

Diagnosis of hypochondroplasia: International Delphi consensus recommendations

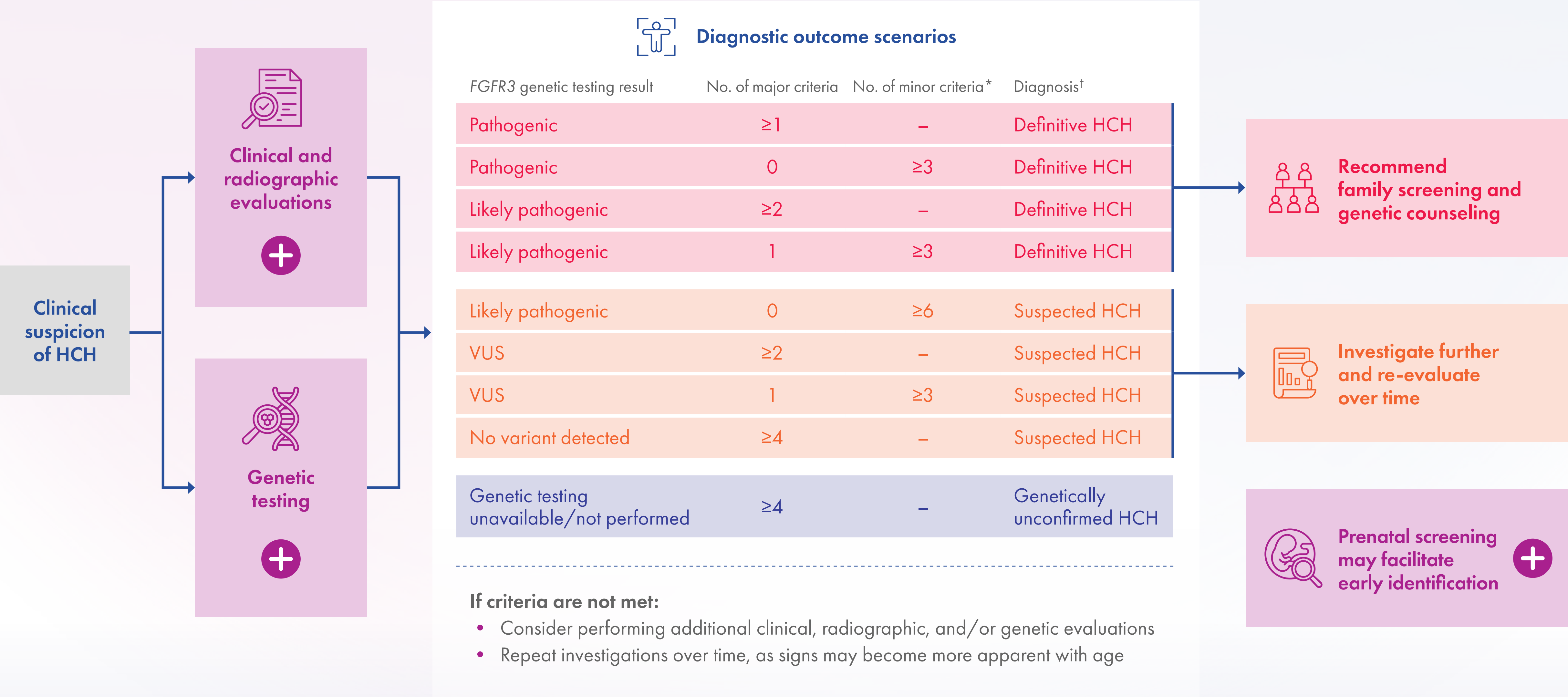
Dauber A, Cheung M et al. *Nat Rev Endocrinol* 2026.
doi:10.1038/s41574-026-01296-z

Diagnosis of hypochondroplasia: international Delphi consensus recommendations

Andrew Dauber^{1,2,27}, Moira S. Cheung^{3,27}, Julie Hoover-Fong⁴, Svein Otto Fredwall^{5,6}, Moeenaldeen ALSayed^{7,8}, Silvio Boero⁹, Alistair D. Calder¹⁰, Valérie Cormier-Daire^{11,12}, Virginia Fano¹³, Takuo Kubota¹⁴, Philip Kunkel¹⁵, Juan Llerena Junior¹⁶, Mohamad Maghnie^{17,18}, Geert Mortier¹⁹, Noriyuki Namba²⁰, Amaka C. Offiah^{21,22}, Keita Okada²³, Sérgio B. Sousa^{24,25} & Ravi Savarirayan²⁶

