An Ethical Challenge: Informing and Counselling Donors About Genetic Findings

Thilo Mengling, Janine Höffer, Jürgen Sauter, Julia Stolze, Alexander H. Schmidt

DKMS, Tübingen, Germany

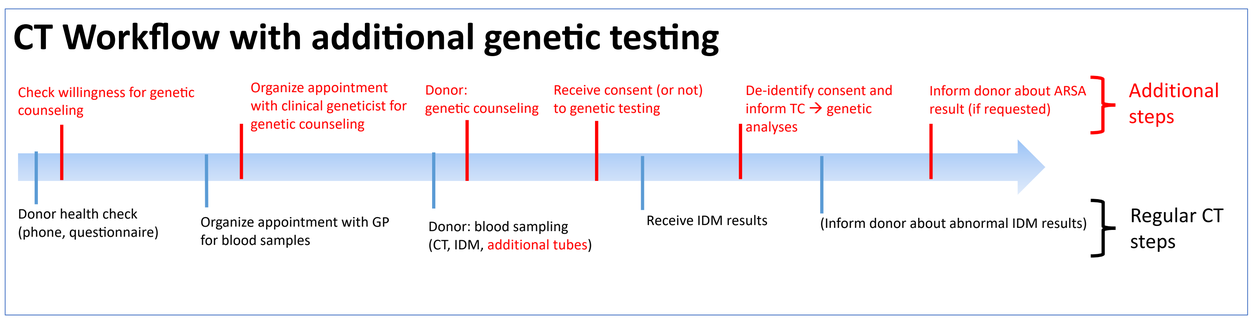
Overview

Genetic diagnostics on HSC donors or indirectly on donor cells after transplantation provide distinct ethical, logistic and legal challenges for donor centers. In order to sensitize for the possible implications and necessary efforts, we present different aspects of genetic findings in donors.
Due to technological advances and stricter regulations, even more findings and subsequent decisions about counselling can be expected in the future. Discussing and aligning strategies to address potential concern for stem cell donors within WMDA could reduce the ethical burden for donor centers and registries.

Genetic Counselling at CT - Level

In 2017, DKMS received CT requests for two patients with metachromatic leukodystrophy. Here, we describe how the requirements to obtain donor consent before arylsulfatase A genotyping were met to ensure donors with wild type ARSA allels for high enzyme activity.

CT Workflow with additional genetic testing



Outcome

- 5x donor consent to testing, 5x interested in results
- 4x tested (1 donor not available for BM donation)
- 4x homozygous wt / wt
- Patients transplanted in July (m) and August (f) 2017
- Both patients doing well regarding TX, m > f (more advanced disease)

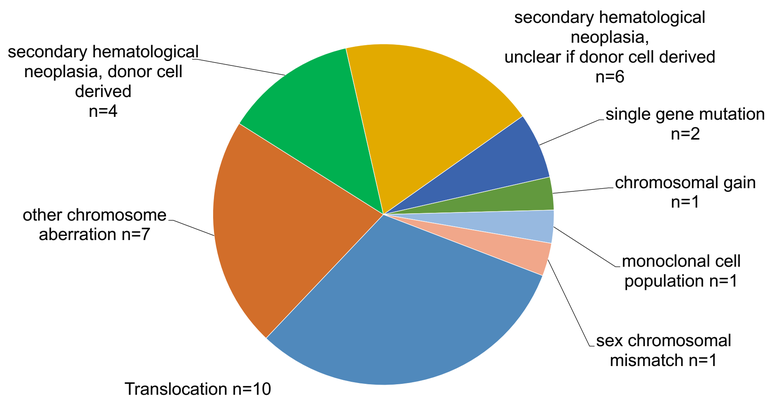
Feasibility as a routine request?

- ✓ Additional genetic testing during CT is feasible, but requires substantial additional resources and time
- ✓ Genetic counselling capacities limited by scarcity of clinical geneticist (1 clinical geneticist for 200 000 inhabitants in Germany)
- ✓ Anonymity rules for unrelated stem cell donation provide additional challenges:
  - ❖ counselling without giving away recipient's diagnosis
  - ❖ Inform donor about test results without disclosing TC identity

Incidencial findings after transplantation

Routine cytogenetic and molecular diagnostics in stem cell transplant recipients can reveal acquired or constitutional abnormalities in donor cells. Due to the lack of a formal consent for genetic testing and uncertainty to which extent donors wish to be informed, the donor center has to decide if clinical relevance for the donor outweighs the right not to know.

