Job Research Foundation Report

Investigating Health Status and Quality of Life in Patients with STAT3-DN-HIES

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Study Background:

Dominant negative mutations in signal transduction and activator of transcription 3 (STAT3) confer a multisystem immunodeficiency syndrome with recurrent staphylococcal pneumonia, eczema, and cutaneous abscess formation in patients with elevated IgE levels (STAT3-HIES). Whilst national registry studies have expanded understanding of the genotype and phenotype of this disease to include connective tissue disease and vasculopathy, description of the health status of this patient group has been limited by its rarity and similarity to other inborn errors of immunity, and there is little understanding of the impact of this disease on quality of life (QOL).

Whilst initially conceived to include patients from the United Kingdom, Italy, and the cohort based at the National Institutes of Health in Maryland, the study has expanded to incorporate patients from other European countries, Central and South America, and Asia and the Middle East.

Preliminary Results:

Data have been collected and analysed for 259 patients from 27 countries. Clinical data are available for 239 patients, and QOL data for 191 patients. Following this preliminary analysis, further data have been collected bringing the total dataset to 346 patients, with clinical data for 301 patients and QOL data for 262 patients.

The results of the preliminary analyses are detailed below.

<u>Demographic Data:</u>

Two hundred and fifty-nine patients have been recruited from 27 countries (children: 112 [43%], adults: 147 [57%]).

Patients were predominately recruited from Europe and North America, and patients from the USA, United Kingdom and Germany accounted for >50% of the cohort.

Geographic Region	Patients	%
Asia and Middle East	66	25.5
Australia	3	1.2
Central and South America	6	2.3
Europe	101	39.0
North America	83	32.0
Total	**259**	**100.0%**

Median patient age was 21.9 years (interquartile range [IQR]: 12.0 – 31.0) and median duration of follow-up from clinical diagnosis to latest review was 11.0 years. There was a positive family history in 53/244 (21.7%) cases. Median age at onset of STAT3-DN-HIES-related symptoms, at clinical diagnosis, and at confirmatory genetic diagnosis were 0.1 years, 5.0 years, and 10.0 years, respectively.

Clinical Characteristics:

STAT3 mutations predominately affected the DNA binding (54.3%) and SH2 domains (33.8%). The majority of mutations were missense (n=203, 92.3%), consistent with previous data. The most commonly affected codons were R382 (corresponding to c.1144C>T/G or c.1145G>A, n=72, 33.5%) and V637 (c.1909G>A, n=23, 10.7%). The domain impacted by STAT3 mutations did not vary significantly by patient ethnicity, but did vary by patient region, with a relative under-representation of DNA binding-domain mutations and over-representation of SH2 domain mutations in European patients.

STAT3 Mutation Site	Asia and Middle East	Europe	North America	P
DNA binding domain	30 (57.7)	34 (41.0)	53 (67.9)	
SH2 domain	17 (32.7)	32 (38.6)	21 (26.9)	
Amino terminal	1 (1.9)	3 (3.6)	0 (0)	0.035
Linker	2 (3.8)	2 (2.4)	0 (0)	
Transactivation	2 (3.8)	10 (12.0)	4 (5.1)	

Characteristic manifestations included pneumonia (87.6%), lung abscess (48.5%), pneumatocoele (43.0%), eczema (90.5%) and delayed exfoliation of primary teeth (67.1%).

Pulmonary disease was common, and 82% of adult patients had >3 lifetime episodes of pneumonia suggesting that while patients typically present early in life with LRTI, patients continue to experience recurrent infection into and throughout adulthood despite antimicrobial prophylaxis. Parenchymal lung disease, defined as presence of bronchiectasis or pneumatocoele, was present in 62% of patients. A multivariable logistic regression model of incidence of bronchiectasis identified that successive episodes of pneumonia increase the odds of a diagnosis of bronchiectasis compared to patients who do not have pneumonia, from 3 times (first episode) to >10 times (beyond 3 episodes).

