**The expanding genetic horizon of primary aldosteronism**

# THE EXPANDING GENETIC HORIZONS OF PRIMARY ALDOSTERONISM

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| Study | Country | Families (n) | Patients (n) | Sex (M/F) | Hypertension (n/tot available) | Spontaneous hypokalemia (n/tot available) | Low renin / elevated ARR (n/tot available) | Elevated hybrid steroids (n/tot available) | Reported symptoms / TOD / CV events / other |
|---|---|---|---|---|---|---|---|---|---|
| **Before the identification of the *CYP11B1/CYP11B2* chimeric gene** | | | | | | | | | |
| Sutherland 1966 (1) | CANADA | 1 | 2 | 2/0 | 2/2 | 2/2 | 2/2 | n.a. | Headache, LVH, retinopathy, death due to cerebrovscular events in 3 siblings of the index case |
| New 1967 (2) | USA | 1 | 1 | 1/0 | 1/1 | 1/1 | 1/1 | n.a. | Polyuria, polidipsia, enuresis, headache, LVH, retinopathy. |
| Miura 1968 (3) | JAPAN | 1 | 1 | 0/1 | 1/1 | 1/1 | 1/1 | n.a. | Headache, retinopathy. Born form consanguineous hypertensive parents |
| Giebink 1973 (4) | USA | 1 | 3 | 2/1 | 3/3 | 2/3 | 3/3 | n.a. | Headache, polyuria, nicturia, retinal arteriolar spasms, LVH. History of cerebral hemorrhage at young age (maternal grandmother) |
| Grim 1980 (5) | USA (Dutch Indonesian origin) | 1 | 3 | 3/0 | 3/3 | 0/3 | 3/3 | n.a. | LVH |
| New 1980 (6) | USA | 2 | 8 | 2/6 | 7/8 | n.a. | 8/8 | n.a. | |
| Ganguly 1981 (7) | USA | 1 | 3 | 1/2 | 3/3 | 3/3 | 3/3 | n.a. | Easy fatiguability, muscle cramps and carpopedal spasms, dizziness, exertional dyspnea, headache. One family member died of cerebral hemorrhage at the age of 21, one of myocardial infarction at the age of 27 |
| Oberfield 1981 (8) | USA | 1 | 5 | 3/2 | 3/3 | n.a. | 3/3 | n.a. | n.a. |
| Lee 1982 (9) | MEXICO | 1 | 1 | 1/0 | 1/1 | 1/1 | 1/1 | n.a. | n.a. |
| Fallo 1985 (10) | ITALY | 1 | 3 | 2/1 | 3/3 | 2/3 | 3/3 | n.a. | The father of the index cases died of stroke at the age of 60 |
| Woodland 1985 (11) | AUSTRALIA | 2 | 2 | 2/0 | 2/2 | 2/2 | 2/2 | n.a. | One patient had strong family history of hypertension; the other was an adopted child |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Connell 1986 (12) | UK | 1 | 2 | 2/0 | 2/2 | 1/2 | 2/2 | 2/2 | n.a. |
| Davis 1988 (13) | UK | 1 | 3 | 3/0 | 3/3 | 1/3 | 3/3 | 3/3 | The mother of the index case had a cerebrovascular event at the age of 47 |
| O'Mahony 1989 (14) | IRELAND | 1 | 4 | 4/0 | 4/4 | 2/4 | 4/4 | n.a. | Strong family history of premature cardiovascular death |
| Yamakita 1989 (15) | JAPAN | n.a. | 12 | 5/7 | 9/12 | 8/12 | 12/12 | n.a. | Retinopathy |
| **Total** | | **16** | **53** | **33/20** | **47/51 (92%)** | **26/40 (65%)** | **51/51 (100%)** | **5/5** | |
| **After the identification of the *CYP11B1/CYP11B2* chimeric gene** | | | | | | | | | |
| **Study** | **Country** | **Families (n)** | **Patients (n)** | **Sex (M/F)** | **Hypertension (n/tot available)** | **Spontaneous hypokalemia (n/tot available)** | **Low renin / elevated ARR (n/tot available)** | **Elevated hybrid steroids (n/tot available)** | **Reported symptoms / TOD / CV events / other** |
| Rich 1992 (16) | USA | 1 | 12 | 2/10 | 8/12 | 1*/12 | 11#/12 | 12/12 | Prevalence of iuretic induced hypokalemia 58%. High prevalence of cerebrovascular events in young age as cause of death |
