TFE3 Associated Neurodevelopmental Disorder
Patient/ carer advice leaflet

Welcome to the *TFE3* community. Following a diagnosis can be a scary and unknown time for you and your family. The good news is - you are not alone. You are now part of a community that has come together to support each other and look for ways to mitigate symptoms and improve quality of life. As a community, we are stronger together and can offer one another the resources that make a difference to our children. Below is a brief leaflet to give you a better understanding of your child's condition. At the end is short list of ways you can connect to others effected by *TFE3*.

Overview

TFE3 stands for Transcription Factor for immunoglobulin heavy-chain Enhancer 3 protein and is coded by the *TFE3* gene. The *TFE3* protein is involved in cell metabolism, maintaining the stability of cells, and helps regulate the specialisation of stem cells into adult cells. *TFE3* also promotes the creation of lysosomes, important organelles located inside the cells.

The *TFE3* gene is located in the X-chromosome and when it has a mutation or pathogenic variant it causes a distinct genetic condition called ***TFE3* Associated Neurodevelopmental Disorder (TAND).** This syndrome is described mainly in females; males usually do have a more severe presentation since they have only one X chromosome and may not survive pregnancy.

This X-linked condition is usually a result of a "*de novo"* mutation, this means a new genetic change, not inherited from parents, and it is unknown why this condition occurs. There are approximately 40 documented patients who are currently diagnosed with TAND.

What can I expect?

TAND presents differently in each child but there are many commonalities. This is a table of the most common symptoms encountered.

	Symptoms Frequency
Neurodevelopmental abnormality	100%
Facial dysmorphia	100%
Growth abnormality	76%
Abnormality of skin pigmentation	70%
Epilepsy	65%
Abnormality of the skeletal system	65%
Abnormality of the eye	

Neonatal features	59%
Autistic/ behavioural abnormalities	53%
Sleep disturbances	47%
Spasticity	35%
Developmental regression	35%
Recurrent infections	29%
Hearing loss	29%
Abnormalities of the respiratory system	29%
Clubbing of fingers	24%
Umbilical hernia	18%
Cardiac abnormalities	18%
Ataxia	18%
Sleep apnea	12%
	6%

The most common symptoms of this condition are neurodevelopmental abnormalities, which occur to varying degrees. These include learning disabilities, walking and speaking difficulties with a large proportion not being able to walk, or walking with assistance and not being able to speak, or able to speak a few words/ sounds. Epilepsy is also common in these patients – causing seizure activity.

Another feature is facial dysmorphia: this means changes in the face such as an upturned nose, or flat nose, almond shaped eyes, fleshy earlobes, coarse facial features, full cheeks, widely spaced eyes, thick lips and facial hair. Growth abnormalities include obesity and reduced growth after birth. The skin pigmentation typically is Blaschkoid pigmentary mosaicism, which means areas of darker and lighter skin that follow a pattern such as streaks or swirls.

Diagnosis

The gold standard test for this condition is genetic testing – by taking a DNA sample from the person affected and from the parents for comparison. Commonly patients have undergone other testing to rule out other conditions. This may include blood tests for other metabolic abnormalities as well as a skin biopsy, lumbar puncture to get spinal fluid, and brain imaging such as an MRI scan.

What to do after diagnosis

There is no current cure for this condition. The mainstay of management is treating the symptoms, such a seizure control in epilepsy. Ongoing management should be coordinated by a pediatrician, geneticist, and/or neurologist and should include a developmental pediatrician. Medications can be given for behavioral, seizures, sleep, and gastrointestinal symptoms. Use of allied healthcare professionals are invaluable, such as: physiotherapy, occupational, speech, and behavioral therapists as well as nutritionist. There may be need for patients to go to specialist schools that are more suited for their needs.

As TAND is such a rare condition, parents are often experts on what to expect and can give emotional and practical support after getting a diagnosis. There are families all around the world who have been connected through *TFE3*.

Living with
There is a Facebook group: "*TFE3* Support Community" and a private WhatsApp group. You can contact Rainbow Solomon at *TFE3*foundation@gmail.com to be added to either. For more anecdotal stories of how the condition presents in different children and up to date information, please look at the TAND website at www.*TFE3*.org. If your child has received a diagnosis please consider sharing your story on the website as well.

Current journal articles and information credited to
Diaz J, Berger S, Leon E, 2020. *TFE3*-associated neurodevelopmental disorder: A distinct recognizable syndrome. *American Journal of Medical Genetics*. 182A pp. 584-590
Lahalle et al. 202. De Novo mutations in the X-linked *TFE3* gene causes intellectual disability with pigmentary mosaicism and storage disorder-like features. *Journal of Medical Genetics*. 57 pp. 808-819
Rare genomics institute: *TFE3*-Associated Neurodevelopmental Disorder (*TFE3*) — Rare Genomics Institute

Ongoing work –
Work is ongoing to create a patient database of current cases. Please get in touch via the *TFE3* website, Facebook group, or to the above mentioned email to be involved in data collection. Currently, this is a US based project on skin biopsies from affected patients.