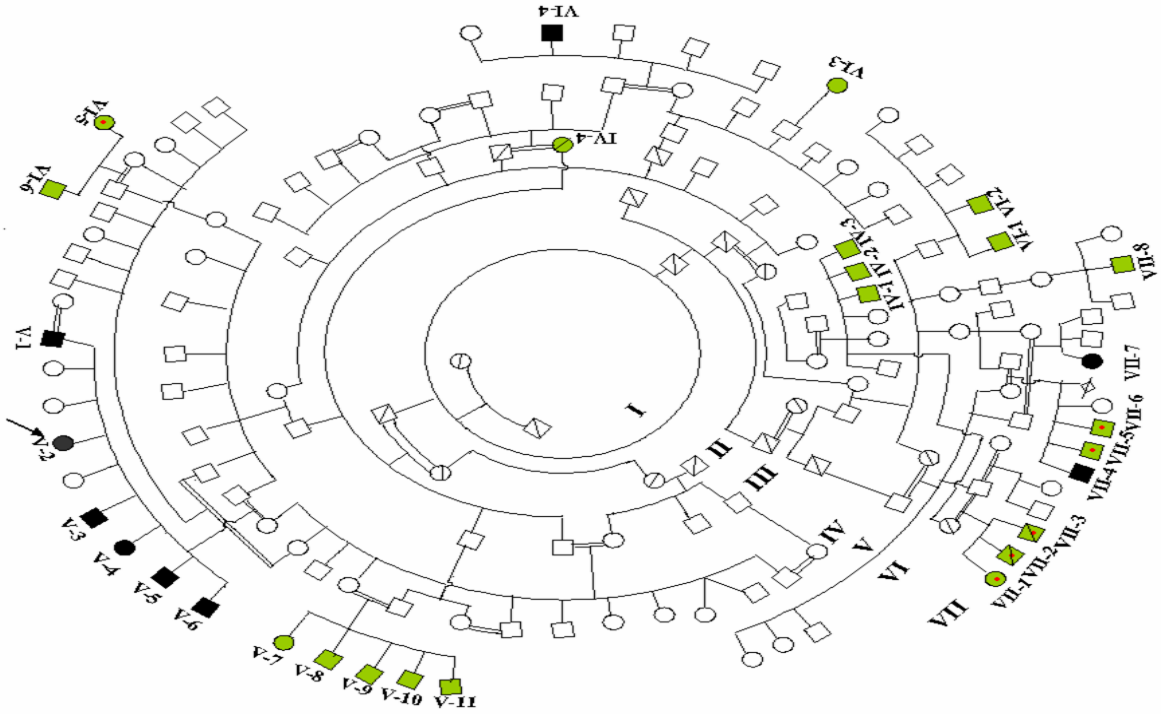
 Kéfi-Ben Atig R. et al. Unpublished data

Consanguineous marriages in MENA region

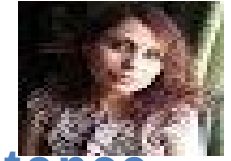
If we have beauty, intelligence and wealth in the family, why look outside? …….