Variable	OR	95% CI	P
Age	1.068	1.039 – 1.097	<0.001
Pneumonia episodes			0.001
1 episode	3.317	0.708 – 15.543	0.128
2 episodes	5.367	1.203 – 23.939	0.028
3 episodes	14.407	2.319 – 89.508	0.004
>3 episodes	10.710	2.922 – 39.254	<0.001
Antimicrobial prophylaxis	1.885	0.775 – 4.586	0.162
IgRT	0.970	0.497 – 1.893	0.929
Constant	0.020		<0.001

Overall, 78/241 (32.1%) patients had a history of pulmonary fungal disease. This was overwhelmingly related to *Aspergillus* species; in addition to these, candida (3 patients) and mucor (1 patient) were also isolated. Manifestations of aspergillus infection were aspergilloma (n=22, 32.5%), IPA (n=16, 23.8%), and ABPA (n=12, 19.5%); for the remainder of cases, no manifestation was documented. *Aspergillus* species isolated included: *fumigatus, niger, sydowii, versicolor, ustus*, and *westerdijkiae*, with *Aspergillus fumigatus* being most common.

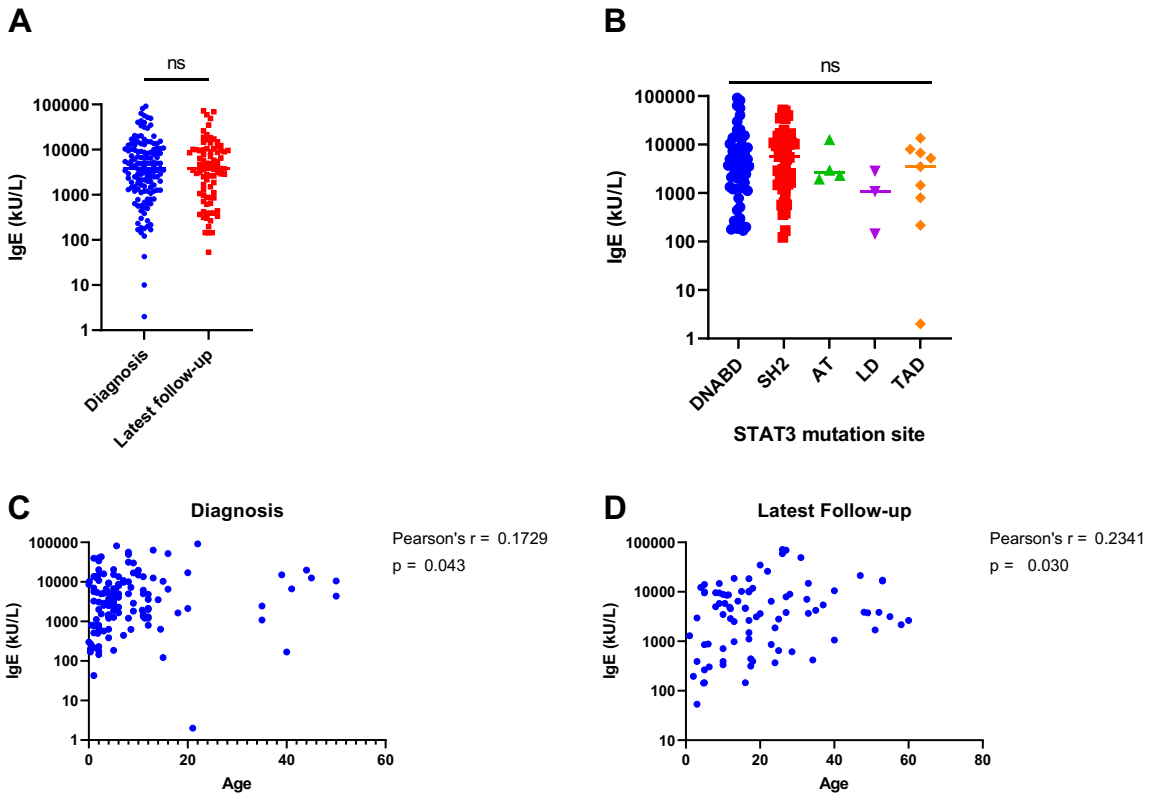
History of pulmonary fungal disease was strongly associated with parenchymal lung disease. Patients with bronchiectasis were 6 times more likely to have fungal infection than those without bronchiectasis (OR 6.72, 95% CI 3.55 – 12.7, p<0.001); a similar finding was seen for pneumatocoele (OR 5.18, 95% CI 2.88 – 9.32, p<0.001).

