*Late Breaking Chromosomes***All Humans, Great or Small, Short or Tall**

Height is a notoriously variable phenotype, which clearly ‘runs in the family’. Because of the latter, variation in height caught the interest of geneticists. Genome-wide association studies (GWASs) demonstrated that at least 180 loci for common variants were associated with adult height. The contribution of each individual locus is small, such that all loci together explain not more than 40% of the variation in height in humans [Lango Allen et al., 2010; Wood et al., 2014; Yang et al., 2010]. GWASs discover loci that may either harbor neutral polymorphisms or pathogenic mutations, but do not allow determining the penetrance, i.e. the phenotypic impact of each individual locus. Since variation in height occurs either as part of Mendelian disorders, or as an isolated clinical phenotype, medical geneticists are interested in finding highly penetrant loci and genes for clinically aberrant height. By classical linkage and positional cloning studies, the loci and genes for many Mendelian syndromes, and by extension, for growth-regulating genes, have been identified. However, most patients with significantly reduced height, also known as idiopathic short stature (ISS), do not fit Mendelian syndromes. Their ISS is an isolated phenotype, and often such patients occur as isolated cases without a family history. Given their high yield, genome-wide searches for copy number variations (CNVs) are the method of choice to detect highly penetrant genetic variants [Hochstenbach et al., 2011].

Recently, 2 groups used SNP arrays to study cohorts of patients with ISS [Zahnleiter et al., 2013; van Duyvenvoorde et al., 2014]. In a cohort of 162 patients from 149 families, van Duyvenvoorde et al. [2014] found 49 CNVs in 43 patients from 40 families. In 6 families, CNVs covered known genes for aberrant height (deletion or duplication of *SHOX* on Xp22.33, or a deletion of *IGF1R* on 15q26.3). In 2 of these cases, a second de novo and potentially pathogenic CNV was detected. The latter constellation has also

been found in patients with intellectual delay (ID), which led investigators to invoke a polygenic model to explain phenotypic heterogeneity among patients with ID and also for patients with ISS and a deletion in region 15q26 [Girirajan and Eichler, 2010; Poot et al., 2011, 2013; Girirajan et al., 2012]. For 24 of the 33 patients with one or more novel potentially pathogenic CNVs, segregation analysis could be performed. Thus, 3 de novo CNVs and 9 CNVs segregating with ISS were found. To determine whether a gene in a CNV may be relevant for ISS, the authors checked rodent homologs: (1) for higher expression in a 1-week-old mouse growth plate than in a 1-week-old mouse lung, kidney and heart, (2) whether the gene showed a significant difference between zones in the 1-week-old rat growth plate, and (3) whether a gene showed significant differences in expression between 3 and 12 weeks of age in the rat growth plate using previously established mRNA expression profiles. Interestingly, 4 CNVs were located near loci associated with height variation in GWAS (*ADAMTS17*, *TULP4*, *PRKG2/BMP3*, and *PAPPA*).

In an independent study, Zahnleiter et al. [2013] investigated a cohort of 170 patients with proportional ISS and 30 with disproportional ISS; 69 patients showed a syndromal form of ISS, while 131 cases had an isolated form of ISS. ID was diagnosed in 51 patients (26%). Patients with growth hormone deficiency, Ullrich-Turner syndrome, and *SHOX* deficiency were excluded. With genome-wide SNP arrays, the authors found 6,338 CNVs in 200 patients, with an average of 32 per case. In 820 healthy controls, they detected 40,935 CNVs. Excluding all CNVs <50 kb, they retained 1,211 CNVs in the patient cohort, of which 733 carried at least one RefSeq gene. As a second triage step, the authors determined whether the CNV had occurred de novo or cosegregated with a parental growth phenotype. In the third step, a gene of interest had to adhere to at least one of the following criteria: (1) being mentioned in the Online Mendelian Inheritance in Man (OMIM) as a human growth-related gene, (2) being a

gene with a growth-related phenotype in a murine transgenic model, (3) being reported as a gene with a role in bone growth or height development, or (4) being reported in DECIPHER with at least one patient with ISS [Firth et al., 2009]. After these triage steps, Zahnleiter et al. [2013] retained 10 duplications and 10 deletions ranging in size from 109 kb to 14 Mb; 7 were de novo ($p < 0.03$) and 13 inherited from an affected parent but absent from the control cohort. Of the 20 likely disease-causing CNVs in patients, 11 (55%) either overlapped with known microaberration syndromes associated with short stature or GWAS loci for height.

However different the approaches to determine plausible pathogenicity of CNVs in these 2 studies were, they converge in several points. An overall yield of 12% [van Duyvenvoorde et al., 2014] or 10% of patients with a likely disease-causing CNV is slightly less than for patients with idiopathic ID, but more than in cases with nonsyndromic autism [Hochstenbach et al., 2011]. This indicates that rare CNVs may be a frequent cause of ISS. The most likely molecular mechanism of pathogenicity for a CNV would be either haploinsufficiency for a gene in a deletion or triplosufficiency for a gene in a duplicated region [Poot et al., 2011]. This assumes a model in which the protein encoded by the gene, which undergoes gene-dosage imbalance due to a CNV, binds to other protein(s) to form a functional complex [Poot et al., 2011]. The *IGF1R* gene (in region 15q26.3), which binds the growth factor IGF, is a case in point. Patients with ISS may also carry a loss of gene function due to gene disrupting mutations such as nonsense, coding indels, and splice acceptor/donor site muta-

tions, as has been found at significantly higher frequency in severe ID, epilepsy and autism [Petrovski et al., 2013]. In addition to CNVs and highly penetrant gene mutations, patients with ISS may carry mutations of a lesser phenotypic effect. The latter may be detected by GWAS. Such constellations have been invoked in disorders with a highly complex genetic architecture, such as severe ID, epilepsy and autism [Petrovski et al., 2013; Poot, 2014]. Such mutations can only be detected by genome-wide exome sequencing or targeted gene sequencing, which may become a future direction of research in ISS genetics.

In 2 out of 6 patients with a CNV known to be associated with ISS, van Duyvenvoorde et al. [2014] found a second CNV that may be involved in ISS. These findings should call for caution on targeted analyses limited to a few loci and genes, and on 'diagnostic fatalism', i.e. halting all further analyses after a single CNV has been found [Poot et al., 2011]. Some patients with deletions in region 15q26.3 initially showed an isolated form of ISS, but later developed behavioral problems. These later developments may indicate a 'hidden' second locus or gene, yet should not bar us from considering treatment options that are supported by a known CNV or gene mutation [Poot et al., 2013]. If a deletion of or an inactivating mutation in the *IGF1R* gene is discovered, ISS may become a disorder amenable to growth hormone treatment [Poot et al., 2013]. However, searching for additional variants of lesser effects has to continue in order for us to grasp the full complexity of the genetic architecture of a relatively simple phenotype as height in humans – short or tall.

Martin Poot

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