These recommendations provide a practical framework to help standardize timely and accurate diagnosis of hypochondroplasia in clinical practice and research

Summary of the diagnostic framework for HCH





The number of major and minor clinical criteria should be counted to inform HCH diagnosis



Major clinical criteria	
1	Disproportionate short stature for age and sex, defined as both: Height or length <-2 SD* for age and sex AND Evidence of disproportion, defined as one of the following: i. Sitting height to standing height ratio >2 SD* ii. Upper to lower body segment ratio >2 SD*
2	Relative macrocephaly with no alternative cause, defined as an HCH-I <-2 HCH-I = height Z-score – $\frac{1}{2}$ head circumference Z-score
3	The major radiographic criterion +
4	Characteristic brain MRI finding in the temporal lobes, defined as ≥ 1 of the following: a. Temporal lobe dysgenesis, including hippocampal dysgenesis b. Sagittal aberrant sulcus and/or deep transverse sulcus within the temporal lobe c. Incomplete hippocampal inversion
5	Family history in a first-degree relative who meets the definitive HCH diagnostic criteria

Minor clinical criteria	
1	Short stature defined as: Height or length <-2 SD* for age and sex† AND/OR Height or length below genetic potential defined as a height or length >2 SD* below mid-parental target height†
2	Evidence of body disproportion , defined as one of the following:† a. Sitting height to standing height ratio >2 SD* b. Upper to lower body segment ratio >2 SD*
3	Absolute macrocephaly defined as a head circumference >2 SD*, with no alternative cause
4	Clinical evidence of changes in the upper limbs consistent with HCH (rhizomelia, limited arm extension and/or broad hands)
5	Asymptomatic ventriculomegaly and/or increased extra-axial fluid
6	History of ≥ 1 afebrile seizure
7	History of ADHD, diagnosed learning difficulties or executive function abnormalities
8	≥ 2 minor radiographic criteria +
9	Family history in a first-degree relative who meets the suspected HCH diagnostic criteria

*SD of population distribution; †If the patient meets major criterion 1 (disproportionate short stature), minor criteria 1 and 2 may not be used
ADHD, attention deficit hyperactivity disorder; HCH, hypochondroplasia; HCH-I, Head Circumference Height Index; MRI, magnetic resonance imaging; SD, standard deviation
Dauber A, Cheung MS et al. Nat Rev Endocrinol 2026. doi:10.1038/s41574-026-01296-z

Major and minor radiographic criteria for HCH diagnosis



Age group	Major radiographic criteria	Minor radiographic criteria
Neonates and infants <12 months old	No major criteria	1 Short sciatic notches 2 Short, relatively broad long bones 3 Broad femoral necks 4 Horizontal acetabular roofs 5 Small iliac bones, with reduced diameter in craniocaudal and transverse directions
Individuals ≥12 months old	1 Radiological signs of progressive lumbar canal stenosis (L1–L4), defined as: On anteroposterior view of lumbar spine: lack of normal widening of the L1 to L4 interpedicular distance AND On lateral view of lumbar spine: L1 to L4 progressive lumbar pedicle shortening	1 Relatively long distal fibulae, defined by position of lower fibular growth plate at or below level of ankle mortise (lower border of lower tibial epiphysis) * 2 Small iliac bones, with reduced diameter in craniocaudal and transverse directions 3 Short and/or broad femoral necks 4 Short, relatively broad long bones; metaphyses may appear flared 5 Prominent sites of muscular insertion, eg at deltoid insertion in humeral diaphysis

* In children 3 years and older, to qualify for minor radiographic criteria, criterion 1 (relatively long distal fibulae) must always be met
HCH, hypochondroplasia; L1/4, lumbar vertebrae 1/4
Dauber A, Cheung MS et al. Nat Rev Endocrinol 2026. doi:10.1038/s41574-026-01296-z

