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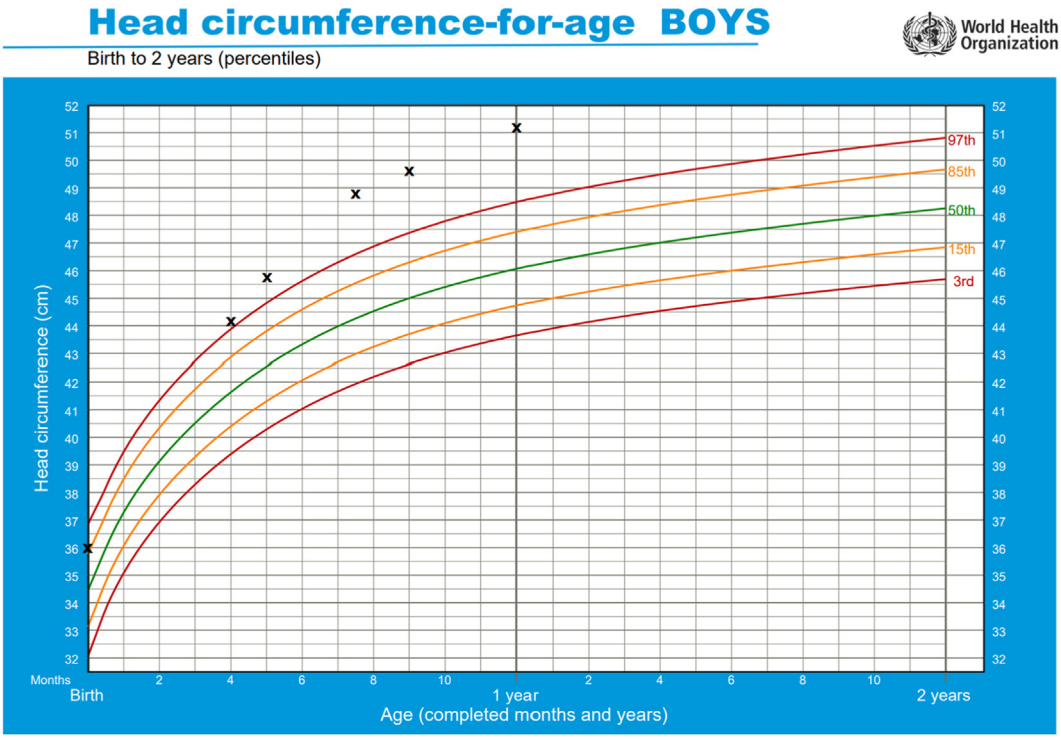
Macrocephaly? Do not Forget *SUFU*

Pathogenic variants in *SUFU* (suppressor of fused homolog) are regularly identified in tumor samples and are linked with malignancy by disinhibition of the sonic hedgehog (SHH) signaling pathway.[1] In rare cases heterozygous germline variants in *SUFU* are identified. This heterozygous state is associated with predisposition for various malignancies. The overall risk for tumor development (of any type) in heterozygous individuals is around 68%.[2] Early-onset medulloblastoma is the most common tumor type found in 50% of the patients with a median age of 18 months at diagnosis.[2] In addition to predisposition to malignancies, *SUFU* haploinsufficiency has also been associated with macrocephaly[3,4] and Gorlin syndrome,[5–7] as well as with a recognizable neurodevelopmental phenotype at the mild end of the Joubert syndrome spectrum.[8–11]

We are presenting the case of a boy referred to our genetics center at age 10 months for prominent macrocephaly with frontal bossing, mild developmental delay, and facial dysmorphisms including a broad nasal bridge and epicanthus. The parents were healthy and nonconsanguineous. The pregnancy was uneventful. The boy was born at 36 weeks through Caesarean section for breech presentation. Occipital frontal circumference was 36 cm (>97%tile). Regular checkups showed progressive macrocephaly up to +3.6 S.D. (Fig). Brain magnetic resonance imaging (MRI) showed normal intracranial brain structures except for benign enlargement of the subarachnoid space in infancy and discrete ventriculomegaly, which did not explain the boy's macrocephaly. Genetic evaluation for macrocephaly identified a *de novo* heterozygous pathogenic (Class 5) nonsense variant (NM_016169.3:c.7G>T, p.(Glu3*)) in *SUFU* at age 16 months.