Newborn skin rash was present in 69% of patients and eczema in 90%. The median

age at onset of first cutaneous bacterial infection was 7.5 months, and for mucocutaneous candidiasis the median age at onset was 1 year. The odds of having mucocutaneous candidiasis were half in males compared to females (OR 0.48 [0.25 – 0.90], p=0.026).

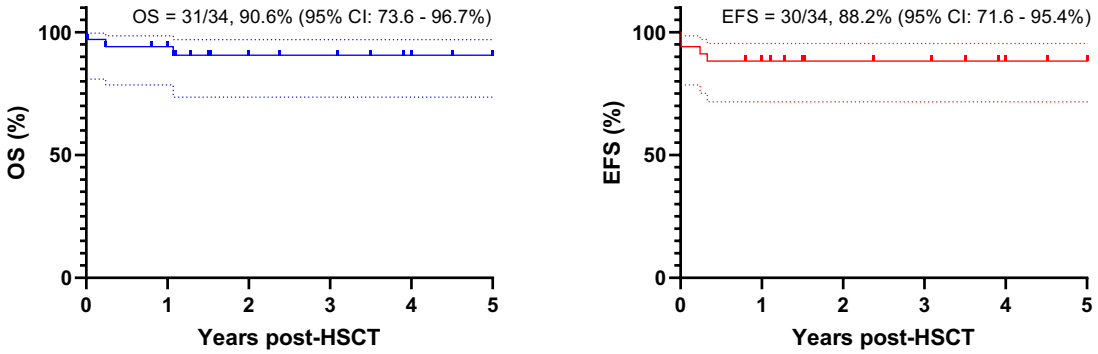
Extra-immune, connective tissue-related disease phenotypes were common in this population, particularly joint hypermobility (62%), scoliosis (60%), and delayed exfoliation of primary dentition (67%). Thirteen patients (5%) had a history of malignancy, all lymphoma, with a median onset age of 20 years.

Total serum IgE was elevated (median at diagnosis: 3771 kU/L, median at latest follow-up: 3843 kU/L). There was no significant difference in serum IgE between these two time points, or by site of STAT3 mutation.



Thirty-two patients underwent allogeneic haematopoietic stem cell transplantation (HSCT). The indication for HSCT was predominately immunodeficiency (n=29), with

three patients transplanted for lymphoma. Median age at HSCT was 13.5 years and 31/34 patients had previous parenchymal lung disease, including seven patients with confirmed previous fungal lung disease. Overall survival was 31/34 patients; mortality resulted from grade IV acute graft-versus-host disease following second and CD34+ stem cell boost, disseminated adenovirus infection, and pulmonary Stenotrophomonas infection leading to massive haemoptysis.