Pedigree of a family affected by achromatopsia mental impairment and/or myopathy

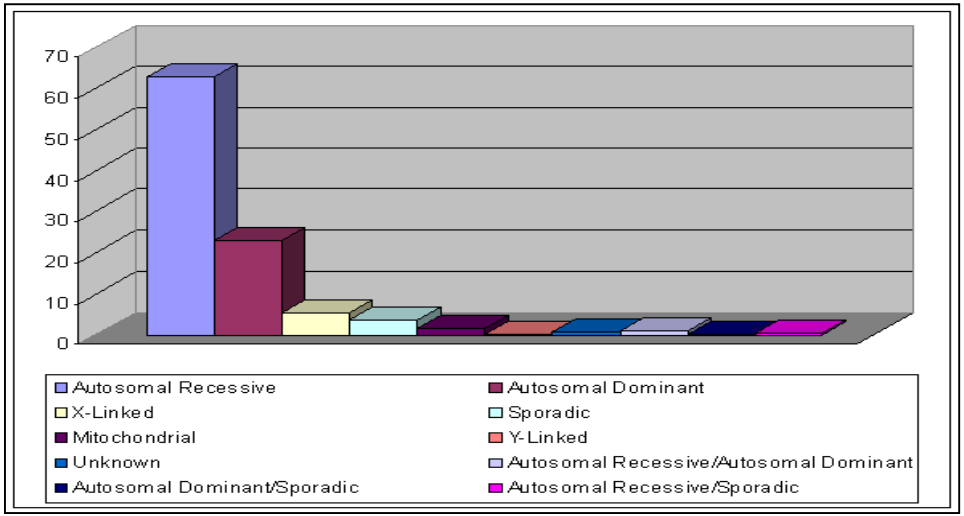


Genetic diseases in Tunisia: > 400



Distribution of genetic diseases by the mode of inheritance

In Tunisia



RESEARCH REVIEW

AMERICAN JOURNAL OF medical genetics

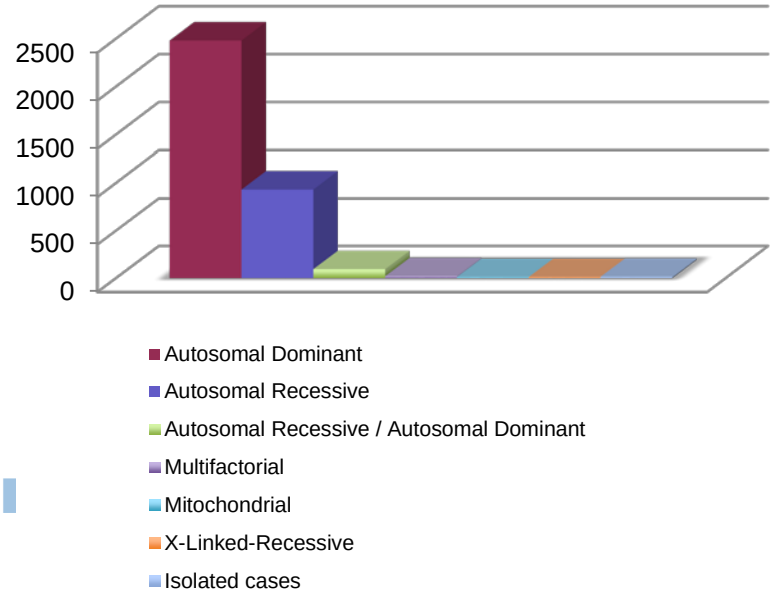
Genetic Diseases in the Tunisian Population

Lilia Romdhane, Sonia Abdelhak* for the Research Unit on Molecular Investigation of Genetic Orphan Diseases† and Collaborators‡

