Nantes Université

Transplantation de cellules souches hématopoïétiques

Jeudi 19 mars 2025 16hr00

Pr Patrice Chevallier / Pr Pierre-Antoine Gourraud

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

Nantes Université

Inserm
Institut national de la santé et de la recherche médicale

Tomorrow's Medicine

"**Les prévisions sont difficiles, surtout lorsqu'elles concernent l'avenir.** " P Dac

Buzz Words
[3-4-6]P Medicine,
Predictive Medicine, Personalized Medicine
3R Medicine, 6V Medicine,
Precision Medicine

Generic

Digital/ Numeric/ IT Technology
Application to Health of generic IT technology
Disruptive practice – no fundamental change.
« Altius Citus Foritus » + Healthism
Ex: On-line Drug catalog

Big Data Technology
Application to Health of generic IT technology
Disruptive practice – infusive change of paradigm – "re-evolution"
Ex: Simulation vs Models
- Machine Learning

Population-based approach of health
(Public Health)
Vs.
Pseudo-singular approach of clinical medicine

Health Condition Specific

Phenotyping technology
Disruption of medical practice by emerging opportunity to see, measure
Ex: Stethoscope, MRI

Performative technology
Direct disruption of medical techniques / intervention Opportunities
Ex: Micro Surgery – drugs – targeted therapies

Cognitive technology
Disruption of explanatory model - understanding differently
Ex: Systems biology – network based drugs design – HMM - SEM

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Intro: Genetics and population as one of the precision medicine « layers »

- The challenge of layers
  - Transdisciplinary issue adopting other point of views
  - Polysemy of Precision medicine (Genetically informed medicine)
    - Reductionism ?

- Allogeneic HSCT : Genetics of finding a donor – International health organization
  - Not a precision medicine anymore haploidentical HSCT (P Chevalier)

- Plan

HSCT : From Immunogenetics in population to individual decision

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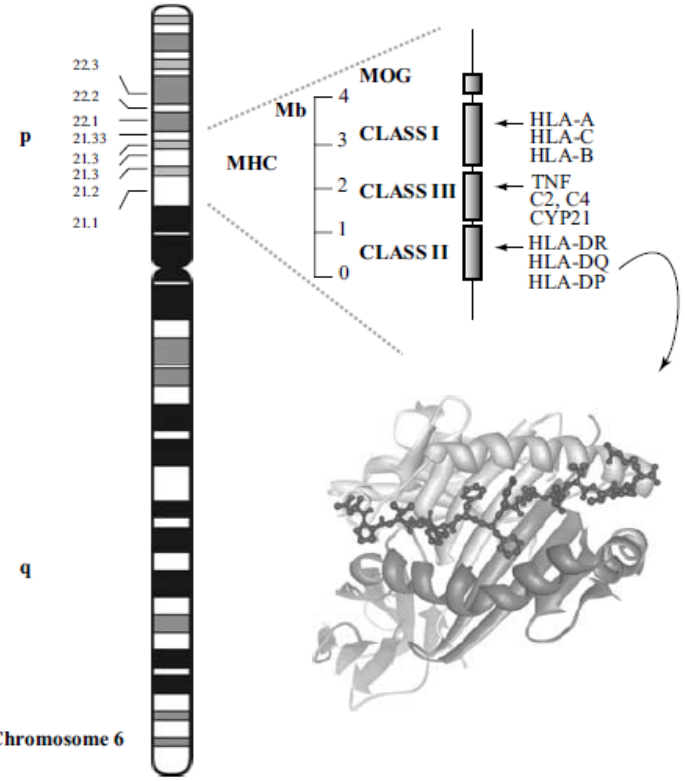
Un peu biologie : *les Gènes "HLA"*

- **La "carte d'identité" génétique pour les greffes**
  - 1‰ of the genome
  - 1% of the genes
  - Highest polymorphism
  - Highest linkage disequilibrium
- **Fonction Immunitaire**
  - Human Leukocyte Antigen Genes
    - HLA genes
    - Self identity
    - Self and foreign antigen presenting



HLA Class I

Gene	A	B	C
Alleles	**2,946**	**3,693**	**2,466**
Proteins	2,077	2,741	1,739
Nulls	138	122	74

HLA Class II

Gene	DRB1	DQB1
Alleles	**1,582**	**712**
Proteins	1,165	473
Nulls	36	17

Un peu de probabilités combinatoires
A vous de jouer !

- Quelle est la diversité HLA théoriquement possible avec ces 5 gènes ?

HLA Class I				HLA Class II		
Gene	**A**	**B**	**C**	**Gene**	**DRB1**	**DQB1**
Alleles	**2,946**	**3,693**	**2,466**	**Alleles**	**1,582**	**712**
Nombre de paires	**?**	**?**	**?**	**Nombre de paires**	**?**	**?**
# Profils Class II	**?**			**# Profils Class II**	**?**	
# Profils I & II	**?**					
	?					

Réponses

HLA Class I				HLA Class II		
Gene	***A***	***B***	***C***	**Gene**	***DRB1***	***DQB1***
Alleles	**2,946**	**3,693**	**2,466**	**Alleles**	**1,582**	**712**
Nombre de paires	**4,340,931**	**6,820,971**	**3,041,811**	**Nombre de paires**	**1,252,153**	**253,828**
	4.3E+06	6.8E+06	3.0E+06		1.3E+06	2.5E+05
# Profils Class II	**90,066,090,529,607,400,000**			**# Profils Class II**	**317,831,491,684**	
	9.0E+19				*3.2E+11*	
# Profils I & II	**28,625,839,903,171,300,000,000,000,000**					
	2.9E+31					
	Presque trois cent mille milliards de millards de milliards					

- **Question:** ***Est ce que ca représente bien la réalité ?***

Du rôle de la modélisation mathématique en Science du vivant …

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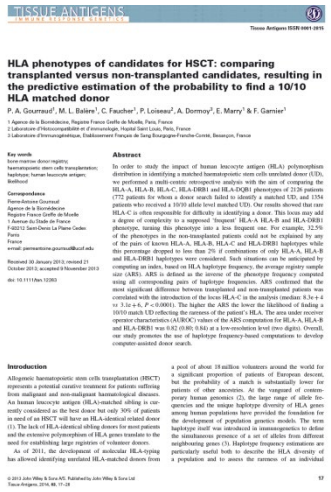
Part 1: Individual decision making with (genetic) data (computations) in HSCT



HLA phenotypes of candidates for HSCT: comparing transplanted versus non-transplanted candidates, resulting in the predictive estimation of the probability to find a 10/10 HLA matched donor

Tissue Antigens, 2014, **83**, 17–26

- P. A. Gourraud1, M. L. Balere1, C. Faucher 1, P. Loiseau2, A. Dormoy3, E. Marry1 & F. Garnier1
- 1 Agence de la Biomedecine, Registre France Greffe de Moelle, Paris, France
- 2 Laboratoire d'Histocompatibilit e et d'immunologie, Hopital Saint Louis, Paris, France
- 3 Laboratoire d'Immunog´en´etique, Etablissement Franc¸ais de Sang Bourgogne-Franche-Comt´e, Besanc¸on, France
- **Member of European Group For Blood and Marrow Transplantation (EBMT)**

