DOCK8 Deficiency: extended clinical phenotypes and the impact of somatic reversions

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Abstract

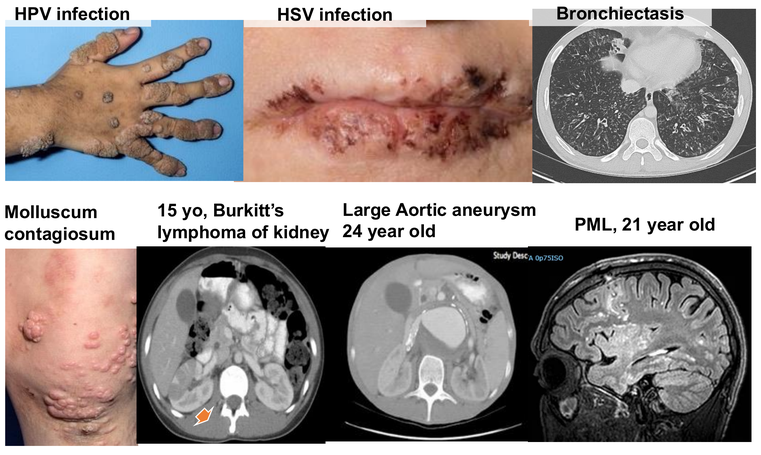
Introduction: DOCK8 deficiency is a rare combined immunodeficiency characterized by atopy, recurrent oto-sinopulmonary infections, viral skin infections, and malignancy. Mortality is approximately 50% by age 20 without curative hematopoietic cell transplantation (HCT). We clinically phenotyped our cohort and assessed whether somatic reversions in lymphocytes impacted clinical severity.

Methods: We reviewed the clinical characteristics, laboratory studies, and outcomes of 59 patients with DOCK8 deficiency evaluated at the NIH Clinical Center. Twenty-one anti-cytokine autoantibodies were screened using a multiplex particle-based assay. Somatic reversions restoring DOCK8 protein expression in lymphocytes were assessed by flow cytometry in 49 patients.

Results: The median age at initial evaluation was 10 years (range 0.5-42), with 54% female. The most common clinical findings were sinopulmonary infections (96.6%), recurrent or chronic viral skin infections (96.6%), and eczema (93.2%). End-organ damage included bronchiectasis (44.1%), liver disease (primarily *Cryptosporidium*-related) (28.1%), and vasculopathy (17.9%). Malignancies (27.1%) included squamous cell carcinoma (13.6%) and lymphoma (23.7%). Laboratory findings showed elevated serum IgE (87.9%), low serum IgM (62.1%), and lymphopenia affecting CD4 (64.9%), CD8 (43.9%), and NK cells (52.6%). The overall survival was 64% (age of death 7-45 years; median 18). Forty-five patients (76.3%) underwent HCT with a survival rate of 75.6%; 14 (23.7%) did not undergo HCT with a survival rate of 21.4%. Neutralizing autoantibodies against type I/II interferons were not detected in 57 patients. Forty-nine patients were assessed for lymphocyte somatic reversions; 23 had reversions in lymphocytes, while 26 either did not have reversions or had mutations (e.g., large homozygous deletions) that could not be reverted. Patients with reversions had milder eczema, an increased incidence of warts, older age at HCT, and less CD8 lymphopenia; other clinical features, including malignancy and mortality did not differ from those without reversions.

Conclusions: DOCK8 deficiency is associated with a high incidence of morbidity and mortality by early adulthood without curative HCT. Neutralizing autoantibodies against type I/II interferon were not present despite a high burden of viral infections. Somatic reversions were common, but did not preclude life-threatening complications including malignancy.

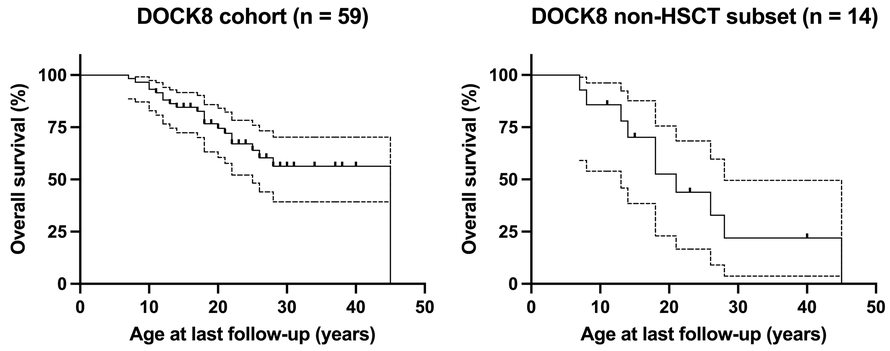
Physical Exam and Clinical Imaging Findings