In our patient presymptomatic genetic diagnosis justified preventive screening and an intensive medical follow-up program. The most important screening method consisted of a brain MRI



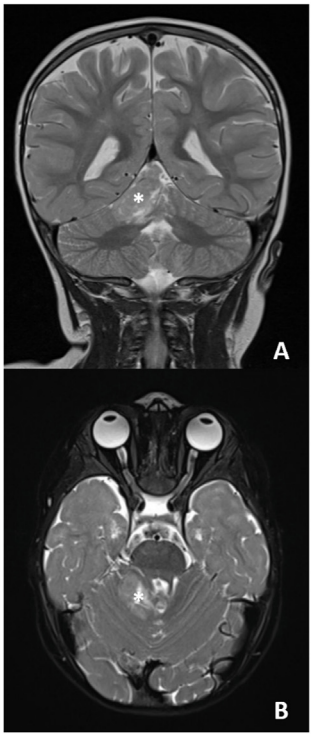


FIGURE. (Left) Occipital frontal circumference (OFC) of the presented patient with progressive macrocephaly plotted on the growth chart. Measurements after age one year are situated above the curve and are not visualized. OFC of the patient stabilized at 53.2 cm at age two years. OFC growth chart provided by the World Health Organization (in percentile). (Right) (A, B) Magnetic resonance images in coronal (A) and axial planes (B) showing the intracranial lesion (*) in the presented patient. The color version of this figure is available in the online edition.

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TABLE.
List of the Most Frequently Associated Malignancies With Median Age at Diagnosis, Lifetime Risk, Preventive Measurements, and Screening Modalities in Patients With Germline *SUFU* Variants

Associated Tumors	Median Age at Diagnosis	Lifetime Risk	Preventive Measurements	Screening
Medulloblastoma	18 months	50%	✓ Solar protection ✓ Avoid radiation in diagnostic and therapeutic settings	✓ Brain MRI every 3-4 months for first 3 years of life, afterward every 6 months until 5 years
Gonadal tumors Ovarian tumors Testicular tumors	14 years	6%		✓ Ovaria: Ultrasound examination every 3 years, starting at age 5 years ✓ Testes: Regular self-examination (palpation)
Basal cell carcinoma	40 years	14.5%		✓ Annual checkup by dermatologist, starting at age 20 years or earlier when the patient had previous radiotherapy
Menigioma	44 years	11%		✓ Brain MRI every 3-5 years • Start after healing of medulloblastoma • Start at age 30 years if no medulloblastoma in medical history

Abbreviation:
MRI = Magnetic resonance imaging
An important sidenote is that 28% of the patients have multiple malignancies. This table is based on Guerrini-Rousseau et al. (2022).

every three to four months because of the high risk of early-onset medulloblastoma linked to heterozygous pathogenic variants in *SUFU*.[2] Other screening modalities are listed in the Table and depend on the patients' age and sex. At age 20 months, brain MRI confirmed the diagnosis of a medulloblastoma in a presymptomatic stage (Fig). The tumor was classified in the medulloblastoma SHH subgroup. The patient underwent surgery and chemotherapy. Radiation was avoided because of the increased risk for developing basal cell carcinoma and meningiomas at the radiation site. After treatment, a fine motor and language delay persisted.

In contrast to our patient, most patients only benefit from a genetic evaluation after cancer diagnosis. In the literature, only two of 83 index patients with a pathogenic germline variant had been diagnosed in a presymptomatic stage.[2] Nevertheless, precancer molecular diagnosis during infancy should be possible. Prominent macrocephaly (>97%tile), with or without facial dysmorphisms and developmental delay, is present in all published pediatric patients from whom occipital frontal circumference is available.[4] Consequently, in young children presenting with unexplained macrocephaly (>97%tile) it is important to initiate genetic testing as soon as possible. *SUFU* and genes involved in the mammalian target of rapamycin (mTOR) pathway should be included in this analysis.

The key phenotypical feature of prominent macrocephaly and frontal bossing in patients with pathogenic germline variants in *SUFU* can be explained by cross talk mechanisms between SHH and the PI3K/AKT/mTOR pathway.[4] The *SUFU* phenotype shows similarities to PI3K/AKT/mTOR pathway-associated overgrowth syndromes.[3]

This case highlights the importance of early genetic evaluation for individuals with unexplained macrocephaly, with or without facial dysmorphisms and developmental delay. Early diagnosis allows for intensive preventive screening, which can improve treatment modalities, patient outcome, and quality of life.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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