ZNF469 heterozygous state found in 9 patients with classical Ehlers-Danlos Syndrome but without Brittle Cornea Syndrome suggests a dominant expression for some ZNF469 genetic abnormalities.

Fraser Burling

Rheumatology and Musculoskeletal Clinic

Auckland, New Zealand

SCIENTIFIC MEETING - RARER TYPES
TOKYO 2019

SCIENTIFIC MEETING
RARER TYPES
TOKYO 2019

Conflicts of interest

- Dr. Burling reports personal fees from Rheumatology and Musculoskeletal Clinic, during the conduct of the study
- Genetic testing was funded solely by the patients or their immediate families.

ZNF469

Zinc finger protein of uncertain function

May be involved in collagen transcription and fibrillogenesis

Associated with corneal thickness in a number of studies (Brady et al 2017) and a genetic risk factor for keratoconus in some populations

Abnormalities in the following areas are some of those already published as pathogenic

c.7508 C>A hetero x 3 cases c.6647delA c.8901-8914 dup c.3304G>T c.5353C>T c.2029G>T c.2150DelT c.9483delG c.10106G>C : c.2019G>A c.2137C>A c.3466G>A c.3749C>T c.4300G>A c.4684G>A c.7262G>A : c.974 del : c.10016G>A : c.5943delA c.9527delG : Compound heterozygote triple c.2035G>A, c.10244G>C, c.11119A>G : c.9831 dupC : c.1705 C>T c.1402-1411del : C.4174G>T

Brittle Cornea Syndrome (BCS)

Autosomal recessive

First association with Ehlers Danlos Syndrome (EDS) noted in 1993 (Cameron) with hypermobility of small and large joints and hyper-elastic skin seen many times since then.

Genetic abnormalities found in PRDM5 and ZNF469

Noted as one of the rare types of EDS and often with a consanguinous relationship producing the homozygous state

However heterozygous state associated with keratoconus has been found in 23% (10:43) of a Maori and Pacific cohort. (Vincent et al 2014)

Compound heterozygosity with Brittle Cornea Syndrome has been found in 4 individuals (Skalicka et al 2019)

The Ehlers Danlos Society
SCIENTIFIC MEETING RARER TYPES TOKYO 2019

New Zealand Cohort

In a private clinic in New Zealand with over 580 EDS patients

Testing performed in those with a classical phenotype according to the New York criteria (American Journal of Medical Genetics March 2017) with GeneDx in America (49-gene panel including 28:30 known EDS genes)

9 patients, from 4 families, have been found to have ZNF469 positive in a heterozygous state. No homozygous recessives yet.

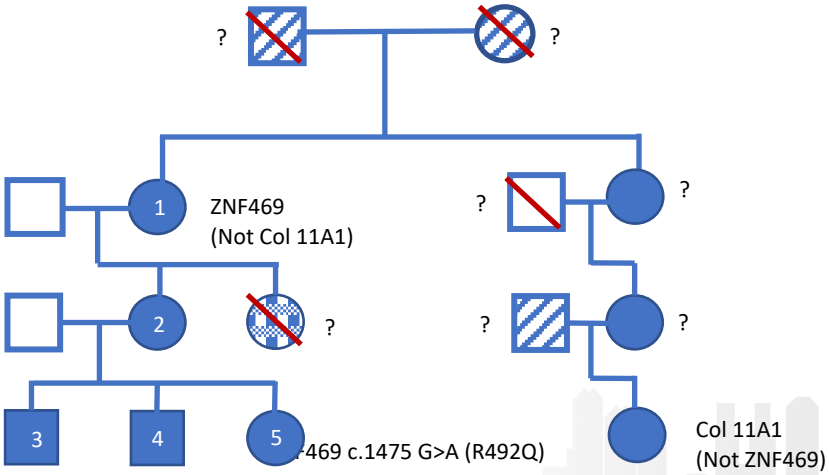
All have had ophthalmology review and none have keratoconus or brittle cornea.