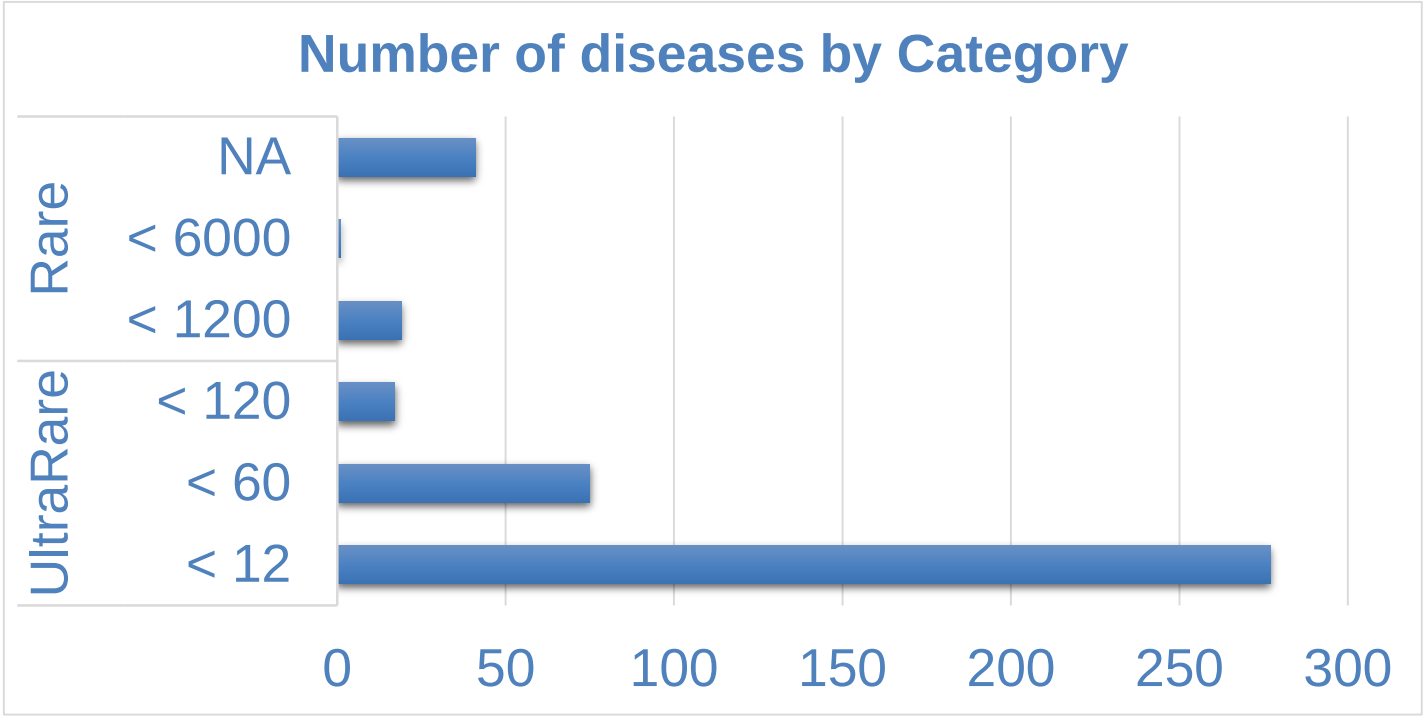
Research Unit on "Molecular Investigation of Genetic Orphan Diseases" Institut Pasteur de Tunis, Tunis, Tunisia

Received 6 September 2009; Accepted 25 August 2010

In OMIM



Number of Rare Diseases in Tunisia according to the number of patients/disease



Romdhane L, Mezzi N, Abdelhak S unpublished data

Will the GM individual have no (other) (genetic) disease?

- Neo-mutation? Mosaicism? Co-occurrence of 2+ diseases?

Original Paper

Public Health Genomics 2013;16:251–254
DOI: 10.1159/000354584

According to our experience in rare diseases in Tunisia, in some cases, 2 or more diseases cosegregate within the same family [9]. Even if this event is rare, the genetic counsellor should be aware of this possibility, in order to avoid the very unlikely case that the foetus is excluded of having the screened mutation but bares another mutation which is responsible for another disease.

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CLINICAL GENETICS
doi: 10.1111/cge.12616

Original Article

Comorbidity in the Tunisian population

Romdhane L., Messaoud O., Bouyacoub Y., Kerkeni E., Naouali C., Cherif Ben Abdallah L., Tiar A., Charfeddine C., Monastiri K., Chabchoub I., Hachicha M., Tadmouri G.O., Romeo G., Abdelhak S. Comorbidity in the Tunisian population.
Clin Genet 2015. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2015

Genetic diseases in the Tunisian population represent a real problem of public health as their spectrum encompasses more than 400 disorders. Their frequency and distribution in the country have been influenced by demographic, economic and social features especially consanguinity. In this article, we report on genetic disease association referred to as comorbidity and discuss factors influencing their expressivity. Seventy-five disease associations have been reported among Tunisian families. This comorbidity could be individual or familial. In 39 comorbid associations, consanguinity was noted. Twenty-one founder and 11 private mutations are the cause of 34 primary diseases and 13 of associated diseases. As the information dealing with this phenomenon is fragmented, we proposed to centralize it in this report in order to draw both clinicians' and researcher's attention on the occurrence of such disease associations in inbred populations as it makes genetic counseling and prenatal diagnosis challenging even when mutations are known.