Introduction: from research analysis

BACKGROUND

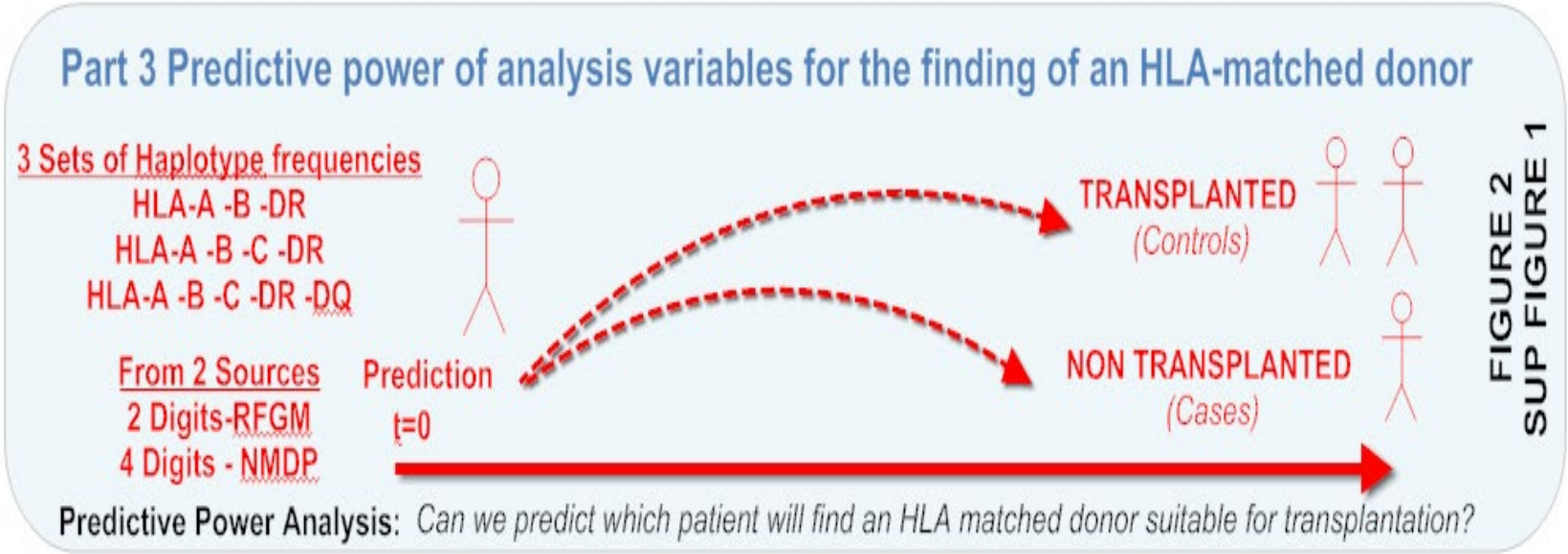
- Only 30% of patients in need for allogeneic HSCT have a Fully-HLA matched Family donor.
- Various levels of HLA polymorphism could argue For Further difficulty For those recipients to Find a unrelated compatible donor.
- Demand From Transplantation Physicians to better understand the HLA determinant
  - RFGM “transplantation strategies” working group

OBJECTIVE:

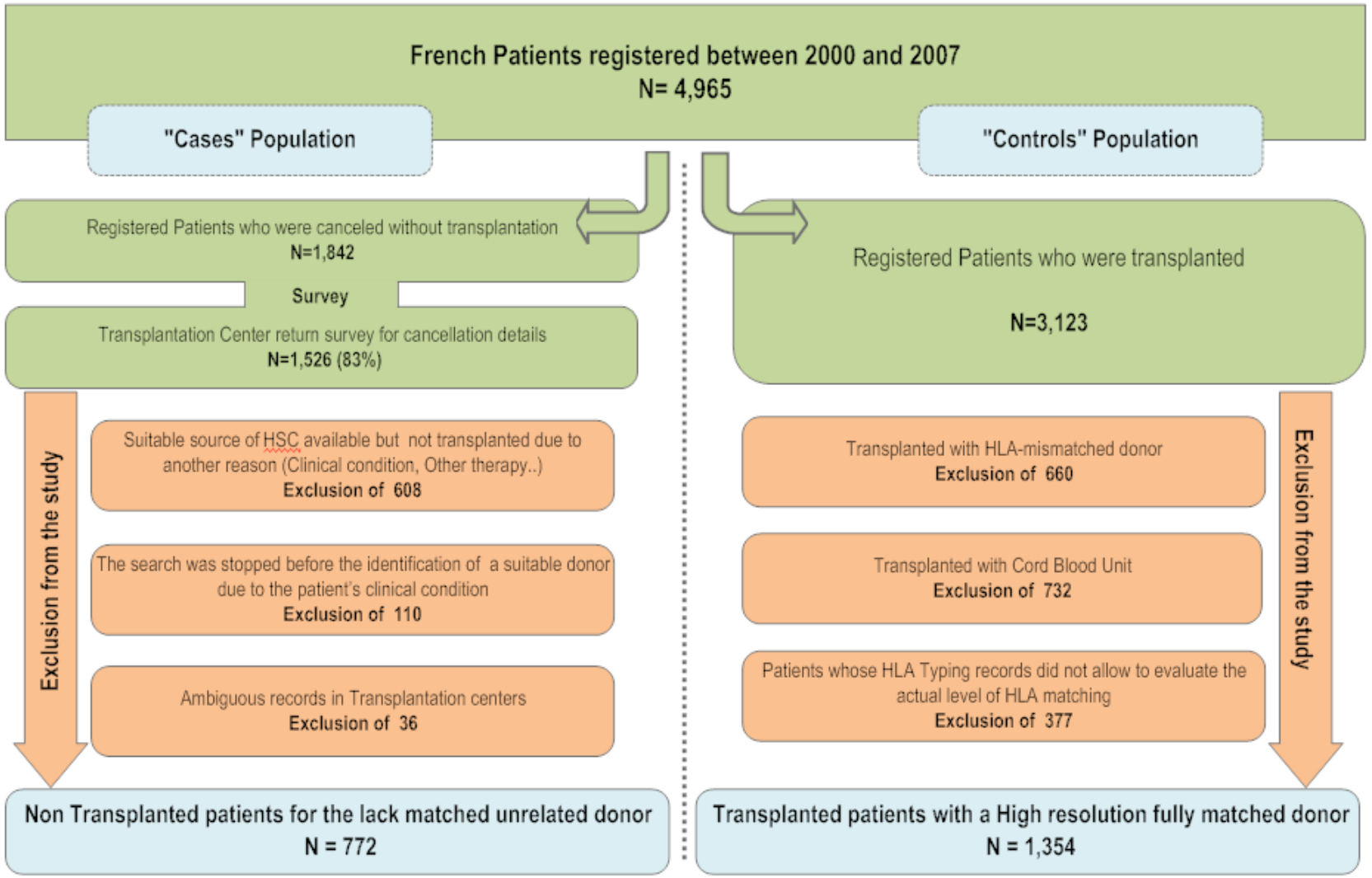
- A retrospective comparison of HLA characteristics
  - HLA of the patients who did Find a 10/10 high resolution HLA matched donor.
  - Vs. HLA of the patients did not Find one.