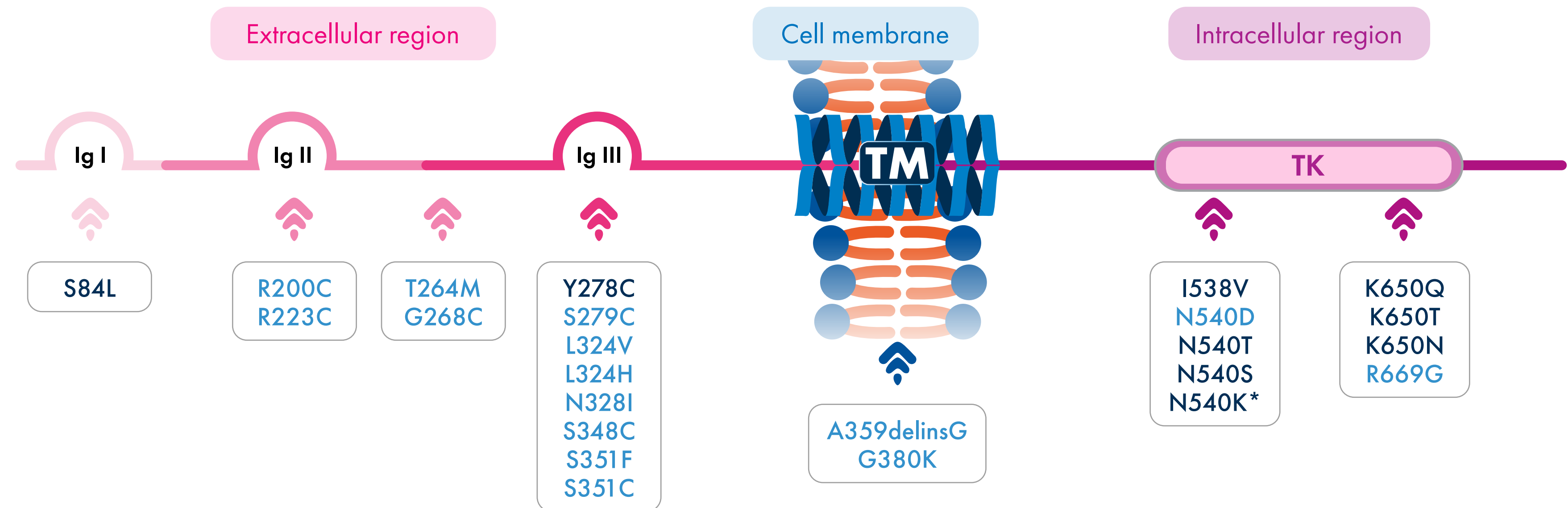


The guidelines discuss HCH-associated *FGFR3* variants, which may be identified by genetic testing



There is a spectrum of *FGFR3* variants spanning benign to pathogenic; pathogenicity should be carefully interpreted to inform HCH diagnosis^{1,2}

HCH-associated pathogenic and likely pathogenic *FGFR3* variants reported in the guidelines¹



Family history should be considered to identify potential autosomal dominant inheritance¹

HCH is most often caused by a **de novo** heterozygous pathogenic *FGFR3* variant
– **Absence of family history does not exclude HCH¹**

Most HCH-causing variants result in the **p.N540K (p.Asn540Lys) substitution**, which accounts for ~50–70% of HCH cases^{1,3}

*The most common HCH-causing variants are those leading to the p.N540K (p.Asn540Lys) substitution¹
A359delinsG, p.A359delinsGTGFCSSALSGGRWLGRQSCQDGRESS; ACMG, American College of Medical Genetics and Genomics; Asn, asparagine; *FGFR3*, gene encoding fibroblast growth factor receptor 3; HCH, hypochondroplasia; Ig, immunoglobulin; Lys, lysine; TK, tyrosine kinase domain; TM, transmembrane
1. Dauber A, Cheung MS et al. *Nat Rev Endocrinol* 2026. doi:10.1038/s41574-026-01296-z; 2. Ziv N et al. Poster presentation at ACMG Annual Meeting; Baltimore, MD, USA; March 10–14, 2026; Poster P107; 3. Mejía RR et al. *J Pediatr Genet* 2020;9:48–52