The Ehlers Danlos Society
SCIENTIFIC MEETING RARER TYPES TOKYO 2019

Summary of patient NY criteria

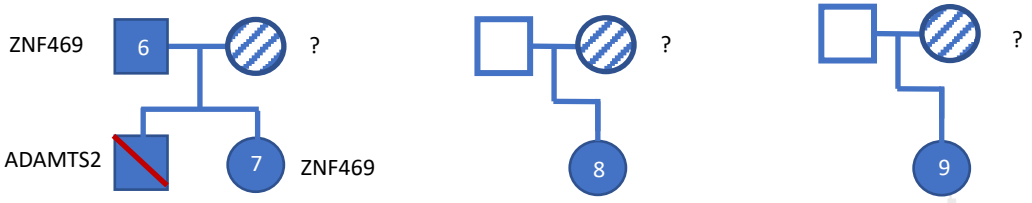
Patient gender	Beighton current, history	Skin stretch: Number out of 5 reaching criteria	Scar stretch	Easy bruising	Soft doughy skin	Stretchmarks or skin fragility	Molluscoid pseudotumours or subcut spheroids	Hernia or Hx	Epicanthal folds	Joint complications	Family History	NY Criteria Major/ minor
1, F	4:7	5	10 mm	yes	yes	yes/no	No	yes	yes	yes	yes	2, 6
2, F	6	5	Nil scars	yes	yes	yes/no	no	no	yes	yes	yes	2, 5
3, M	6	5	Nil scars	yes	yes	no	no	no	no	yes	yes	2, 4
4, M	6	5	Nil scars	yes	yes	no	no	no	no	yes	yes	2, 4
5, F	8	5	Nil scars	yes	yes	no	no	no	no	yes	yes	2, 4
6, M	0:4	5	5 mm	yes	yes	yes/no	no	yes	yes	yes	yes	2, 6
7, F	5	5	10 mm	yes	yes	yes/yes	no	yes	yes	yes	yes	2, 7
8, F	7:9	5	Nil scars	yes	yes	yes/yes	no	yes	no	yes	yes	2, 6
9, F	7:9	5	12 mm	yes	yes	yes/yes	no	yes	no	yes	yes	2, 6

Family Tree Patients 1-5



- ZNF469 c.1475 G>A (R492Q)

Family trees Patients 6-9



- ZNF469 c.5695C>T(P1899S)

ZNF469 c.8621 C>T (T2874M)
with Col2A1 c.4378-4380delCTCinsTTT (L1460F

ZNF469 c.1550 G>T (S517I)
with Col9A1 c.133 C>A (P45T)

Notes

- While patients 8, and 9, have more than one potential source for their phenotypic expression of cEDS, the two families with expression of cEDS in multiple generations are likely to have the heterozygous ZNF469 genotype as the cause for their cEDS indicating that ZNF469 may have a dominant expression for cEDS without BCS.

- I have only seen scar stretch >20mm in patients with Col5A1: none of my other patients with positive genetics in other EDS genes have that degree of scar stretch.

Discussion

- Other genes have both dominant and recessive characteristics (Col9A1-3, Col11A1, Col12A1)

- Other genes have more than one clinical condition (e.g. Col1A1 with osteogenesis imperfecta, and classical EDS)

- These results suggest that ZNF469 has both recessive and dominant features and that the BCS may be a recessive feature but classical EDS may be a dominant feature with some genetic abnormalities.

- There are 4 new mutations noted in this study, of which two have demonstrable dominant features. The other two could be from the other gene abnormality or as a result of a compound heterozygote status.

Questions

- Is the Col5A1 dominant in literature because only those with significant scar stretch, not just skin stretch, were being tested?
- Or because of it being one of the first genes discovered?

Further question

- In New Zealand we have a significant number of positive results from testing those with classical phenotype, but only a couple of them have Col5A1 (and these are the only ones with >2cm scar stretch).
- Even my Col3A1 pathogenically-positive results patients have less than 1cm scar stretch if scars are present at all.
- We are getting multiple rare types though with supposedly recessive genes, but in the heterozygous state they have classical EDS but not the classic features of the rare type expected from the homozygous state.
- These patients shown are the only patients where we have families affording the genetics – but if we could get funding for the family screening of the other patients:-
- How many might show a dominant pattern coming through from previously recessive genes but without the dominant feature of the recessive state?

Thank you for your time.

SCIENTIFIC MEETING
RARER TYPES
TOKYO
2019