Central concept of the Methods measuring **HLA rareness of phenotype: Predictive metric**

- **Depend on a "mathematical model" and population genetics "parameters"**
- Variation in **model and Parameters span a large array of HLA Features** potentially involved in the lack of HLA-matched donors

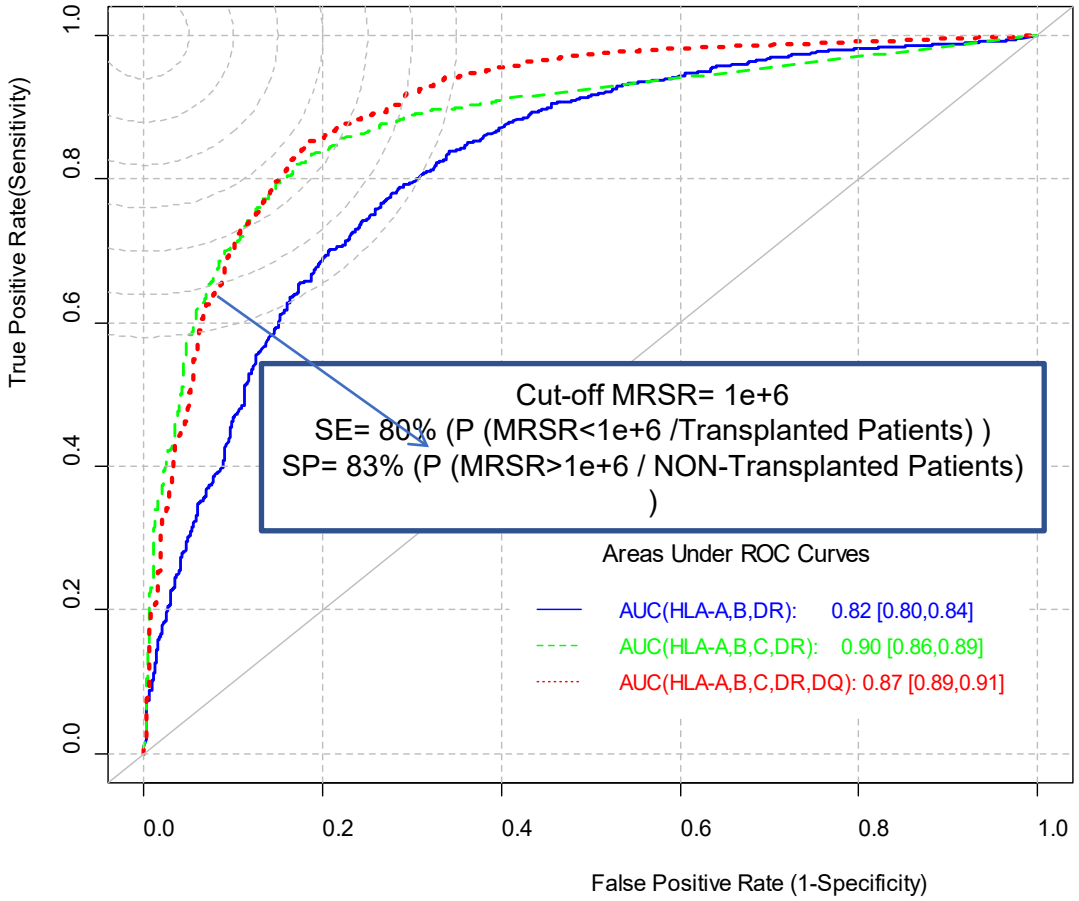


Comparative design “case” vs. “controls”



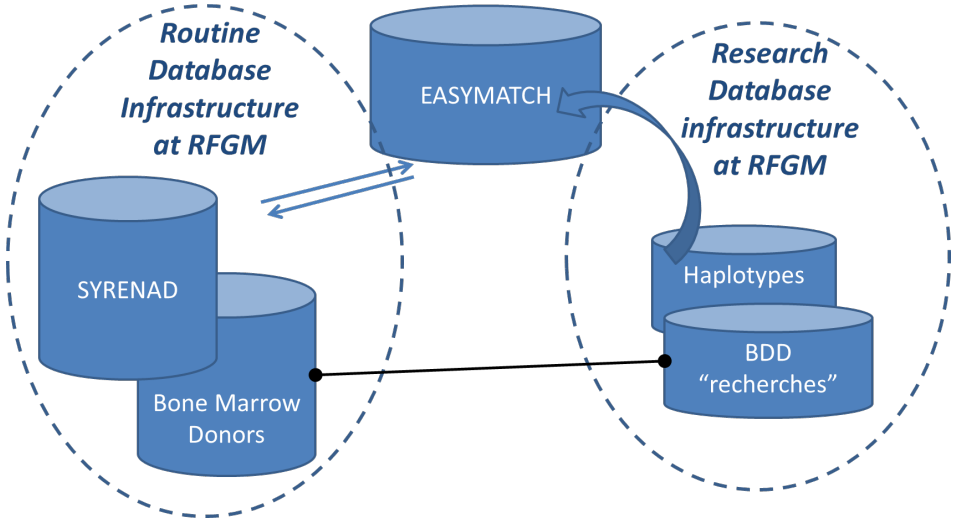
Predict of transplanted and non transplanted patients

- **Prospective use of the tool of the retrospective Population Genetics Analysis**
  - With HLA-C
    - AUC ~ 0.90
    - 85% good classification rate

