BHS British Hypertension Society

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Liddle Syndrome

This very rare inherited form of hypertension was first described in 1963 by the American endocrinologist Grant Liddle. Inheritance follows an autosomal dominant pattern usually with high penetrance (see McKusick Catalogue at http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=177200). Its exact frequency is not known but the published literature amounts to only a few tens of pedigrees.

Presentation and diagnosis:

Subjects present with hypertension that occurs early (often diagnosed in the teens), is often severe and shows a typical biochemical profile of hypokalemia, metabolic acidosis and a suppressed plasma renin and aldosterone i.e. the appearances of pseudo*hyper*aldosteronism. However, the hypertension in some pedigrees has been noted to be mild and variable (e.g. only pregnancy associated)[1]. The hypokalaemia may also be absent or variable[2], but all affected subjects show impaired aldosterone secretion. This can be assessed either by measurement of plasma aldosterone after synthetic ACTH stimulation (250 μg synacthen IV with collection of a venous blood sample 30 minutes later) or based on 24 h urinary aldosterone excretion[1].

The hypertension is characteristically very responsive to a combination of salt restriction (<100mmol/day) and antihypertensives targeting the epithelial sodium channel (ENaC) i.e. amiloride and triamterene. Aldosterone receptor antagonists such as spironolactone are not effective, since the syndrome is not mineralocorticoid-driven. However, excessive liquorice consumption or exogenous mineralocorticoid can mimic this syndrome and should be excluded.

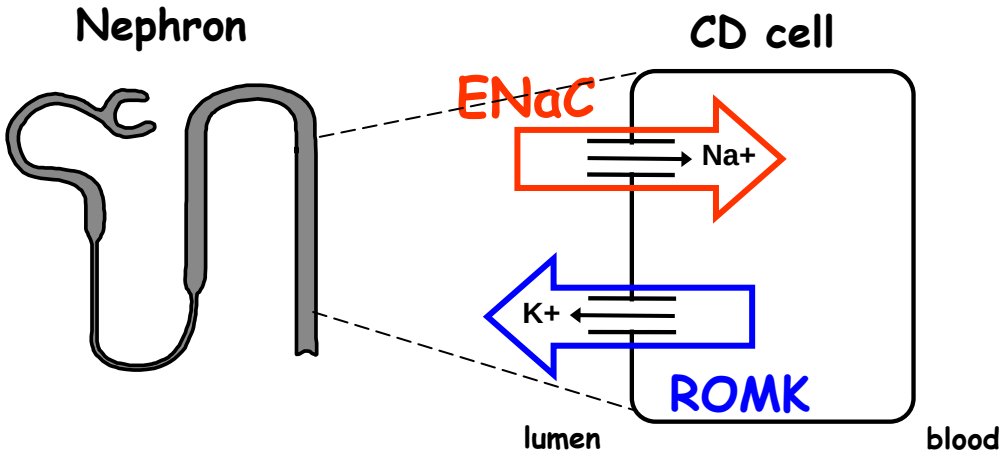
Molecular basis for the syndrome:

Liddle's original 1963 case eventually developed end-stage renal failure and was given a renal transplant. Strikingly, the procedure also normalised her blood pressure. This was reported in 1994 shortly after ENaC was first cloned and the two observations soon led to the identification of the disease mutations for Liddle's within 2 of the 3 subunits of the ENaC channel. ENaC is actually made up of 3 homologous subunits (α,β and γ). The α subunit can form an ion channel in vitro, but its activity is very low unless the ancillary β and γ subunits are co-expressed to form the full native channel.

The Liddle mutations (with a single exception) cluster in the C-terminal region of the β and γ subunits. This region plays a key role in trafficking of ENaC and especially its removal from the surface membrane by endocytosis. An amino acid motif (PY) within the C-terminal has been identified as essential for the binding of a protein called Nedd4. Once bound to the PY motif, Nedd4 regulates the attachment of ubiquitin, which in turn triggers endocytosis of ENaC. The Liddle mutations either mutate one of the amino acids of the PY motif or remove it completely by creating a premature upstream stop codon. The resulting defect in removal from the surface membrane leads to high constitutive levels of ENaC expression. A single mutation has been identified upstream of the C-terminal in the extracellular loop[3]. This mutation does not affect expression of ENaC but increases individual channel currents by affecting open channel probability.