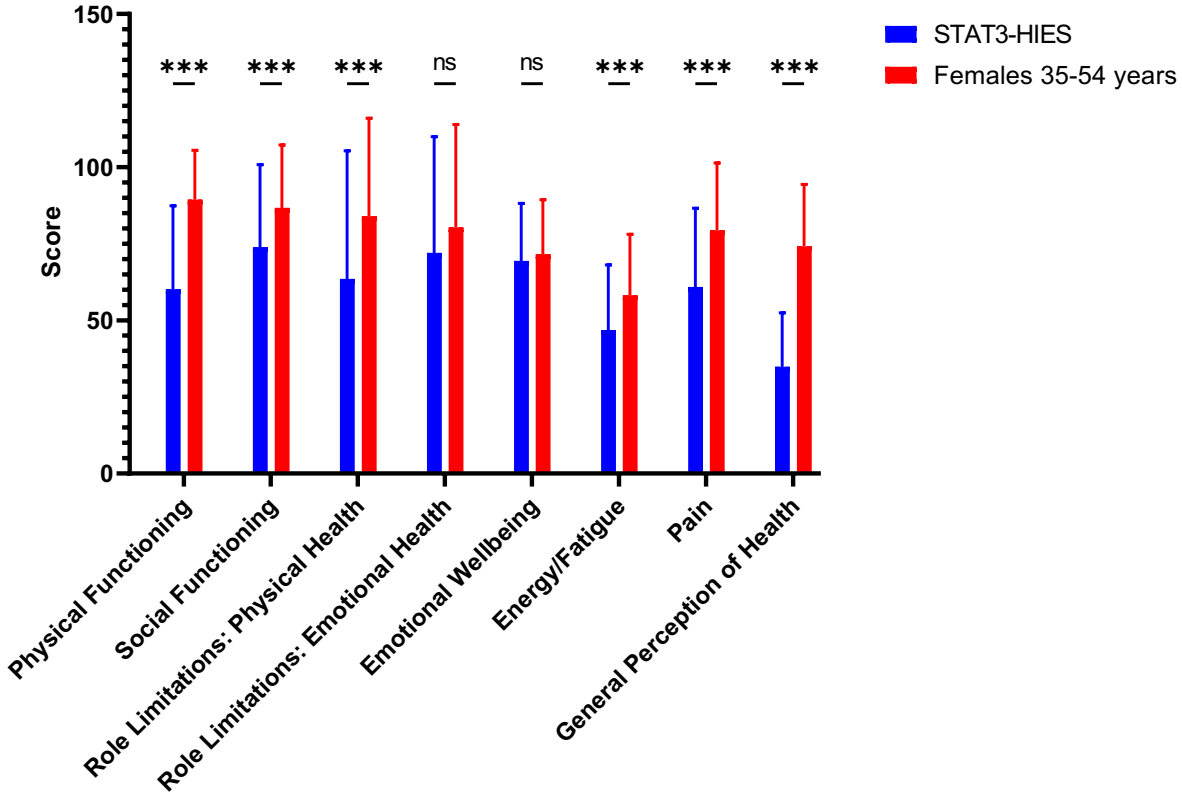


Median follow-up was 4.0 years but ranged 0.8 – 27.0 years post-HSCT. Reduced rates of respiratory infection were reported in 27/31 patients, and skin disease improved in 30/31 patients. For non-infectious manifestations, seven patients had post-HSCT fractures and two patients had progression of scoliosis. One patient had significant vasculopathy (ectatic coronary artery leading to anterior ST-elevation myocardial infarct aged 26 years).

Quality of Life Data:

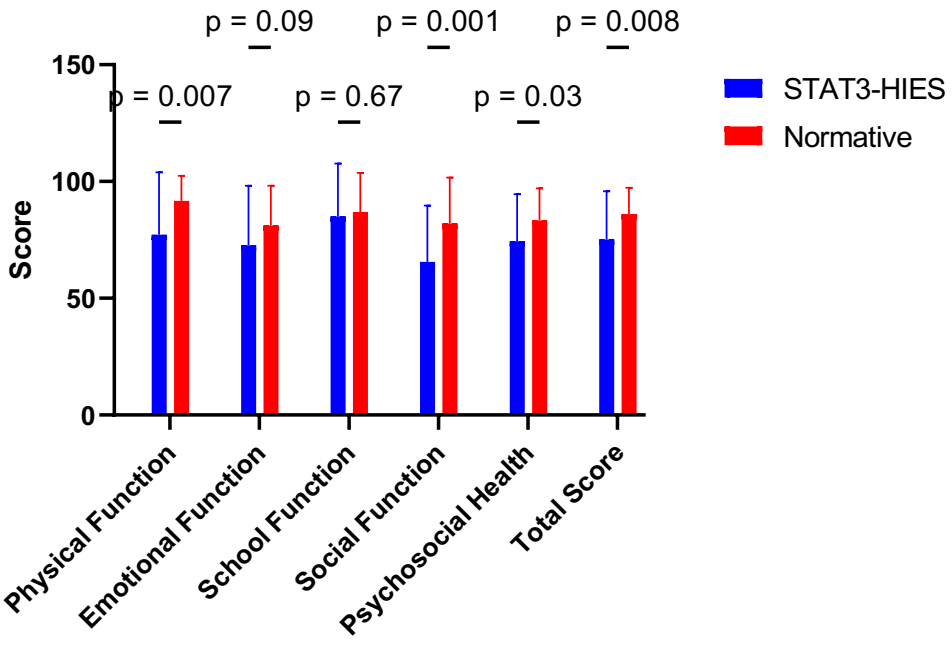
Health-related QOL data were collected using the SF-36 and PedsQL™4.0 instruments, for adults and children respectively; higher scores indicated better health-related quality of life.

Adults with STAT3-DN-HIES had poorer QOL across most domains compared to a normative sample of UK females drawn from the general population:



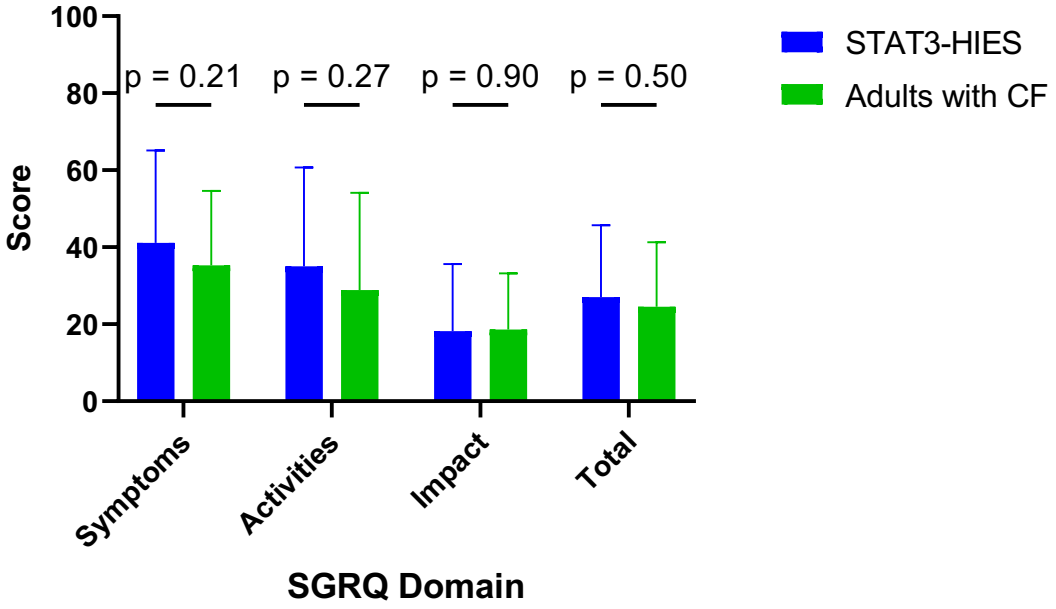
On univariate analysis, increasing age, increasing number of lifetime pneumonia episodes, and pulmonary fungal infection associated with poorer QOL.

In paediatric patients, there was strong concordance between child- and parental proxy-reported scores. Compared to a normative sample, children with STAT3-DN-HIES had poorer scores in physical, emotional, and social function. On multivariate analysis, increasing number of pneumonia episodes was the only significant factor associating with poorer physical function.