Overview of incidental genetic findings in DKMS donors from 2014 – 2017



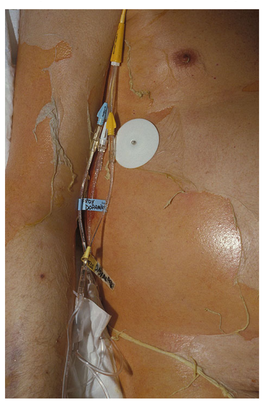
ID	Sex	Age	Counseling recommended	Type of abnormality	Karyotype / abnormality
1	M	56	Yes	translocation	46XY, t(6;16) (p10;10)
2	M	41	Yes	inversion	46XY, inv(7) (p21p13) (15)
3	F	30	Yes	translocation	46XX, ?t(4;6) (p12;p22)c(20)
4	M	49	No	secondary hematological neoplasia (donor cell derived)	MDS 2y after TX, monosomy 7 in 30%, 98% donor chimärismus
5	M	30	No	chromosomal gain	gain on the TCF3 gene in about 73% cells @d100, later normalized
6	M	30	Yes	translocation	46XY, t(6;17) (q13;p13)
7	M	47	No	secondary hematological neoplasia (donor cell derived)	13% malignant plasmacell population in the BM, 180d after TX, 100% chimerism
8	F	60	No	secondary hematological neoplasia (donor cell derived)	MDS 10y after TX
9	F	42	No	inversion	inv(2)(p11.2q13)
10	M	56	Yes	numerical chromosome aberration	XXY
11	M	35	No	secondary hematological neoplasia (donor cell derived?)	lymphoplasmacytic lymphoma 4m after TX; normal BM, no clonal population 1m later
12	F	53	No	secondary hematological neoplasia (donor cell derived?)	B-cell lymphoma with extensive plasmacytic differentiation 2y after TX
13	M	38	Yes	translocation	reciprocal translocation 46 XY,t(11;22)(q23;q11)c(allograft)[8+12c]
14	M	34	Yes	translocation	t(5;11) (p1?3;q2?1)
15	M	25	No	secondary hematological neoplasia (donor cell derived?)	suspected AML 2y after TX, trisomy 8 and 21 in 29% of cells
16	F	35	No	secondary hematological neoplasia (donor cell derived?)	relapse or 2nd MDS 2y after TX
17	M	29	No	single gene mutation	deletion in the CFHR1 gene **assoc.** with HUS (*presumed* CoD)
18	M	33	Yes	translocation	45XY, t(13;14)
19	F	56	N	secondary hematological neoplasia (donor cell derived?)	relapse or 2nd ALL 1y after TX
20	M	48	No	secondary hematological neoplasia (donor cell derived)	AML 17y after TX
21	M	24	Yes	translocation	45, XY, rob der(13;14) (q10; q10)
22	(M)	34	Yes	sex chromosomal mismatch/single gene mutation	SRY+ XX
23	F	43	Yes	translocation	45XX, rob(13;14)(q10;q10)
24	F	22	No	secondary hematological neoplasia (donor cell derived?)	Smoldering Multiple Myeloma 15 months, partial chimerism
25	M	23	Yes	translocation	46 XY, t(4;10)
26	M	27	unclear	inversion (waiting for confirmation)	chromosome 10 inversion NOS
27	M	42	Yes	monoclonal cell population *in the product*	abnormal B cell population (CD19+ und CD20-)
28	M	51	Yes	deletion	del 20q (relapse after 1y WITHOUT del20)
29	M	40	Yes	single gene mutation	hemochromatosis
30	F	47	Yes	numerical chromosome aberration	Turner mosaic, single X-chromosome (donor, 5/25) / normal female karyotype (donor, 20/25)
31	F	26	Yes	translocation	balanced chromosome translocation of t(10,22)
32	F	34	No	insertion	additional material on the long arm of chromosome 7 (not entirely clear if in donor or recipient cells), Chimerism @ d100

Conditions associated with HLA alleles

Conditions associated with HLA alleles

HLA-B27	ankylosing spondylitis, reactive arthritis
HLA-DQB1*06:02	Narkolepsy
HLA-A*31:01	Carbamazepine
HLA-B*15:02	Carbamazepine
HLA-B*57:01	Abacavir
HLA-B*58:01	Allopurinol

Toxic epidermal necrolysis



Source: Wikimedia

From **"Amendments to the product information of the nationally authorised medicinal products"**

Section 4.4 Special warnings and precautions for use:
The HLA-B*5801 allele has been shown to be associated with the risk of developing allopurinol related hypersensitivity syndrome and SJS/TEN. The frequency of the HLA-B*5801 allele varies widely between ethnic populations: up to 20% in Han Chinese population, 8-15% in the Thai, about 12% in the Korean population and 1-2% in individuals of Japanese or European origin.

Screening for HLA-B*5801 should be considered before starting treatment with allopurinol in patient subgroups where the prevalence of this allele is known to be high. (…) The use of genotyping has not been established in other patient populations.
If the patient is a known carrier for HLA-B*5801 **allopurinol should not be started unless there are no other reasonable therapeutic options**

http://www.ema.europa.eu/docs/en_GB/document_library/Periodic_safety_update_single_assessment/2017/10/WC500237281.pdf

DKMS
WIR BESIEGEN BLUTKREBS

DKMS gGmbH
Kressbach 1
72072 Tübingen, Germany
www.dkms.de

Author contact:
tmengling@dkms.de