The consequence of the Liddle mutations is to cause excessive sodium uptake through ENaC in the collecting duct (CD) of the kidney and hence salt-sensitive hypertension (see cartoon). Hypokalaemia can be explained as a direct consequence of the Na+ uptake because ENaC is electrogenic and its activity makes the lumen of the collecting duct more negative. Since

transepithelial potential drives K^+ secretion into the lumen through the ROMK K-channel, the increased negative potential within the collecting duct causes increased K^+ secretion (kaluresis). This mechanism explains why salt restriction is effective in these patients and that hypokalaemia will be most easily detected on a high salt diet.



Genetic diagnosis:

To identify the causative mutation, the C-terminal regions of the genes encoding the β (SCNN1B) and γ (SCNN1G) subunits of ENaC should be directly sequenced. If this identifies only wild-type sequences, then both subunits should be completely sequenced in the light of the report of a

disease mutation occurring upstream of the C-terminal[3]. Novel mutations should ideally be studied in vitro to confirm that they can affect either ENaC expression or its channel activity. This is especially important if the mutation does not truncate the β or γ subunit C-terminal or otherwise destroy the PY motif. If no mutation is detected it may be worth considering mutation scanning of other genes involved in ENaC trafficking, such as Nedd4 itself. There is currently no referral service available in the UK to carry out mutation detection for Liddle syndrome.

In terms of published mutations (see table), a number of missense mutations or deletions/insertions causing premature stop codons have been identified in SCNN1B. (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=SCNN1B). Only 3 mutations have been reported in SCNN1G (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=SCNN1G).

Table of published mutations causing Liddle Syndrome

Accession Number*	Codon change	Amino acid change	Codon number
βENaC subunit: SCNN1B			
CM941273	gCGA-TGA	Arg-Term	564
CM941274	cCAG-TAG	Gln-Term	589
CM984126	ACG-ATG	Thr-Met	592
CM981791	gCCC-TCC	Pro-Ser	615
CM050080	CCC-CGC	Pro-Arg	616
CM951144	CCC-CTC	Pro-Leu	616
CM983944	cCCC-TCC	Pro-Ser	616
CM961268	cTAT-CAT	Tyr-His	618
CG973531	32 bp nt. 1735-1766 (described at genomic DNA level)		
CD942124	GACACG^GCCCcCCGCAGCCCC		593
γENaC subunit: SCNN1G			
CM023449	AAC-AGC	Asn-Ser	530
CM951145	TGG-TAG	Trp-Term	573
CM014826	TGG-TAG	Trp-Term	575

* Accession numbers refer to the Human Genome Mutation Database (http://www.hgmd.cf.ac.uk)

A common forme fruste of Liddle Syndrome?

An obvious question is whether there is a role for common functional polymorphisms in ENaC amongst the wider hypertensive population. There are two documented polymorphisms in the C-terminal of the βENaC subunit: 563R>Q and 594T>M. The 594T>M polymorphism is the most

thoroughly investigated. It does not affect the proline-rich NEDD binding motif, but does affect a protein kinase C site that is thought to regulate channel activity. It is present in up to 8% of black Africans, and subjects in South-London carrying this allele were reported to be particularly responsive to inhibitors of ENaC[4]. However, this has not been borne out in larger subsequent studies. The most recent study using >1500 Black Caribbean hypertensives in Texas found that carriage of the 594M allele did not predict BP or response to amiloride treatment[5]. There is currently no good evidence to support the routine mutation screening of either Black African and/or low-renin hypertensive patients for the T594M or other SCNNB1 alleles.

Reference List

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2. Botero-Velez M, Curtis JJ, Warnock DG. Liddle's Syndrome Revisited -- A Disorder of Sodium Reabsorption in the Distal Tubule. N Engl J Med 1994; 330(3):178-181.

3. Hiltunen TP, Hannila-Handelberg T, Petajaniemi N et al. Liddle's syndrome associated with a point mutation in the extracellular domain of the epithelial sodium channel gamma subunit. J Hypertens 2002; 20(12):2383-2390.

4. Baker EH, Duggal A, Dong Y et al. Amiloride, a specific drug for hypertension in black people with T594M variant? Hypertension 2002; 40(1):13-17.

5. Hollier JM, Martin DF, Bell DM et al. Epithelial Sodium Channel Allele T594M Is Not Associated With Blood Pressure or Blood Pressure Response to Amiloride. Hypertension 2006; 47(3):428-433.