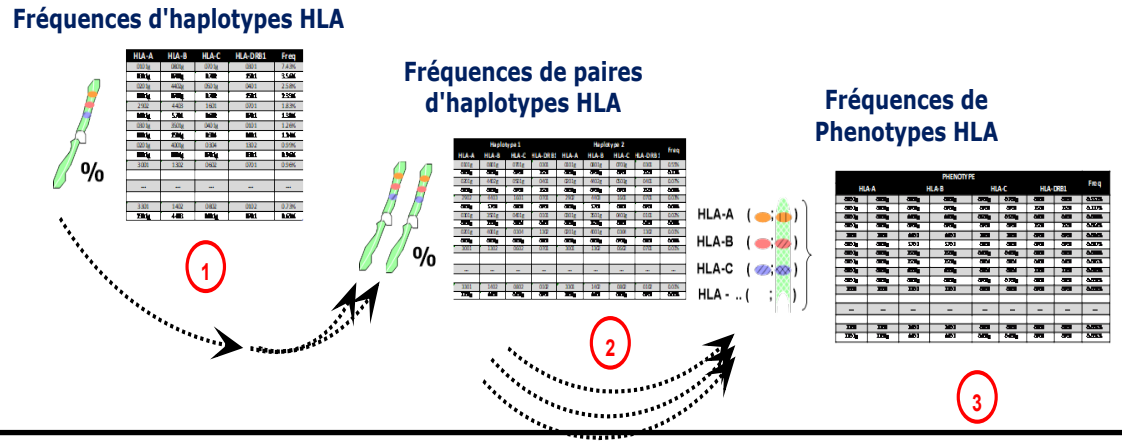


Part 2 : From research to tools

Easymatch



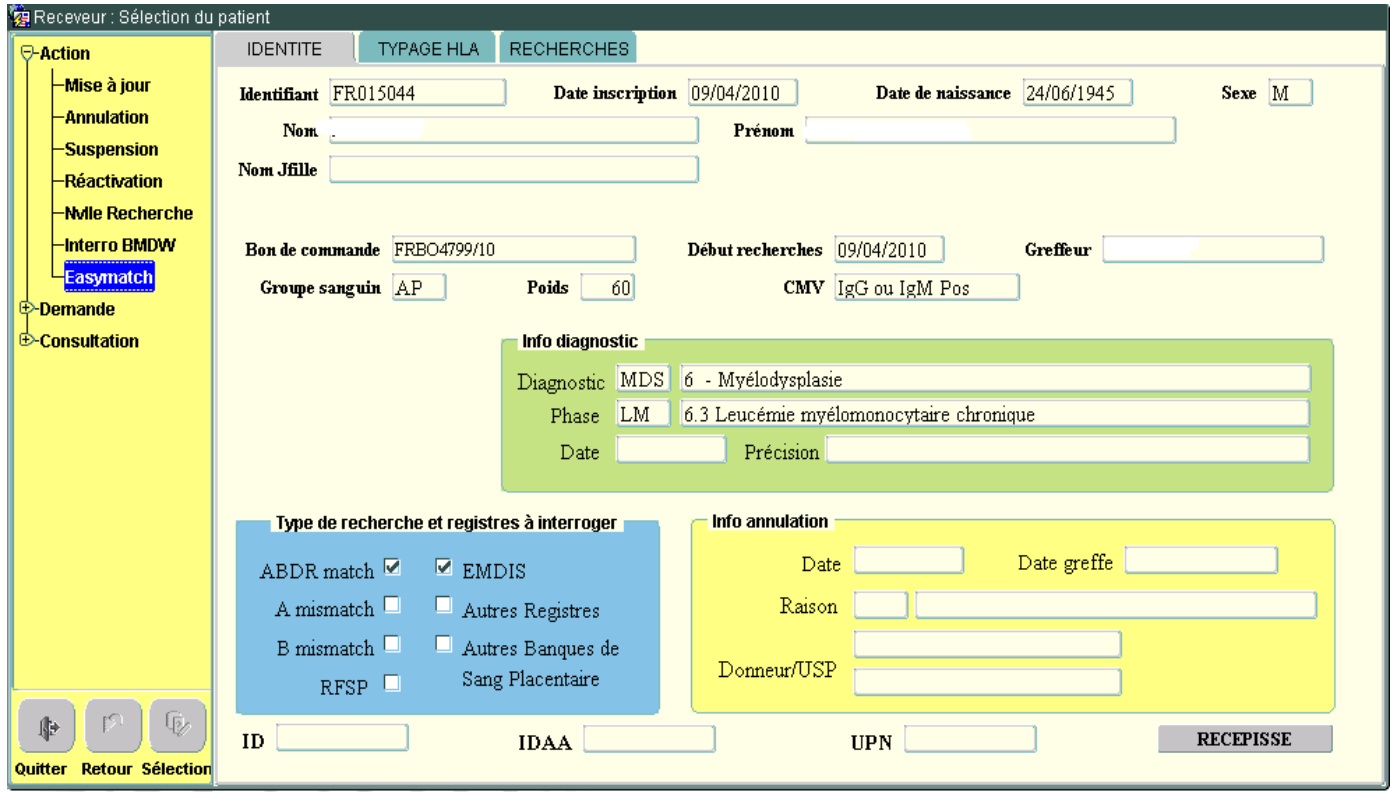
- ***Leveraging haplotype frequencies*** *Frequencies of plausible HLA phenotypes in potential donors of various ancestries*



The Easymatch Application

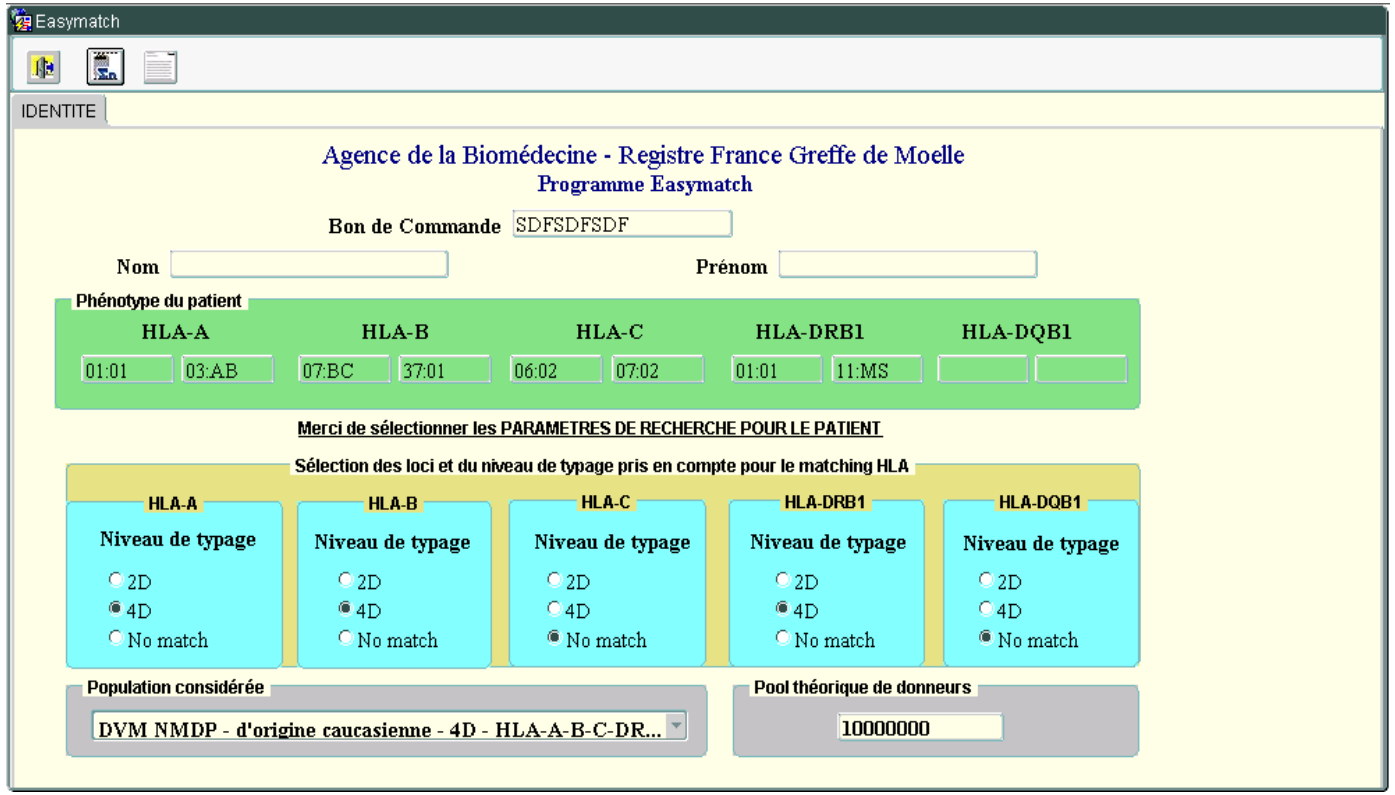
Encrypted Web-Application "On Premise"