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[a]Biomedical Genomics and Oncogenetics Laboratory, Institut Pasteur de Tunis, Université Tunis El Manar, Tunis, Tunisia, [b]Department of Biology, Faculty of Science of Bizerte, Université Tunis Carthage, Zarzouna, Tunisia, [c]Laboratoire de Pharmacologie, Faculté de Médecine de Monastir, Université de Monastir, Monastir, Tunisia, [d]EPS Fattouma Bourguiba, Centre de Maternité & de Néonatologie de Monastir, Service de Réanimation et de Médecine Néonatale, Monastir, Tunisia, [e]Service de Pédiatrie, CHU Hédi Chaker, Sfax, Tunisia, [f]Faculty of Public Health, Jinan University, Tripoli

Do we really know that much about genetic diseases?

ARTICLE

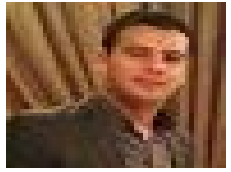
The American Journal of Human Genetics 93, 90–102, July 11, 2013

Long Runs of Homozygosity Are Enriched for Deleterious Variation

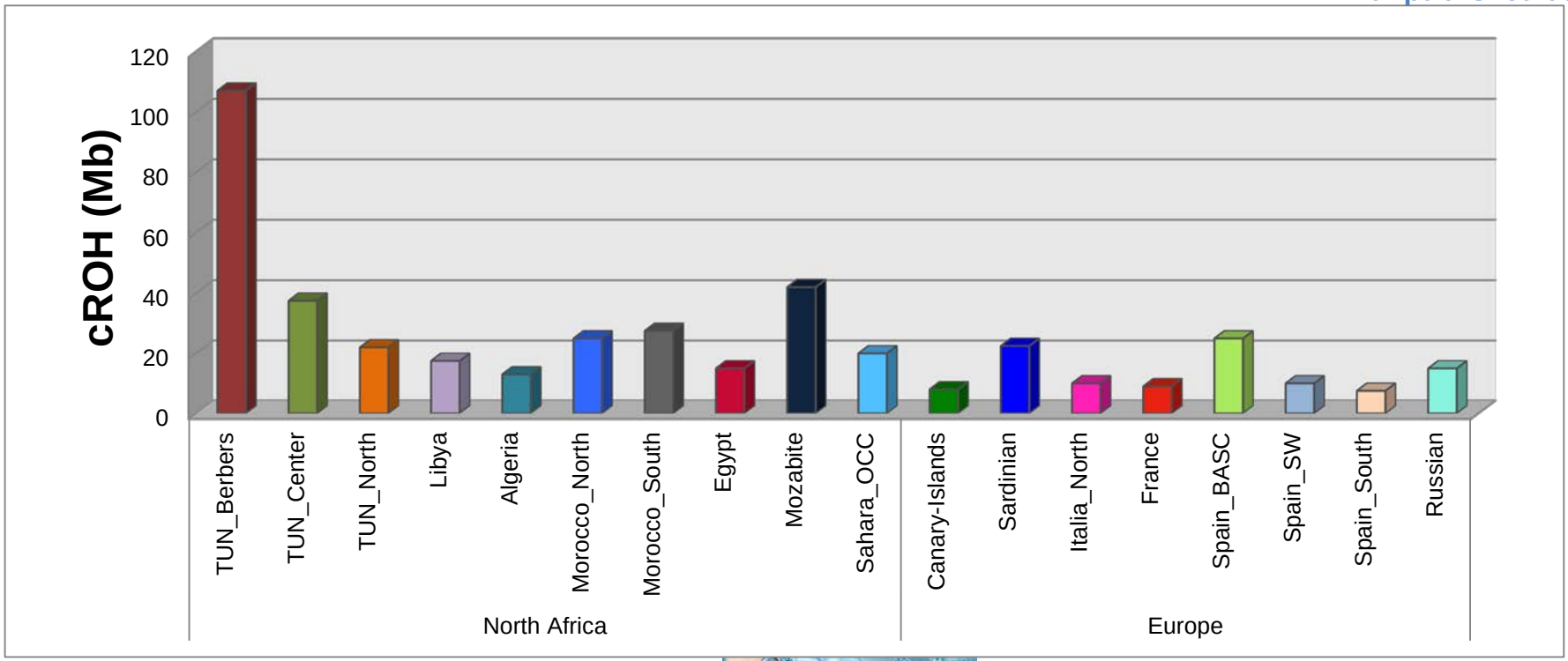
Zachary A. Szpiech,[1,2,*] Jishu Xu,[3] Trevor J. Pemberton,[2,4] Weiping Peng,[3] Sebastian Zöllner,[5,6] Noah A. Rosenberg,[2,7] and Jun Z. Li[3,7]

