Clinical benefit for the community
Ethical issues and opportunities involved in mass genotyping of blood groups

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Clinical benefit

- enhanced sensitivity
- enhanced specificity
- less invasive procedures
- more specific, „individualized“ therapy
- proactive ethics
- cost containment
- addressed in all contributions to this symposium

Clinical benefit: sensitivity

- detection of clinically relevant signals
  - that are too weak for detection by serology
- finds signals that escape detection by current serology
  - detects weaker signals
    - or
  - allows for less invasive procedures
    - or both

Clinical benefit: specificity

- detection of clinically relevant signals
  - that cannot be discriminated by antibodies
- is based on the „building blocks“ rather than the „constituting“ signals
  - detects very polymorphic systems = large number of variants
    - or
  - allows discrimination of any minute difference, if clinically required
    - or both

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“Several age-old controversies about blood group genetics have been resolved.“

- many serologic entities
  - confirmed by molecular methods
  - with disputed serologic distinctions were proven correct
- “cut-off“ between various A antigens
- one vs. three gene hypothesis in RhD
- specific discrimination: D pos. - D neg.
- weak D antigens are distinct D antigens
- “lack“ of anti-Fy^b in Fy^b neg. recipients

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Examples: sensitivity

- there is a multitude of examples for much enhanced sensitivity
  - prenatal diagnosis (D pos./neg.)
  - polytransfused patients (Fy/Jk)
  - *RHD* testing in D neg. donors
- molecular, usually PCR-based, methods are almost invariably more sensitive than antibody-based methods

Examples: specificity

- detection of the “building blocks“ enables discrimination power unmatched by serology:
  - alleles expressing weak antigens
    - for instance, A_x and A_{el} or Fy^x alleles
    - in particular, weak D alleles
  - alleles expressing slightly differing antigens
    - in particular, partial D alleles
  - *RHD* deletion in heterozygous fathers

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Allele polymorphism - more complex than anticipated

- Caveat
  - molecular methods may “see“ more than needed for safe patient care
    - clearly true, but “cut off“ needs to be defined anew
- Opportunity
  - unless we have “seen“ it, we may not know, if it is needed for patient care
- Examples
  - A alleles
  - “D neg.“ donors, some weak D types
  - *Fy*^{b} vs. *Fy*^{x}

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Examples: what we have not "seen" before

- D neg. donor was found to be weak D type 1
  - look back to 1 recipient
  - revealed 1 anti-D immunization event
    - Transfusion 44(2004)Suppl. 9S:114A
- D neg. donor was found to be D+/D- chimera
  - look back to some of the 13 recipients
  - revealed at least 2 anti-D immunization events
    - BMC Genet 2(2001)10
- Anti-D in D neg. recipient
  - trace back to 7 donors
  - revealed a weak D type 2 donor
    - Transfusion 40(2000)428

Cost containment effects by individualized therapy

- fetal DNA testing from maternal plasma
  - to avoid anti-D prophylaxis, if fetus is D neg.
  - in about 40 % of all current indications
- specific detection of weak D types
  - to avoid anti-D prophylaxis, if mother carries any prevalent weak D type
  - to avoid loss of D neg. units, if recipient is weak D pos.
  - in up to 5 % of current applications

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Blood group databases

- are one of the largest medical datasets available
  - within a given population
    - cover often about 10 % of the whole population
  - among different populations world-wide
    - have been collated and improved since 1920s
- provide the framework to evaluate and improve modern blood group genotyping

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Economies of scale

- > 15 mio ABO/Rh testings required per year in blood centers in Europe

- may be safely used in repeat donations
  - to confirm known ABO/Rh results
  - to provide antigen typing for other blood group systems, like FY and JK
- would provide a platform technology

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Why suitable as platform technology?

- basic research issues resolved recently
- large number of testings required
  - blood banks are used to handle such large volumes
- can easily be extended to genes other than blood groups
  - DNA & RNA testing for viral markers in blood donors
  - HLA for platelets and bone marrow/organ transplants
- blood group genotyping may well be accepted as a worthwhile investment by the community
  - Why is this?

Public is rightfully concerned with genotyping issues in general

- however, utility of blood group genotyping has been proven
  - new interpretation issues arising for years
  - have been resolved by standard techniques
- current knowledge framework provides
  - firm basis for a viable and sound approach
  - to ethical issues in genotyping
- public is used to immuno“genetics“ with blood groups

Proactive ethics: no adverse ethical or legal issues

- “standard“ blood group antigens
  - are usually not disease associated
- clinical relevance can be resolved by utilizing standard immunohematology
  - this is in difference to most genotyping applications, like tumor genotyping
- blood group immuno“genetics“
  - the community is used to it for decades
  - the public feels comfortable with it

Genetic information: a joint account?

- genetic information is often considered highly personal
- yet, in transfusion medicine family members are approached, because of a patient‘s blood group
  - common practice for decades
  - extensive experience by transfusion medicine specialists
  - hardly controversial
- most often, no risk of serious harm to index patients or their relatives
  - BMJ 329(2004)165

Tranfusion medicine is a discipline with a future *

- immunohematology will partake in and contribute to this future
- because we advance technology in a field of relevance to the community
- expertise gained by mass genotyping for blood groups
  - may be applicable to genotyping in general
  - may provide a platform technology for other genotyping approaches

* J McCullough, Transfusion 42(2003)823

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Genotyping is an ethically challenged field.

Blood group genotyping will allow us to contribute to this field in an ethically sound and proactive way for the benefit of the patients and the community.

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