The Easymatch Application



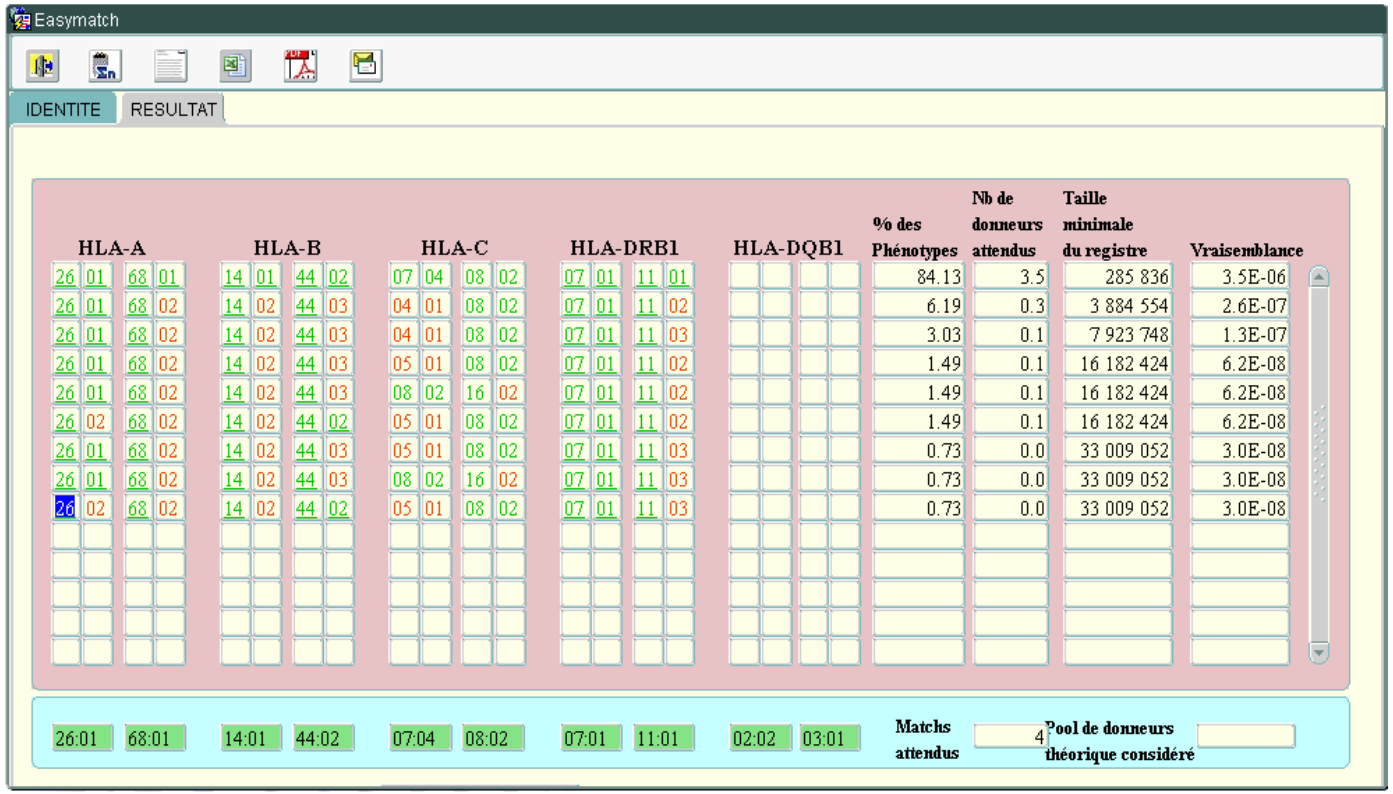
Patient oriented

The Easymatch Application



Parameters of the searches

The Easymatch Application



Evaluation of phenotypes and frequencies in potential donors

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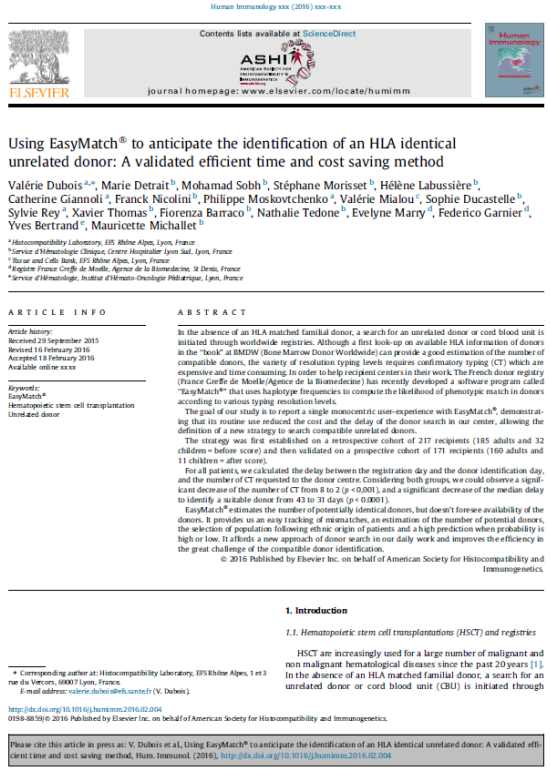
Easymatch

- *Easymatch evaluates the most likely phenotypes and frequencies of donors matching the patient's phenotype before getting results of confirmatory and additional typing.*
  - *Tools to select the minimal level of confirmatory and additional typing needed*
  - *Adopt patient centric approach + deployed in over 30 centers*
- *Training is needed and may be hosted by RFGM – On-line Assistance*
  - *Over 5,000 uses*
  - *Service could be open to any registry in the world*
- ***Validation***
  - *Reduction time to decision (50%)*
  - *$$ Saving on unnecessary confirmatory typing / blood samples*
  - *User – reported*

Easymatch in Use

- Applicatin in secure Registry IT
- Publication by users
  - Dubois et al. 2016 HIM



Human Immunology xxx (2016) xxx–xxx

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Using EasyMatch® to anticipate the identification of an HLA identical unrelated donor: A validated efficient time and cost saving method

Valérie Dubois [a,*], Marie Detrait [b], Mohamad Sobh [b], Stéphane Morisset [b], Hélène Labussière [b], Catherine Giannoli [a], Franck Nicolini [b], Philippe Moskovtchenko [a], Valérie Mialou [c], Sophie Ducastelle [b], Sylvie Rey [a], Xavier Thomas [b], Fiorenza Barraco [b], Nathalie Tedone [b], Evelyne Marry [d], Federico Garnier [d], Yves Bertrand [e], Mauricette Michallet [b]

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ABSTRACT

In the absence of an HLA matched familial donor, a search for an unrelated donor or cord blood unit is initiated through worldwide registries. Although a first look-up on available HLA information of donors in the "book" at BMDW (Bone Marrow Donor Worldwide) can provide a good estimation of the number of compatible donors, the variety of resolution typing levels requires confirmatory typing (CT) which are expensive and time consuming. In order to help recipient centers in their work, The French donor registry (France Greffe de Moelle/Agence de la Biomedecine) has recently developed a software program called "EasyMatch®" that uses haplotype frequencies to compute the likelihood of phenotypic match in donors according to various typing resolution levels.

