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Revised Diagnostic Criteria for Neurofibromatosis Type 1 (NF1)

A. The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if ≥2 of the following are present:

1. ≥6 café-au-lait macules (CALMS)[a]
   - >5 mm in greatest diameter (prepubertal)
   - >15 mm in greatest diameter (postpubertal)
2. Freckling in the axillary or inguinal region[a]
3. ≥2 neurofibromas of *any type*
4. One plexiform neurofibroma
5. Optic pathway glioma
6. ≥2 iris Lisch nodules identified by slit lamp examination
7. ≥2 choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
8. A distinctive osseous lesion, such as sphenoid dysplasia,[b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone
9. A heterozygous pathogenic NF1 variant allele fraction of 50% in apparently normal tissue such as white blood cells

B. A child of a parent who meets the diagnostic criteria specified in section A merits a diagnosis of NF1 if ≥1 of the criteria in section A are present

[a]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis, such as Legius syndrome. At least one of two pigmentary findings (café-au-lait macules or freckling) should be bilateral; [b]sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

Diagnostic Criteria for Mosaic Neurofibromatosis Type 1 (NF1)

The diagnostic criteria for mosaic NF1 are met in an individual if any of the following are present:

1. A pathogenic heterozygous *NF1* variant with a variant allele fraction of significantly less than 50% in apparently normal tissue, such as white blood cells, AND one other NF1 diagnostic criterion (except a parent fulfilling diagnostic criteria for NF1)
2. An identical pathogenic heterozygous *NF1* variant in two anatomically independent affected tissues (in the absence of a pathogenic *NF1* variant in unaffected tissue)[a]
3. A clearly segmental distribution of café-au-lait macules or cutaneous neurofibromas AND either:
   a. Another NF1 diagnostic criterion (except a parent fulfilling diagnostic criteria for NF1)[b] OR
   b. Child fulfilling diagnostic criteria for NF1
4. A child fulfilling the criteria for NF1 AND only one NF1 diagnostic criterion, including freckling in the axillary and inguinal region, optic pathway glioma, two or more Lisch nodules or two or more choroidal abnormalities, distinctive osseous lesion typical for NF1, two or more neurofibromas or one plexiform neurofibroma

[a]Neurofibroma and overlying hyperpigmented skin count for one tissue only; different tissues originating from the same primary affected lesion count for one tissue only; [b]if only café-au-lait macules and freckling are present, the diagnosis is most likely mosaic NF1 but rarely might be mosaic Legius syndrome or constitutional mismatch repair deficiency (CMMRD) syndrome.

Legius E, et al. *Genet Med*. 2021