Exome sequencing offers the potential to study the population-genomic variables that underlie patterns of deleterious variation. Runs of homozygosity (ROH) are long stretches of consecutive homozygous genotypes probably reflecting segments shared identically by descent as the result of processes such as consanguinity, population size reduction, and natural selection. The relationship between ROH and patterns of predicted deleterious variation can provide insight into the way in which these processes contribute to the maintenance of deleterious variants. Here, we use exome sequencing to examine ROH in relation to the distribution of deleterious variation in 27 individuals of varying levels of apparent inbreeding from 6 human populations. A significantly greater fraction of all genome-wide predicted damaging homozygotes fall in ROH than would be expected from the corresponding fraction of nondamaging homozygotes in ROH ($p < 0.001$). This pattern is strongest for long ROH ($p < 0.05$). ROH, and especially long ROH, harbor disproportionately more deleterious homozygotes than would be expected on the basis of the total ROH coverage of the genome and the genomic distribution of nondamaging homozygotes. The results accord with a hypothesis that recent inbreeding, which generates long ROH, enables rare deleterious variants to exist in homozygous form. Thus, just as inbreeding can elevate the occurrence of rare recessive diseases that represent homozygotes for strongly deleterious mutations, inbreeding magnifies the occurrence of mildly deleterious variants as well.

Cumulative Runs of Homozygosity (cROH) in Europe and in different Southern Mediterranean country



Nagara et al.
unpublished data



Unanticipated findings in “routine” mutational screening: non penetrant homozygous individuals

Charfeddine C. et al.
unpublished data

“Unaffected” homozygous carriers: individuals in a family screened positive for a deleterious recessive mutation:

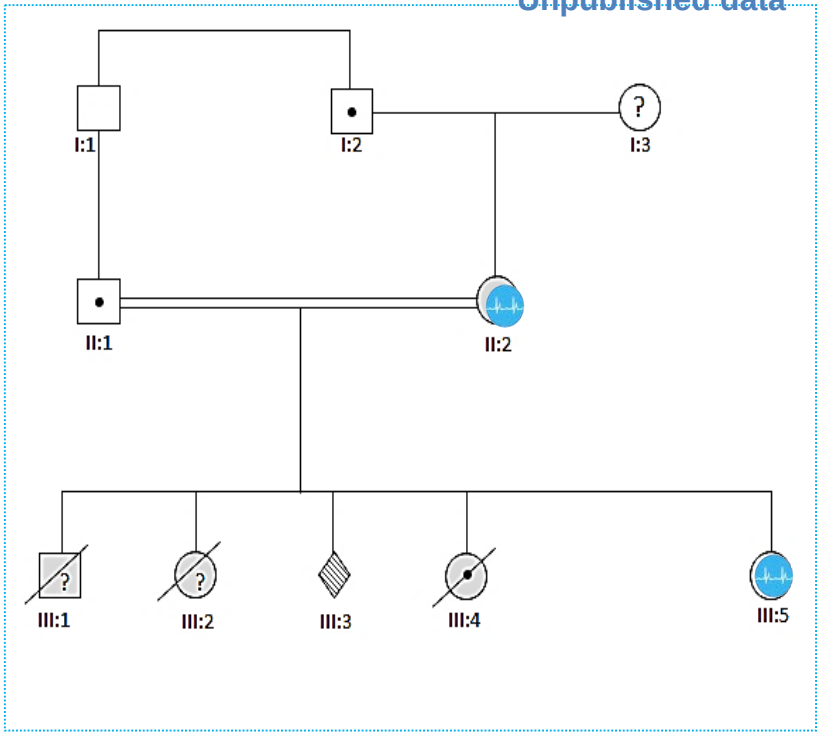
- Fanconi anemia (*FANCA* mutated siblings screened for bone marrow transplant).
- Niemann-Pick disease type B (homozygous mothers)
- Primary hyperoxaluria
- Gaucher disease
- Hypogonadotropic hypogonadism (transient fertility/infertility)

Are we sure to target the right gene? variant?

Molecular investigation (WES) of a consanguineous family with Sudden Cardiac Death (SCD)

Jaouadi H et al.
Unpublished data

Variant	Phénotype	Score-CADD
OBSCN : p.Arg6855Ser	CMH|CMD	35
DSC2 : p.Ser868Phe	CAVD	31
VCL : p.Leu682Phe	CMH15|CMD	23.3
RBM20 : p.Ser455Leu	CMD	23.3
RYR2 : p.Asp1220Glu	TVPC|CAVD	23.2
AKAP9 : p.Arg1609Lys	LQT11	22.8
CACNA1C : p.Gly1795Arg	LQT8| Sd. Timothy	17.26



A “new” gene and a “new” phenotype?