The goal of our study is to report a single monocentric user-experience with EasyMatch®, demonstrating that its routine use reduced the cost and the delay of the donor search in our center, allowing the definition of a new strategy to search compatible unrelated donors.

The strategy was first established on a retrospective cohort of 217 recipients (185 adults and 32 children = before score) and then validated on a prospective cohort of 171 recipients (160 adults and 11 children = after score).

For all patients, we calculated the delay between the registration day and the donor identification day, and the number of CT requested to the donor centre. Considering both groups, we could observe a significant decrease of the number of CT from 8 to 2 ($p < 0{,}001$), and a significant decrease of the median delay to identify a suitable donor from 43 to 31 days ($p < 0.0001$).

EasyMatch® estimates the number of potentially identical donors, but doesn't foresee availability of the donors. It provides us an easy tracking of mismatches, an estimation of the number of potential donors, the selection of population following ethnic origin of patients and a high prediction when probability is high or low. It affords a new approach of donor search in our daily work and improves the efficiency in the great challenge of the compatible donor identification.

1. Introduction

1.1. Hematopoietic stem cell transplantations (HSCT) and registries

HSCT are increasingly used for a large number of malignant and non malignant hematological diseases since the past 20 years [1]. In the absence of an HLA matched familial donor, a search for an unrelated donor or cord blood unit (CBU) is initiated through

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0198-8859/

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- Web accessible “Easy-HLA”
- Research-use only – to recommend typing strategies

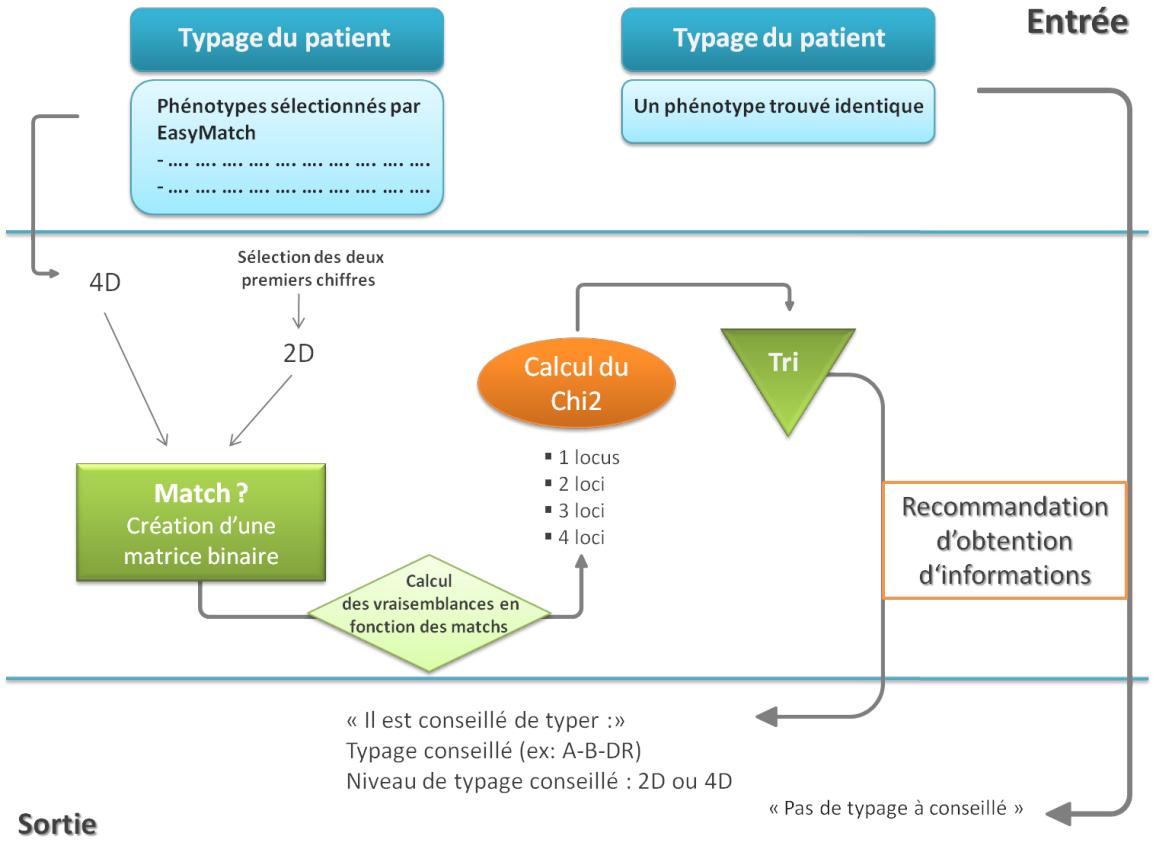
Easy-HLA

Algorithme de recommandation de prescription de typage(s) à effectuer

Il est préférable de faire :

- un typage 2D plutôt qu'un typage 4D
- un typage sur 1 locus plutôt que plusieurs

Basé sur la formule du Chi2 d'ajustement qui permet la mesure globale de l'écart entre des données observées et des données théoriques.(à minimiser)



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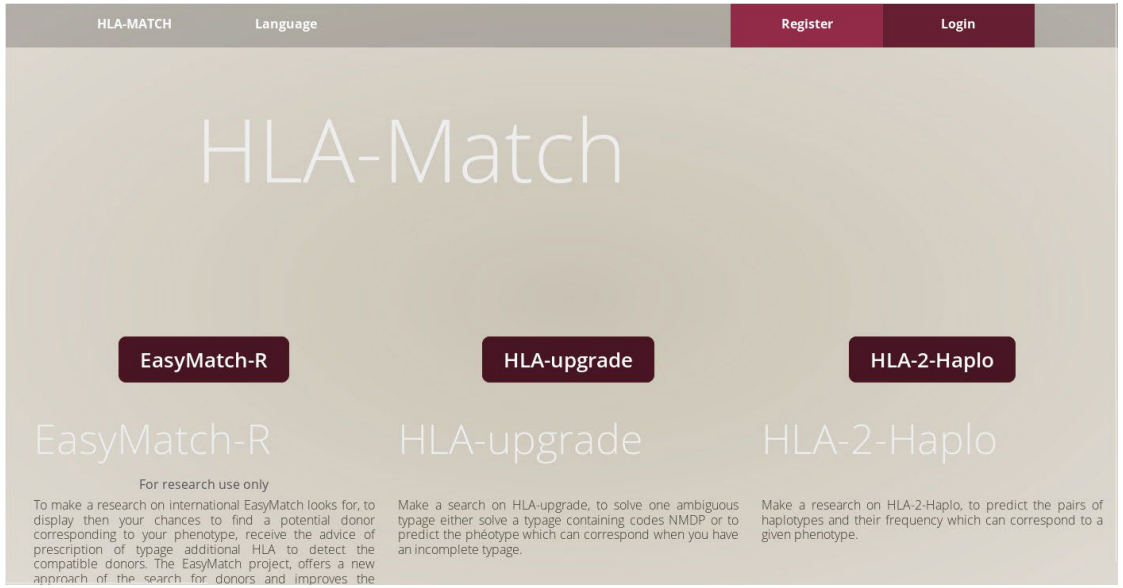
Recommandation d'obtention d'informations en médecine personnalisée