| Comiter 1995 (17) | USA | 1 | 1 | 0/1 | 1/1 | 0/1 | 1/1 | 1/1 | Family history of early onset hypertension and death for cerebrovascular events at young age in 4/10 1st and 2nd degree relatives |
| Jamieson 1995 (18) | UK | 5 | 19 | 10/9 | 14/19 | 6/19 | 19/19 | n.a. | n.a. |
| Pascoe 1995 (19) | FRANCE | 1 | 7 | 4/3 | 7/7 | n.a. | n.a. | n.a. | n.a. |
| Gates 1996 (20) | USA | 2 | 30 | 17/13 | 26/30 | 4/15 | n.a. | n.a. | LVH, retinopathy. Family history of cerebral haemorrhage |
| Hsieh 1997 (21) | CHINA | 1 | 1 | n.a.§ | n.a.§ | n.a.§ | n.a.§ | n.a.§ | n.a.^ |
| Litchfield 1998 (22) | USA | 27 | 167 | 87/80 | 43/54 | n.a. | n.a. | n.a. | 18 cerebrovascular events in 15 patients with proven GRA |
| Stowasser 2000 (23) | AUSTRALIA | 5 | 26 | 13/13 | n.a. | 6/26 | 17/20 | 18/18 | Family history of stroke in some of the families |
| Gates 2001 (24) | UK | 4 | 14 | 8/3 | 8/10 | 2/11 | n.a. | n.a. | Family history of cerebral haemorrhage at young age |
| Yokota 2001 (25) | JAPAN | 1 | 3 | 0/3 | 3/3 | 0/3 | 3/3 | n.a. | General fatigue, pregnancy induced hypertension. History of not fatal stroke |
| Ding 2002 (26) | CHINA | 1 | 4 | 2/2 | 3/3 | 3/3 | 3/3 | n.a. | Headache, muscle weakness, flaccid paralysis, tatany, |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | nicturia, palpitation, stroke in one patient |
| Mulatero 2002 (27) | ITALY | 1 | 21 | 6/15 | 8/21 | 0/21 | 17/21 | 21/21 | No history of stroke in the affected family members |
| Fallo 2004 (28) | ITALY | 1 | 3 | 2/1 | 2/3 | 1/3 | 1/3 | 3/3 | LVH |
| Vonend 2007 (29) | GERMANY | 1 | 3 | 3/0 | 3/3 | 0/3 | 3/3 | 3/3 | Microalbuminuria |
| Lee 2010 (30) | KOREA | 1 | 3 | 2/1 | 3/3 | 0/3 | 3/3 | n.a. | Two cerebral aneurysms in the same patient |
| Aglony 2011 (31) | CHILE | 3^ | 10^ | 6/4 | 7/10 | 2/10 | 9/10 | n.a. | 1 cerebellar stroke |
| Mulatero 2011 (32) | ROMANIA | 1 | 2 | 1/1 | 2/2 | 0/2 | 2/2 | n.a. | Family history of aortic dissection at young age |
| Kamrath 2011 (33) | SCOTLAND | 1 | 4 | 2/2 | 4/4 | 2/3 | 4/4 | 2/2 | 1 cerebral aneurysm, family history of stroke |
| Carvajal 2012 (34) | CHILE | 1 | 24 | 11/13 | 18/23 | 1/24 | 10/24 | 24/24 | |
| **Total** | | **60** | **357** | **178/175** | **162/211 (77%)** | **29/162 (14%)** | **105/131 (80%)** | **84/84** | |

**Supplemental table S1.** Main clinical and biochemical features of patients affected by Familial Hyperaldosteronism type I before and after the identification of the *CYP11B1/CYP11B2* chimeric gene. Hypertension was defined according to the 2013 ESH guideline[35]; hypokalemia was defined as serum $K^+$ < 3.5 mmol/L; low renin was defined as PRA < 1 ng/ml/h (12.7 pmol/L/min)[36]; elevated ARR was defined as > 30 ng*dL$^{-1}$/ng*ml$^{-1}$*h$^{-1}$ (60 pmol*L$^{-1}$/pmol*L$^{-1}$*min$^{-1}$)[33] TOD = target organ damage; CV events = cardiovascular events; LVH = left ventricular hypertropy.

* spontaneous hypokalemia was reported at diagnosis of hypertension, but the patient was found to be normokalemic at further evaluations; # one patient had normal PRA (2.06 ng/L*s) under treatment with $K^+$ sparing diuretic; § full text not available in English; ^ compared to the original manuscript, one family and three patients have been omitted since they are included in Carvajal 2012 (33).

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