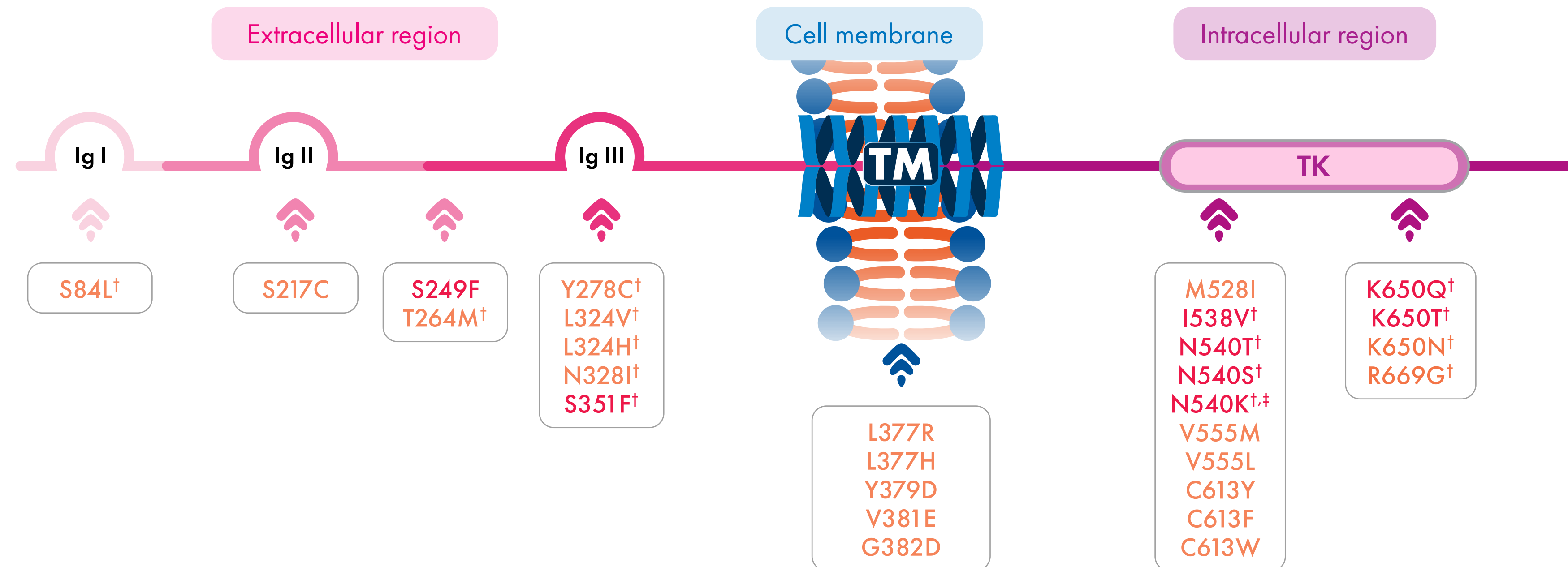


Additional HCH-associated *FGFR3* variants have been identified in a genomic analysis by Ziv *et al.*



Novel variants were identified through database screening;* known variants were reclassified via saturation mutagenesis assay¹

HCH-associated pathogenic and likely pathogenic *FGFR3* variants reported in a genomic analysis by Ziv *et al.*¹