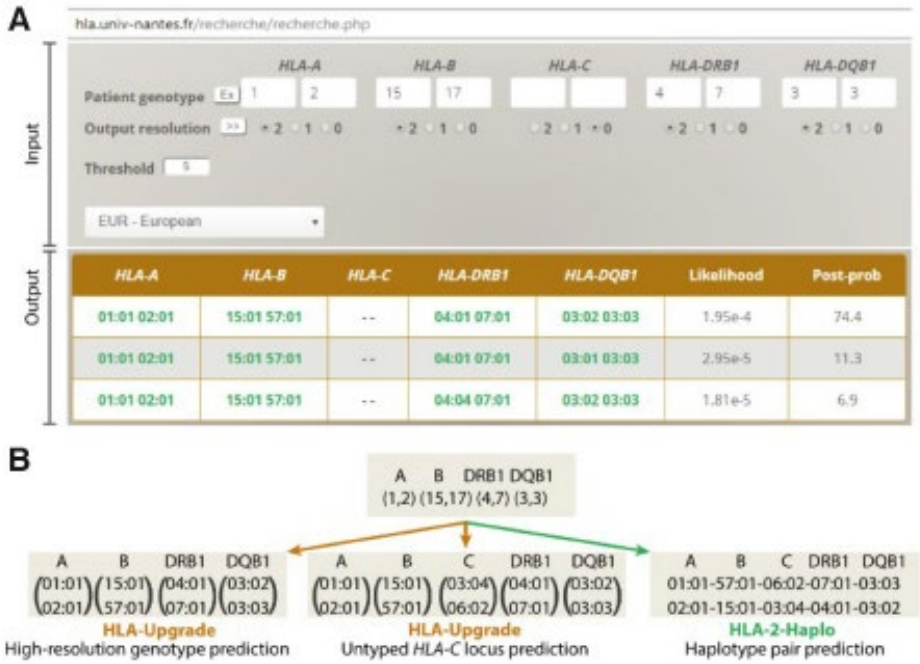
- Site web fonctionnel
HLA.univ-nantes.fr

- Algorithme réalisé avec R, optimisé et intégré dans le site EasyMatch International.
- Création d'une base de données : composé d'haplotypes HLA représentatif de la population mondiale et leur vraisemblance dans la population.
- Mise en place du serveur et mise en ligne du site.
- Développement de 2 nouveaux outils basés sur les fréquences haplotypiques des HLAs(HLA-2Haplo & HLA-upgrade).



From research to tools and back to clinic

- Precision medicine - Starting point is a single Patient
- Patient of interest (POI) ; n= 1



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Advance Access Publication Date: 21 November 2019
Original Paper
OXFORD

Genetics and population analysis

Easy-HLA: a validated web application suite to reveal the full details of HLA typing

Estelle Geffard[1,*], Sophie Limou[1], Alexandre Walencik[1,2], Michelle Daya[3], Harold Watson[4], Dara Torgerson[5], Kathleen C. Barnes on behalf of CAAPA[3], Anne Cesbron Gautier[2], Pierre-Antoine Gourraud[1,*] and Nicolas Vince[1]

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*To whom correspondence should be addressed.
Associate Editor: Alfonso Valencia

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Abstract

Motivation: The HLA system plays a pivotal role in both clinical applications and immunology research. Typing HLA genes in patient and donor is indeed required in hematopoietic stem cell and solid-organ transplantation, and the histocompatibility complex region exhibits countless genetic associations with immune-related pathologies. Since the discovery of HLA antigens, the HLA system nomenclature and typing methods have constantly evolved, which leads to difficulties in using data generated with older methodologies.

Results: Here, we present Easy-HLA, a web-based software suite designed to facilitate analysis and gain knowledge from HLA typing, regardless of nomenclature or typing method. Easy-HLA implements a computational and statistical method of HLA haplotypes inference based on published reference populations containing over 600 000 haplotypes to upgrade missing or partial HLA information: 'HLA-Upgrade' tool infers high-resolution HLA typing and 'HLA-2-Haplo' imputes haplotype pairs and provides additional functional annotations (e.g. amino acids and KIR ligands). We validated both tools using two independent cohorts (total $n = 2500$). For HLA-Upgrade, we reached a prediction accuracy of 92% from low- to high-resolution of European genotypes. We observed a 96% call rate and 76% accuracy with HLA-2-Haplo European haplotype pairs prediction. In conclusion, Easy-HLA tools facilitate large-scale immunogenetic analysis and promotes the multi-faceted HLA expertise beyond allelic associations by providing new functional immunogenomics parameters.

Availability and implementation: Easy-HLA is a web application freely available (free account) at: https://hla.univ-nantes.fr.

Contact: easyhla@gmail.com or pierre-antoine.gourraud@univ-nantes.fr

Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

HLA genes from the major histocompatibility complex (MHC) encode a specific group of cell surface molecules mediating recognition of non-self-antigens by the immune system. HLA plays key roles in transplantation management and success. HLA matching between a patient and potential donors is essential in hematopoietic stem cell transplantation (HSCT) (Copelan, 2006; Loiseau *et al.*, 2007) and solid-organ transplantations (Held *et al.*, 1994). Donor-recipient compatibility is defined by the number of alleles shared across HLA-A, -B, -C, -DRB1 and -DQB1 genes. The chance of graft success is optimal when donor and recipient are fully compatible and have the lowest number of HLA alleles mismatches (Lee *et al.*, 2007; Zachary and Leffell, 2016). The level of typing resolution is positively correlated with the probability of allele matching during donor search. Additionally, time restrictions in solid-organ transplantation from deceased donors often make HLA allele high-resolution typing impossible, and only intermediate resolution or even low-resolution genotyping may be available at the time of organ allocation. Beyond these major clinical impacts, HLA has