Anti-Cytokine Antibodies

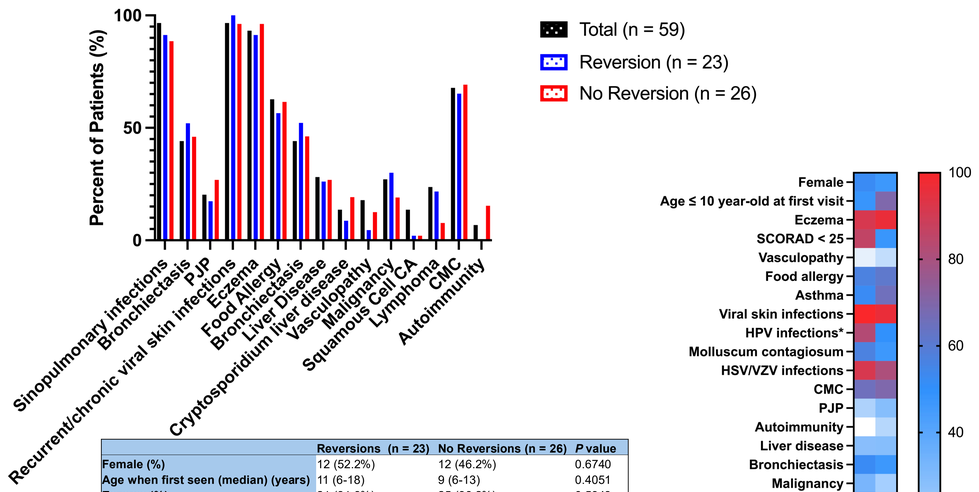
Due to the high incidence of viral skin infections, patients' plasma was screened for the presence of Interferon Type I/II auto-antibodies. Neutralizing antibodies were not found.

Survival Curves



Survival curve with 95th percentile confidence intervals. Without transplant, survival appears similar to prior reports with about 50% mortality around 20 years of life highlighting the need for definitive therapy with HSCT.

Clinical Features and Impact of Reversions



	Reversions (n = 23)	No Reversions (n = 26)	*P* value
Female (%)	12 (52.2%)	12 (46.2%)	0.6740
Age when first seen (median) (years)	11 (6-18)	9 (6-13)	0.4051
Eczema (%)	21 (91.3%)	25 (96.2%)	0.5943
SCORAD (median) *	14.8 (6.5-21.3)	25.0 (15.6-36.9)	0.0404
Vasculopathy (%)	1/22 (4.5%)	3/24 (12.5%)	0.6093
Food allergy (%)	13 (56.5%)	16 (61.5%)	0.7214
Viral skin infections (%)	23 (100.0%)	25 (96.2%)	1.0000
HPV infections (%)	19 (82.6%)	13 (50.0%)	0.0338
Molluscum contagiosum (%)	13 (56.5%)	12 (46.2%)	0.4687
HSV/VZV infections (%)	21 (91.3%)	21 (80.8%)	0.4238
PJP (%)	4 (17.4%)	7 (26.9%)	0.5062
Autoimmunity (%)	0 (0.0%)	4 (15.4%)	0.1124
Liver disease (%)	6 (26.1%)	7 (26.9%)	0.9473
Bronchiectasis (%)	12 (52.2%)	12 (46.2%)	0.6740
Malignancy (%)	7 (30.4%)	5 (19.2%)	0.3627
SCC (%)	2 (8.7%)	3 (11.5%)	1.0000
Lymphoma (%)	5 (21.7%)	2 (7.7%)	0.2300
Age at HCT (median) (years)	19 (12-22)	10 (9-15)	0.0055
Death (%)	4 (17.4%)	11 (42.3%)	0.0714
HCT-related death (%)	3/4 (75.0%)	7/11 (63.6%)	1.0000
Elevated Serum IgE	20 (87%)	23 (88.5%)	1.0000
Low CD3 (%)	11 (47.8%)	18 (69.2%)	0.3571
Low CD4 (%)	13 (56.5%)	18 (69.2%)	0.3571
low CD8 (%)	6 (26.1%)	14 (53.8%)	0.0485
low NK (%)	11 (47.8%)	12 (46.2%)	0.9068
Low B cells (%)	1 (4.3%)	2 (7.7%)	1.0000

* SCORAD was available only for 14 with reversions and 26 without reversions

Impact of Reversions: Significant differences were seen between those with reversions and those in severity of eczema (worse in those without), chronic wart infection (more in those with reversions), age at transplant (older for those with reversion), and CD8 lymphopenia (more common in those without). The increased HPV may relate to the older age at HSCT.

Mortality

Overall Survival: 64% (38/59)	
Survival without Transplant:	
Alive	29% (4/14)
Ages at death: 7-45 years (median 18)	Causes: Malignancy (6), bacteremia (1), pulmonary failure (1), heart failure (1), PML (1)
Survival with Transplant:	
Alive	76% (34/45)
Median age at transplant: 14yrs (6-31)	Current median age for those surviving post-HSCT: 29years (11-40)
Prior malignancy in 10 pre-HSCT, 3 of whom died of HSCT complications	Prior Cryptosporidium-related liver disease in 8 pre-HSCT, 2 of whom died of liver related complications post-HSCT

Conclusion

- The most common clinical features included: sinopulmonary infections, atopy, cutaneous viral infections, and CMC.
- Vasculopathy/vasculitis affecting cerebral vessels and the aorta remain poorly understood and are infrequent but can cause significant morbidity and affect management, therefore requiring consideration and screening.
- Cryptosporidium was increasingly recognized to cause biliary/liver disease as PCR techniques became available. Two transplant deaths were related to Cryptosporidium- related liver disease thus highlighting the importance of screening by PCR when liver disease is present and HSCT prior to end-organ toxicity.
- Reversion mutations were common and had some clinical effects. However, differences were not seen in significant causes of morbidity and mortality such as malignancy including lymphoma. HSCT should be considered despite presence of reversions. Future work will entail delineating the cell types affected and degree of reversions.

References

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