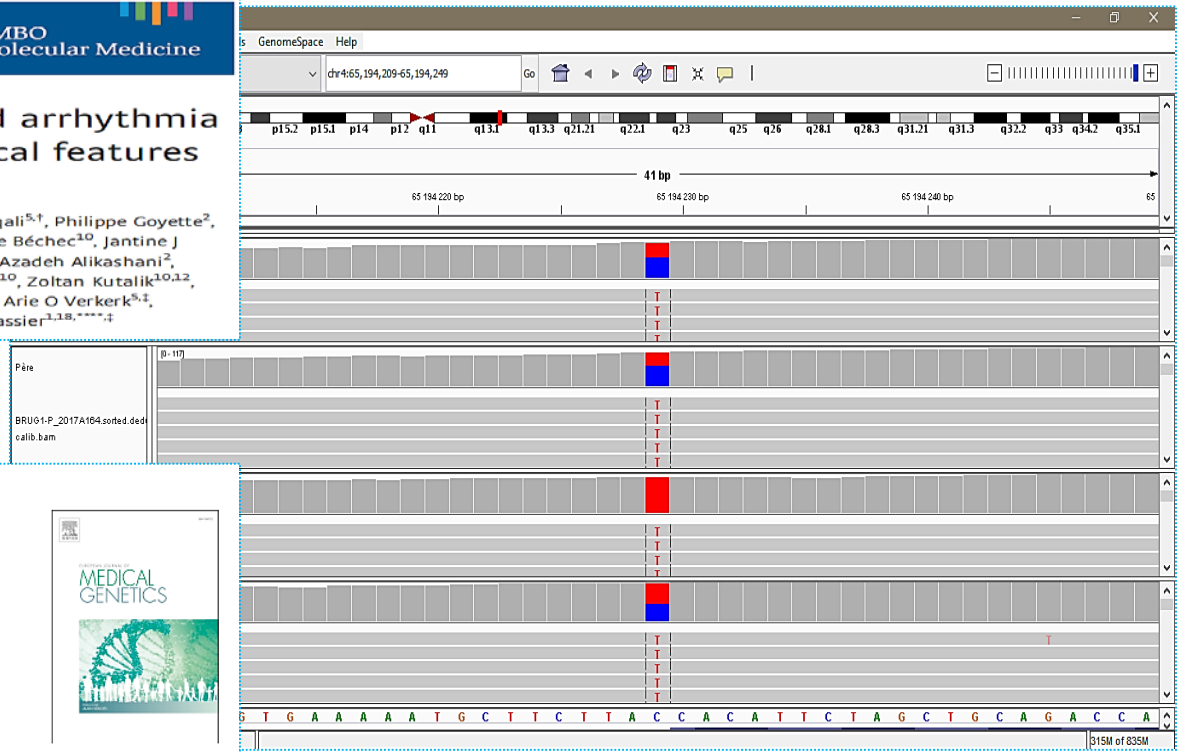
Research Article **2017**

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

TECRL, a new life-threatening inherited arrhythmia gene associated with overlapping clinical features of both LQTS and CPVT

Harsha D Devalla[1,*,†], Roselle Gélinas[2,3,†], Elhadi H Aburawi[4,†], Abdelaziz Beqqali[5,†], Philippe Goyette[2], Christian Freund[1,6], Marie-A Chaix[2,3], Rafik Tadros[2,3,5], Hui Jiang[7,8,9], Antony Le Béchec[10], Jantine J Monshouwer-Kloots[1], Tom Zwetsloot[1], Georgios Kosmidis[1], Frédéric Latour[2], Azadeh Alikashani[2], Maaike Hoekstra[5], Jurg Schlaepfer[11], Christine L Mummery[1], Brian Stevenson[10], Zoltan Kutalik[10,12], Antoine AF de Vries[13,14], Léna Rivard[2,3], Arthur AM Wilde[15,16], Mario Talajic[2,3], Arie O Verkerk[5,‡], Lihadh Al-Gazali[4,‡], John D Rioux[2,3,**,†,‡], Zahurul A Bhuiyan[17,***,‡] & Robert Passier[1,18,****,‡]



Accepted Manuscript **2019**

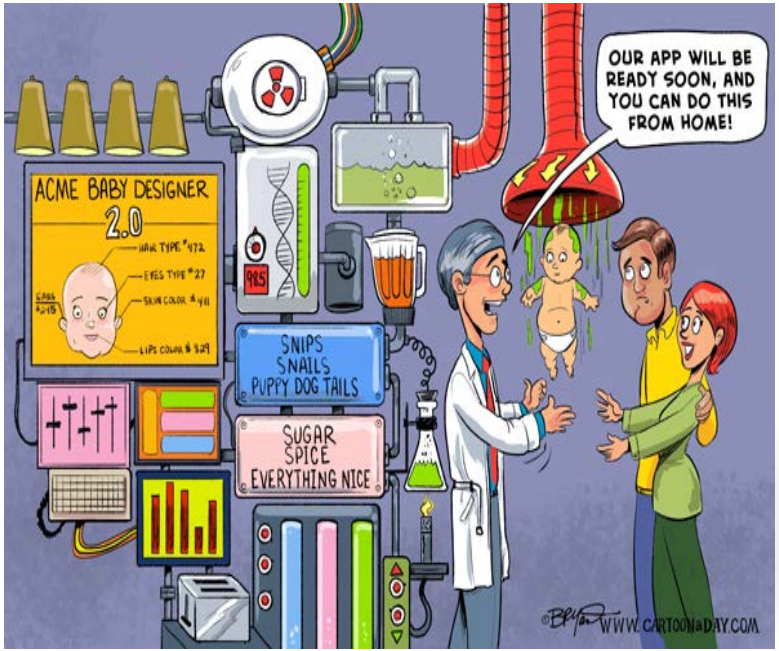
A compound heterozygosity of Tecrl gene confirmed in a catecholaminergic polymorphic ventricular tachycardia family