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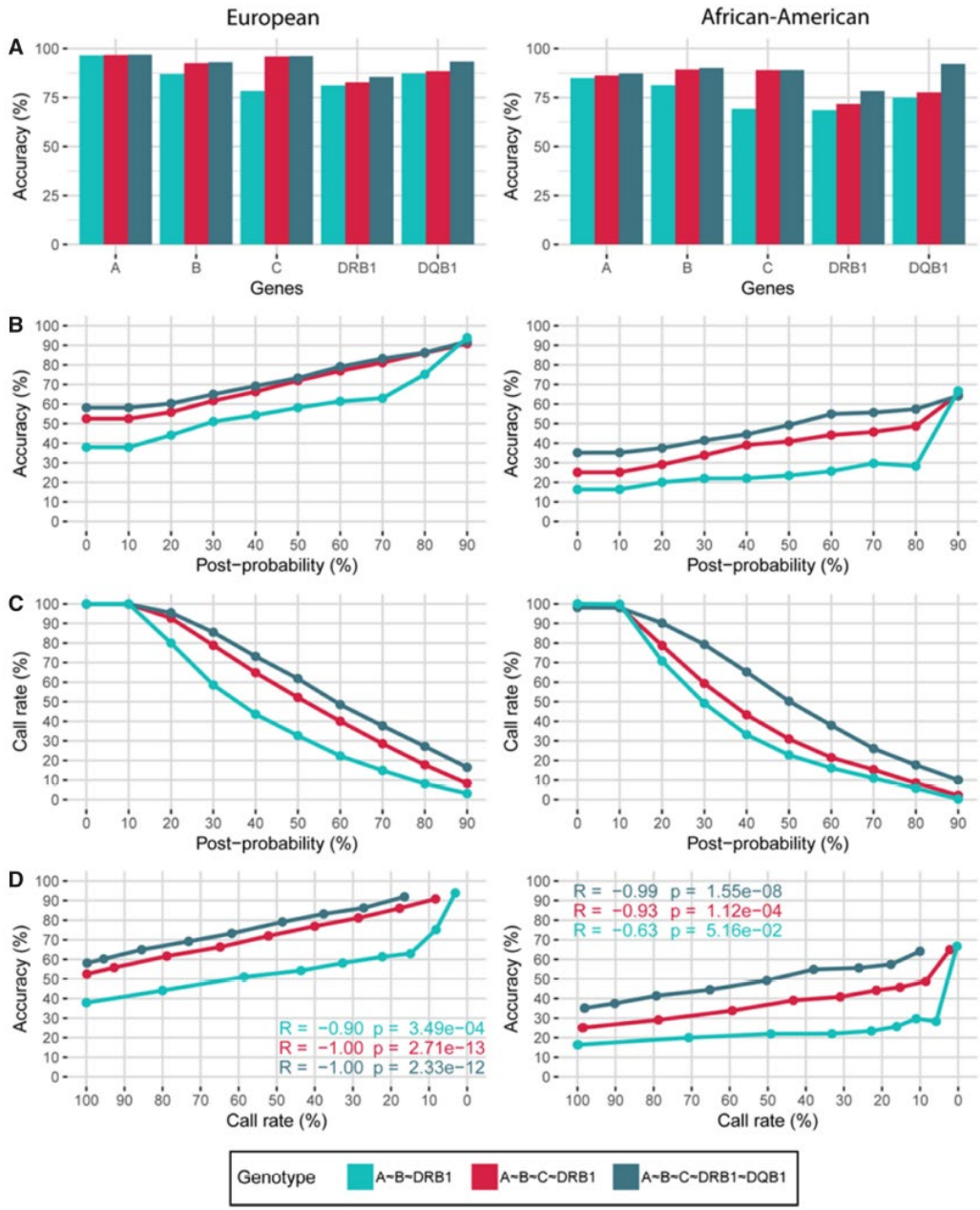
Tools need validations…

- **Method:**
  - To validate prediction in various ethnic background
  - Accordine multiple

- **Results :**
- Ancestral background matters
- Variable by locus
- At genotype level.



Pôle Santé
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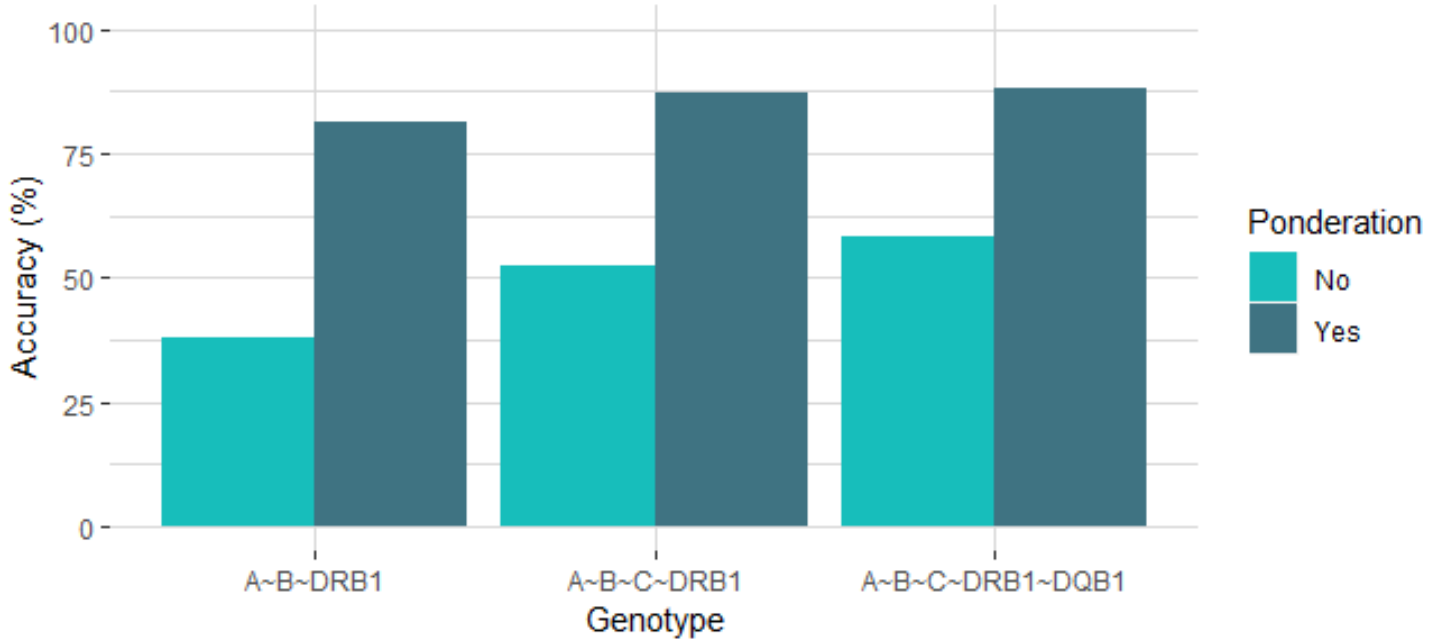
It is all about weights …

Figure S5 – Comparison of HLA-Upgrade accuracy prediction with and without weighting in the European population (post-probability threshold set at 0%).

- *HLA-A~B~C~DRB1~DQB1* high-resolution genotypes were predicted from different gene combinations of first-field genotypes: *HLA-A~B~DRB1*, *HLA-A~B~C~DRB1* , *HLA-A~B~C~DRB1~DQB1*.
- Calculation of accuracy using weighting by multiplying post-probability by genotype frequencies (dark blue). Original accuracy considers all genotypes as equal and is calculated as: correctly predicted genotypes / predicted genotypes.
- Weighted accuracy considers genotypes frequencies in the equation and is calculated as: sum of the frequencies of correctly predicted genotypes / sum of the frequencies of predicted genotypes.



Conclusion

- **Precision Medicine:** is bridging the gap between population complexity and individual decision making using Statistical models and IT tools
- *Illustration HSCT*
  - *quantitative assessment of Rare / frequent types*
  - *Research in pop → prediction in individuals → tool → secured expert usage → open access*
- Data + Mathematical modelling + decision
- Defer decision to algorithm or substantiate decision making with data ?

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Jeudi 1 février 2024 14hr00

Pr Patrice Chevallier / Pr Pierre-Antoine Gourraud

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