Protocol for investigating atypical NF cases

Phenotypic characterization:

Clinical examination,

full ophthalmological examination including slit lamp and corneal nerve morphology

specific attention to dermatological features

CAL spots and pigmentation abnormalities

skin tumors of externally visible tumors

skeletal abnormalities and growth parameters

Neurological examination

body asymmetry, local overgrowth

Radiological examination

MRI scan of the brain

Total body MRI if tumors are suspected

ultrasonography of abdominal organs

skeletal X-rays of body region with asymmetry or other abnormalities that might be associated with skeletal abnormalities (scoliosis, regional overgrowth, ...)

Pathological examination

all tumor types that were surgically removed

Psychometric examination

if learning disabilities or if intellectual disabilities are present or suspected

Genetic analysis:

Mutation analysis of peripheral blood cells

NF1 gene (including RNA based mutation analysis, and deletion analysis such as MPLA)

NF2 gene

SMARCB1

any other relevant gene such as *RET, PTEN, PRKAR1A* that can be associated with neurofibromas, neurinomas, schwannomas etc.

exclude *KIT* and *PDGFRA* mutations if multiple non-epithelial intestinal tumors are present

high resolution array-CGH analysis

mutation analysis of "affected tissue" (*NF1, NF2, SMARCB1*, ...)if available.

affected tissue can be tumor tissue, primary Schwann cell cultures from peripheral nerve sheath tumors, cultured melanocytes from pigmentation abnormalities if present.

GNAS1 McCune-Albright mutation on melanocytes if CAL spots are present

high resolution array-CGH analysis on affected tissues.

Pooling of clinically, radiologically and pathologically similar cases for exome sequencing analysis on peripheral blood DNA and (if) available "affected tissue" DNA.