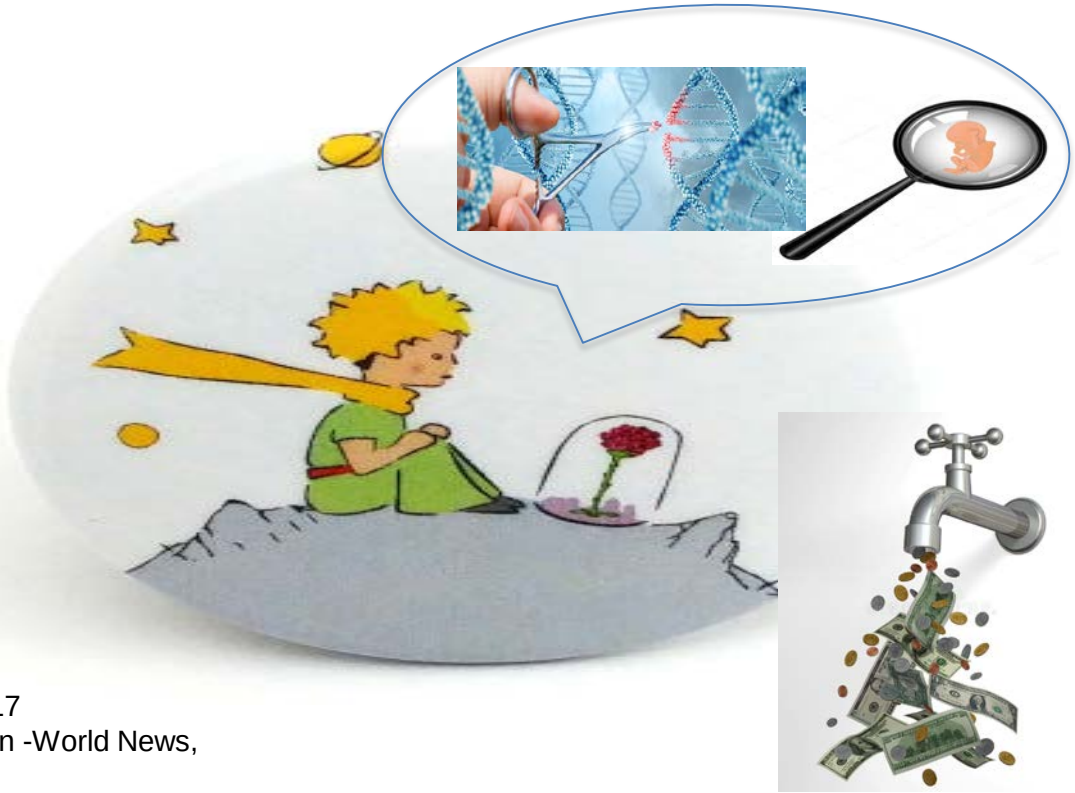
Lijian Xie, Cuilan Hou, Xunwei Jiang, Jian Zhao, Yun Li, Tingting Xiao

PND, disease phenotypes and socio-economic considerations

- What could be considered as an “acceptable” or “non acceptable” disease?
- Parents of children with PKU requesting PND
- Patients/parents/family resilience.

Capable to take the risk?





Designer Baby Cartoon By Bryant Arnold Published: May 7, 2017
Posted in: Conceptual Artwork, Digital Painting, Editorial Cartoon -World News, Modbook Artwork, Pen and Ink Cartoons

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