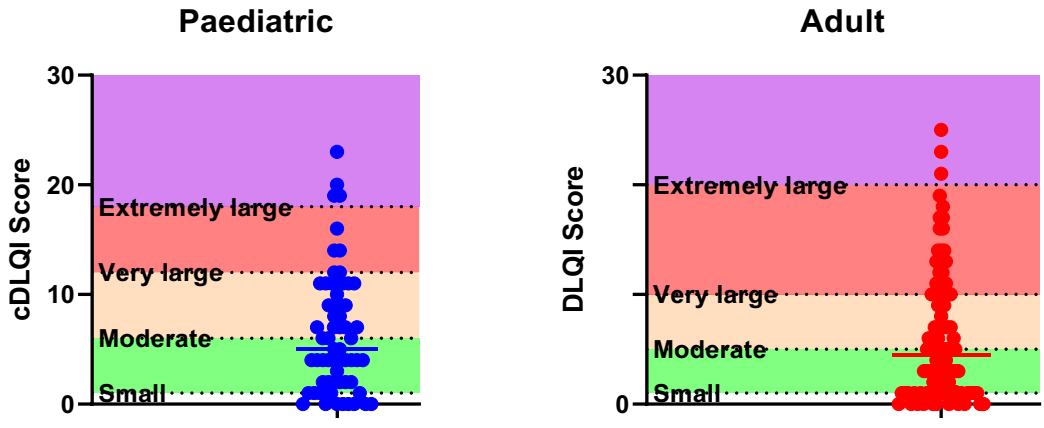


Respiratory QOL data were collected using the St George Respiratory Questionnaire (SGRQ), with higher scores indicating a worse burden of symptoms.

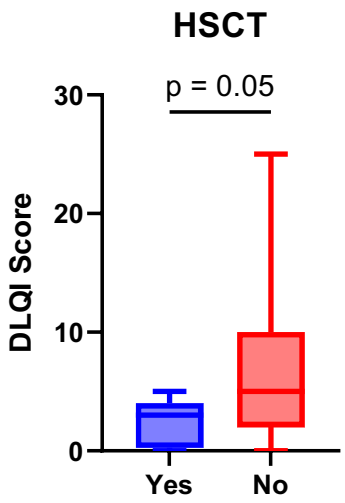
SGRQ scores correlated negatively and significantly with measures of HRQOL, demonstrating the impact respiratory symptoms have on QOL. Adults with STAT3-HIES have poorer respiratory QOL than healthy norms, comparable to patients with CF or with XLA, both diseases that require regular therapy and cause bronchiectasis. Children with STAT3-HIES have similar scores to adults with CF.



Patients with STAT3-HIES demonstrate a range of impairment in dermatological QOL, measured using the Dermatology Life Quality Index (DLQI) or its paediatric version. The DLQI is scored 0-30, with higher scores indicating worse symptoms. Over one-third of patients, regardless of age, demonstrate scores in keeping with "moderate" effect on life or worse:



For adult patients, DLQI scores correlated with HRQOL indices. Patients who have undergone HSCT had a median DLQI score 3 points lower than those who have not.



Preliminary Conclusions:

This international study has expanded the phenotype and clinical landscape of this disorder, and has provided the first description of the impact of disease aspects on quality of life in this patient group. Collection of data from patients who have undergone HSCT has allowed us to better characterise the potential benefits and limitations of this treatment strategy.

STAT3-DN-HIES is a rare, multisystem disorder with immune and extra-immune manifestations that requires the involvement of multiple clinical specialties. Patients diagnosed with this disease are likely to develop recurrent pneumonia, eczema, skin infection and connective tissue abnormalities, and experience impaired quality of life in both its most general sense and with relation to perceived health, skin and respiratory symptoms, and mental health.

Future Work:

Data collection and processing are expected to be completed by the end of 2023, with draft manuscripts detailing clinical results, quality of life data, and outcome of HSCT prepared in 2024.