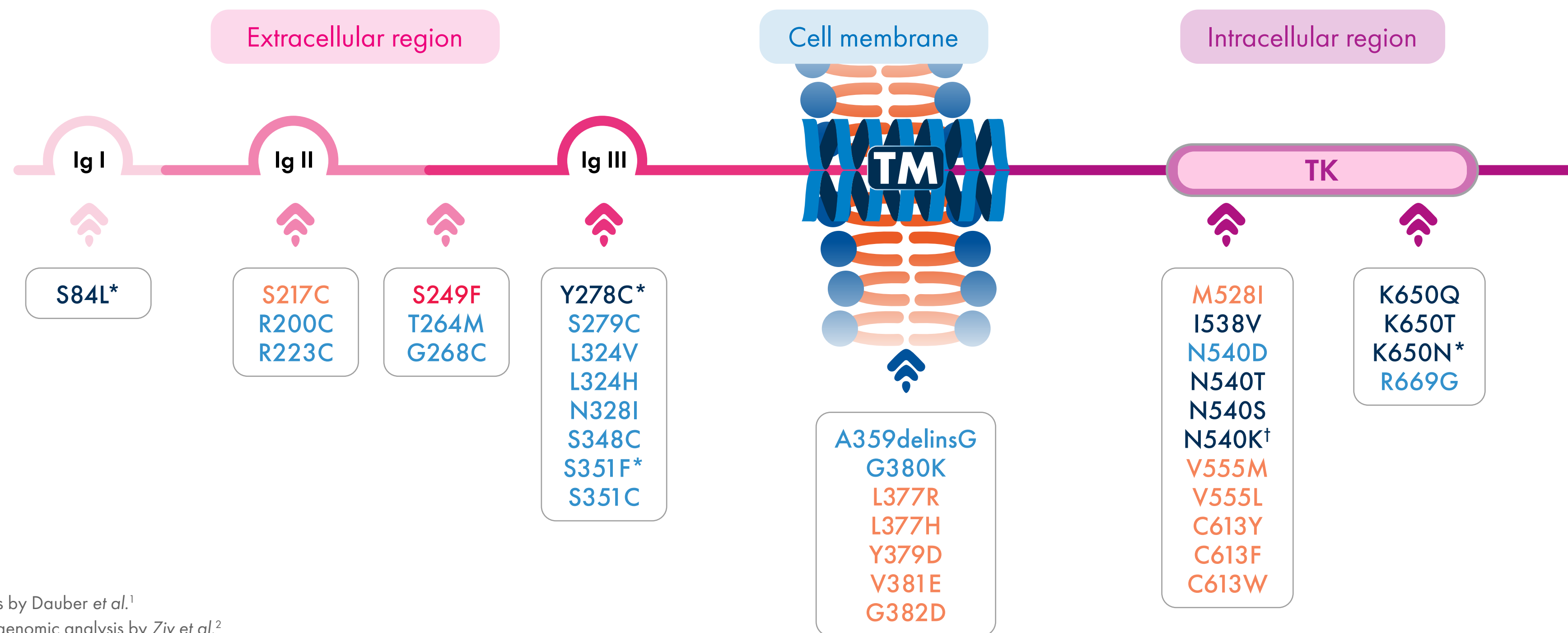
*Genomic and phenotypic data were taken from UK Biobank, All of Us, and a cohort from the US Discover Dysplasias¹; [†]Variant also reported in the guidelines by Dauber *et al.*^{1,2}; [‡]The most common HCH-causing variants are those leading to the p.N540K (p.Asn540Lys) substitution²
ACMG, American College of Medical Genetics and Genomics; Asn, asparagine; *FGFR3*, gene encoding fibroblast growth factor receptor 3; HCH, hypochondroplasia; Ig, immunoglobulin; Lys, lysine; TK, tyrosine kinase domain; TM, transmembrane
1. Ziv N *et al.* Poster presentation at ACMG Annual Meeting; Baltimore, MD, USA; March 10–14, 2026; Poster P107; 2. Dauber A, Cheung MS *et al.* *Nat Rev Endocrinol* 2026. doi:10.1038/s41574-026-01296-z



Combined overview of *FGFR3* variants reported across the guidelines and genomic analyses



HCH-associated pathogenic and likely pathogenic *FGFR3* variants reported across the guidelines and genomic analyses^{1,2}



*Classification assigned in Ziv *et al.* differed from the classification assigned in Dauber *et al.*^{1,2}; [†]The most common HCH-causing variants are those leading to the p.N540K (p.Asn540Lys) substitution¹
ACMG, American College of Medical Genetics and Genomics; Asn, asparagine; *FGFR3*, gene encoding fibroblast growth factor receptor 3; HCH, hypochondroplasia; Ig, immunoglobulin; Lys, lysine;
TK, tyrosine kinase domain; TM, transmembrane
1. Dauber A, Cheung MS *et al.* *Nat Rev Endocrinol* 2026. doi:10.1038/s41574-026-01296-z; 2. Ziv N *et al.* Poster presentation at ACMG Annual Meeting; Baltimore, MD, USA; March 10–14, 2026; Poster P107



Prenatal screening may facilitate early identification of HCH



**10
weeks**

NIPS is available in some countries to screen for HCH-associated gene variants from **10 weeks** of gestation

**20
weeks**

HCH features may be detectable prenatally by ultrasound from **20 weeks** of gestation

Key indicators: shortening of long bones and relative macrocephaly



*Or absence of prenatal genetic testing
FGFR3, gene encoding fibroblast growth factor receptor 3; HCH, hypochondroplasia; NIPS, non-invasive prenatal screening
Dauber A, Cheung MS *et al. Nat Rev Endocrinol* 2026. doi:10.1038/s41574-026-01296-z